Annual Report
July 1, 2022 - June 30, 2023

and

24th Annual Scientific Conference
September 11, 2023
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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 250 researchers, clinicians, and staff from 14 organizations. The Consortium’s seven principal institutions include Arizona State University, Banner Alzheimer’s Institute, Banner Sun Health Research Institute, Barrow Neurological Institute, Mayo Clinic Arizona, the Translational Genomics Research Institute (TGen), and the University of Arizona. Its six formally affiliated organizations include Banner Alzheimer’s Institute-Tucson, the Critical Path Institute (CPATH), Midwestern University, Northern Arizona University, TGen North, and the University of Arizona College of Medicine, Phoenix, and it has a close working relationship with the Veterans Administration Health System in Phoenix. Established in 1998, the Consortium is intended to make a transformational difference in the scientific fight against AD and 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 within the next few years.

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 with the greatest possible impact. It receives critical support from the state of Arizona (through the Arizona Department of Health Services [ADHS]), the participating organizations, the National Institute on Aging (NIA)-sponsored Arizona 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; Jessica Langbaum and Ali Atri are the ADRC’s Associate Directors. Carol Barnes chairs the Consortium’s 24-member Internal Scientific Advisory Committee (ISAC), and Jeffrey Kordower kindly served as interim chair during Dr. Barnes’s sabbatical last year. David Jerman is the Administrative Director of the Consortium’s state and organizationally supported research Consortium and Andrea Schmitt is Administrative Director of the NIA-sponsored Arizona ADRC. Leading officials from each of the Consortium’s principal organizations serve on its 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 ADRD. They conduct annual site visits, review the progress and productivity of both the Consortium and ADRC, and provide formal feedback and recommendations to researchers, the 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, computational, mathematical, statistical, artificial intelligence/machine learning, and other big data analyses of complex data sets, the basic, translational, cognitive, and behavioral neurosciences, and clinical, experimental
therapeutics, and neuropathology research. It has made pioneering contributions to the scientific understanding of AD, including unusually early detection, tracking, study and diagnosis of AD, the accelerated evaluation of putative AD prevention therapies, and the scientific understanding of the aging mind and brain. It has introduced new ways for different stakeholders to work together, provided data, biological samples and interested research participants for researchers inside the state and around the world, and introduced promising cognitive care models for patients and family caregivers. The Consortium continues to attract new researchers and clinicians and support other biomedical research developments in the state, making Arizona a destination center for the advancement of research and care for AD and ADRD.

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

Shared Resources to Advance the Study of AD

Since securing NIA’s first statewide Center grant in 2001, Arizona has received highly competitive, continuous grant funding from the National AD Research Centers (ADRCs) Program and continues to play a prominent role in the national ADRC community. The Arizona ADRC’s Administrative, Clinical, Data Management and Statistics, Biomarker, Neuropathology, and Outreach, Recruitment and Engagement Cores provides the leadership, expertise, mentorship, well characterized research participants, biological samples, and privacy-protected data needed to support researchers throughout the state, foster collaborations with colleagues around the world, help establish the next generation of research leaders, and have a profound impact on the fight against AD and ADRD. While the early detection and prevention of AD and age-related cognitive decline continue to be our over-arching themes, the ADRC has placed additional emphases on the development, validation, and use of BBBMs in the early detection, tracking, diagnosis, study, treatment and prevention of AD/ADRD, and their generalizability to under-represented groups.

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

Together, our Arizona ADRC grant, an NIA grant for the study of cognitively unimpaired persons at six levels of genetic risk based on their APOE genotype, a Gates Ventures grant, other major NIH grants, and state, organizational and philanthropic funds permit our researchers to provide shared resources of data and biological samples for neuropathological study and
diagnostic validation of BBBMs for AD/ADRD, including blood samples from several hundred brain donors in the last years of life who have comprehensive neuropathological assessments after they die. In addition to their other contributions, ADRC and Consortium funds provide data and biological samples needed to confirm the accuracy of BBBMs in Hispanic/Latino and American Indian participants using cerebrospinal fluid (CSF) and brain imaging measurements, setting the stage to dramatically increase the use of biomarkers in these and other underrepresented groups. They support the study of “preclinical AD” and non-pathological aging in cognitively unimpaired participants who are at differential genetic risk, including those with and without biomarker evidence of AD, and permit researchers inside Arizona and around the world to incorporate more affordable, scalable, and repeatable BBBMs in independently funded studies. Some (but not all) of our developing resources are summarized in the table below:

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<th>Productivity, Progress and Impact</th>
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The Arizona Alzheimer’s Consortium is the leading statewide AD Center in the nation and one of the most productive AD research programs in the world. Since its inception in 1998, its researchers have generated thousands of publications, grants, and contracts, and more than $2 billion in new investments. Consortium researchers have made pioneering contributions to the study of AD and ADRD, along with that of the aging mind and brain:

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

2. They continue to generate invaluable public resources of longitudinal, neuropathological, and gene expression data for the field, including what we predict will be an invaluable resource of DNA sequencing, laser-capture micro-dissected, and single nucleus RNA sequencing data from different brain cell types and brain regions that are differentially affected by AD pathology in 100 brain donors with and without AD. Consortium researchers continue to use these and other resources to implicate disease networks, risk factors, and potential drivers at which to aim new AD treatments.

3. They continue to introduce new data-sharing, biological sample-sharing, and collaborative paradigms to assist researchers in Arizona and around the world—including data and samples from their own observational studies and prevention trials, data from a growing number of clinical trials of AD and other disorders through the Critical Path for AD (e.g., CPAD, https://copath.org/programs/cpad/), online memory tests and other information that have been generated in >400,000 participants in the MindCrowd project (www.mindcrowd.org), and the largest resource of privacy-protected longitudinal electronic health record (EHR) data and biological samples from under-represented groups in the national All of Us Research Program.
4. They and their colleagues have played leadership roles in the early detection and tracking of AD, including the detection and tracking of progressive brain imaging, other biomarkers, and cognitive changes—as well as the detection of neurodevelopmental changes—in cognitively unimpaired persons at genetic risk. They introduced new research paradigms, image-analysis techniques, and other approaches to help in this endeavor. Their work anticipated and advanced the conceptualization of preclinical AD.

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

6. They have worked with their Colombian colleagues to establish a registry of about 6,000 persons from the world’s largest Autosomal Dominant AD (ADAD) cohort, including nearly 1,200 mutation carriers who are virtually certain to develop AD and become cognitively impaired at the median age of 44, conducted pioneering studies of preclinical AD and recently completed the world’s first AD prevention trial. They have begun to provide invaluable resources of data and biological samples to advance the preclinical study and prevention of AD.

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

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

9. They and their collaborators have played leadership roles in the study of chronic traumatic encephalopathy (CTE) through “DIAGNOSE CTE”, a national NINDS-sponsored longitudinal study which aims to characterize clinical, cognitive, PET, CSF, neuropathological, and 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.

10. They continue to provide a world-leading scientific resource of longitudinal and neuropathological data, as well as brain and body tissues for the study of AD, Parkinson’s disease, and ADRD in their Brain and Body Donation Program. As previously noted, they have begun to incorporate ante-mortem biomarkers and new post-mortem brain tissue resources to help researchers address their goals with even greater impact.

11. They have begun to show the promise of BBBMs in the early detection, tracking, study, and diagnosis of AD and the evaluation of AD-modifying and prevention therapies. They continue to acquire and provide a shared resource of annual blood samples to support the neuropathological validation and head-to-head comparison of these and other biomarkers of AD and ADRD, and they used this shared resource to support the generalizability of these tests to under-represented Hispanic/Latino and American Indian groups. They believe that BBBMs have the potential to transform AD/ADRD research, treatment development, and clinical care, and galvanize the inclusion of persons from under-served and under-represented groups.

12. Consortium researchers and their colleagues continue to characterize cognitive, biomarker, neuropathological, and other effects of COVID-19 infection in living persons and expired brain
13. Led by Arizona researchers, the Alzheimer's Prevention Initiative (API) helped launch a new era in AD prevention research, introduced research paradigms and methods to accelerate the evaluation and potential approval of AD prevention therapies in cognitively unimpaired persons who, based on their genetic background and age or biomarker evidence of AD, are at increased risk for the clinical onset of the disease, and co-led a growing number of AD prevention trials. API introduced the first NIH-supported prevention trial of a putative disease-modifying drug therapy, showed that prevention trials were possible, and found ways to value research participants, including those from vulnerable populations in developing countries as partners in this endeavor, and it has co-led a growing number of potentially groundbreaking trials since then, with support from industry, NIH, and philanthropy. It established precedent-setting public-private partnerships, data and biological sample sharing commitments, and strategies to support the potential development of surrogate biomarker endpoints in the accelerated evaluation and approval of prevention therapies. API continues to provide better tests of the amyloid hypothesis than failed clinical trials in later stages of the disease, extremely large research registries and APOE gene-matching programs to support interest and enrollment in prevention trials.

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

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

New Developments, Opportunities and Initiatives

Clinically effective amyloid plaque-clearing antibody therapies. In definitive clinical trials, the amyloid plaque-clearing antibody therapies lecanemab and donanemab dramatically reduced biomarker measurements of amyloid plaques and incompletely slowed down clinical decline in mildly impaired persons with biomarker evidence of AD. In addition to the implications for patients who may be eligible for treatment, these findings provide compelling support for the role of amyloid aggregates in the development, treatment and potential prevention of AD. Furthermore, they support the possibility that a treatment’s effects on PET and BBBM of amyloid plaques are “reasonably likely” to predict a clinical benefit. Ongoing prevention trials of donanemab (co-led by API and Eli) and lecanemab (co-led by Eisai and researchers from Harvard and USC) in cognitively unimpaired persons with PET or BBBM evidence of plaques now have a realistic chance to find and support the accelerated approval of these secondary prevention therapies within the next three years. Self-administered subcutaneous amyloid plaque-clearing antibody therapies now in development have the potential to support the approval and availability of more widely accessible secondary prevention therapies in persons with biomarker evidence of AD and, indeed, support their approval in the primary prevention of AD, starting in cognitively unimpaired donors, and they will continue play important roles in the national effort to characterize and provide care for these long-term brain and body effects (also known as “Long COVID” or “post-acute sequelae SARS-CoV-2 infection [PASC]”).
persons with known genetic risk factors who do not yet have biomarker evidence of amyloid plaques, and do so within the next five years.

**Other developing medical and non-medical treatments.** Researchers continue to work on developing other promising drugs for the treatment and prevention of AD, including a small number of treatments that are now in clinical trials. The investigational drugs have sought to target some of the pathophysiological processes involved in the development of amyloid aggregates, potentially damaging or beneficial neuroinflammatory changes, the phosphorylation, aggregation, and cell-to-cell transmission of tau, neuronal injury and degeneration, APOE, and other factors involved in the predisposition to and protection from AD. They include small molecules, antibody and vaccine therapies, and reversible and irreversible gene therapies, and potentially repurposed drugs. With the advent of partially but incompletely effective plaque-clearing drugs, new paradigms will be needed to find combination or sequential treatments that could have a more profound therapeutic impact after the disease is already extensive. In the meantime, numerous studies continue to have characterize the impact of health-promoting medical management, healthy diets, and lifestyle interventions on age-related cognitive decline, and the biomarkers to which they are related. Arizona researchers are actively involved in the development and evaluation of these promising treatments, including the use of “theragnostic” biomarkers to help find effective disease-modifying and prevention therapies as quickly and efficiently as possible.

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

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

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

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

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

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

Looking Ahead

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

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

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

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

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

We are extremely grateful to the state of Arizona, NIH, and our participating organizations, our heroic research participants, and all of our other supporters, for the chance to make a profound difference in the fight against AD and find effective prevention therapies as soon as possible.
Arizona Alzheimer's Consortium
24th Annual Scientific Conference – Monday September 11, 2023
Mayo Clinic Arizona (Host Institution)
Arizona State University
Memorial Union
301 E Orange St., Tempe, AZ 85281

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

9:25 – 9:40AM VIDEO & WELCOME
William Faubion Jr., M.D.
Dean of Research, Mayo Clinic in Arizona
Associate Medical Director, Center for Regenerative Biotherapeutics

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
Risk Reduction Strategies for Primary Prevention of Dementia
Kristine Yaffe, MD
Professor of Psychiatry, Neurology, and Epidemiology
UCSF Weill Institute for Neurosciences
Roy and Marie Scola Endowed Chair
Vice Chair of Research in Psychiatry
Director, Center for Population Brain Health
University of California, San Francisco

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

12:30 PM Student Group Photo – Arizona Ballroom

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

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

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

4:15 – 4:30PM CLOSING REMARKS
Eric M. Reiman, M.D.
SESSION I  Moderators: David W. Coon, PhD & Matthew Huentelman, PhD

11:15 – 11:27 AM  The dawn of a new era of Alzheimer’s Disease therapeutics: Plaque-lowering monoclonal antibodies – benefits, risks, caveats and appropriate use considerations. Presenting Author: Alireza Atri, MD, Banner Sun Health Research Institute, Brigham and Women’s Hospital, Harvard Medical School


11:54 – 12:06 PM  A longitudinal investigation of physical and cognitive activities and the outcome of trajectories of AD Neuroimaging Biomarkers: The Mayo Clinic Study of Aging. Presenting Author: Janina Krell-Roesch, PhD, Karlsruhe Institute of Technology, Mayo Clinic

12:07 – 12:19 PM  Differential effects of vascular comorbidities on AD risk in males versus females. Presenting Author: Franchell Vazquez, MD, University of Arizona
SESSION II  Moderators: Heather Bimonte-Nelson, PhD & Zaven Khachaturian, PhD

3:00 – 3:12 PM  Combining structural MRI and blood-based biomarkers to improve the classification of persons with or without amyloid plaques.  
Presenting Author: Yanxi Chen, MS, Arizona State University

3:13 – 3:25 PM  Potential greater relative reduction of white matter hyperintensity accumulation with intensive systolic blood pressure control at younger ages.  
Presenting Author: Jeremy Pruzin, MD, Banner Alzheimer’s Institute

3:26 – 3:38 PM  Diffusion MRI-based measures of hippocampal microstructure are associated with delayed verbal memory performance in cognitively unimpaired persons at genetic risk for AD.  
Presenting Author: Scott Beeman, PhD, Arizona State University

3:39 – 3:51 PM  Cerebral white matter rarefaction has both neurodegenerative and vascular causes and may primarily be a distal axonopathy.  
Presenting Author: Geidy Serrano, PhD, Banner Sun Health Research Institute

3:52 – 4:04 PM  Rehabilitating language in primary progressive aphasia with targeted phonological treatment and transcranial direct current stimulation (TDCS).  
Presenting Author: Aneta Kielar, PhD, University of Arizona


5. **FLORBETAPIR PET UPTAKE IN WHITE MATTER IN AGING AND ALZHEIMER’S DISEASE.** Bhargava V, Luo J, Chen Y, Ghisays V, Malek-Ahmadi MH, Sohankar J, Lee W, Protas HD, Reiman EM, Su Y. University of Arizona College of Medicine, Phoenix; Banner Alzheimer’s Institute; Translational Genomics Research Institute; University of Arizona; Arizona State University; Arizona Alzheimer’s Consortium.


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


17. APPROACHES TO ALZHEIMER’S DISEASE (AD) DETECTION IN URINE AND FECES THROUGH WASTEWATER-BASED EPIDEMIOLOGY. Ellershaw A, Newell ME, Babrah A, Driver EM, Aravindan A, Halden RU. Arizona State University; OneWaterOneHealth, Arizona State University Foundation; Arizona Alzheimer’s Consortium.

18. CEREBRAL AMYLOID ANGIOPATHY AND WHITE MATTER RAREFACTION ARE NOT ASSOCIATED WITH FASTER PROGRESSION TO MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER’S DISEASE. Ellsworth B, Malek-Ahmadi M, Arce R, Serrano GE. University of Arizona College of Medicine, Phoenix; Banner Alzheimer’s Institute; Banner Sun Health Research Institute; Arizona Alzheimer’s Consortium.


20. BLOOD BRAIN BARRIER INJURY DETECTED IN THE SERUM OF PATIENTS WITH A HISTORY OF STROKE AND TRANSIENT ISCHEMIC ATTACK. French SR, Arias JC, Bolakale-Rufai IK, Serrano GE, Beach TG, Reiman EM, Weinkauf CC. University of Arizona; Sarver Heart Center; Banner Sun Health Research Institute; Banner Alzheimer’s Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.


22. VOLUMETRIC APPROACHES TO HUMAN BRAIN STRUCTURAL MRI ANALYSIS WITH APPLICATIONS TO ALZHEIMER’S DISEASE RESEARCH. George JV*, Chen Y*, Su Y, Farazi M, Chen K, Caselli RJ, Reiman EM, Wang Y, for the Alzheimer’s Disease Neuroimaging Initiative. Arizona State University; Banner Alzheimer’s Institute; Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

23. NOVEL MAGNETIC RESONANCE IMAGING SIGNATURES DETECT NEUROINFLAMMATION AFTER EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY. Giordano KR, Griffiths DR, Hutchinson EB, Lifshitz J. University of Arizona College of Medicine-Phoenix; Phoenix VA Health Care System; University of Arizona; Arizona Alzheimer’s Consortium.


27. THE CONTRIBUTION OF SEMANTIC AND PHONOLOGICAL ABILITIES TO CATEGORY FLUENCY PERFORMANCE PATTERNS IN LOGOPENIC VARIANT OF PRIMARY PROGRESSIVE APHASIA. Jebahi F, Nickels KV, Frazier NJ, Egleson L, Kielar A. University of Arizona; Arizona Alzheimer’s Consortium.

28. CHARACTERIZATION OF MACROVASCULAR AND MICROVASCULAR PERFUSION IN ALZHEIMER’S DISEASE AND VASCULAR DEMENTIA. Keeling EG, McElvogue MM, Ott LR, Sabbagh M, Burke A, Bakkar N, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer’s Consortium.


32. UTILIZING SHORT STORIES TO UNDERSTAND THE IMPACT OF CONTEXT ON PATTERN SEPARATION AMONG OLDER AND YOUNGER ADULTS. Martinez AC, Karnafel MJ, Palmer JM, Ryan L. University of Arizona; Arizona Alzheimer’s Consortium.

33. STABILITY IN LOCUS COERULEUS CELL POPULATIONS IN COGNITIVELY IMPAIRED RHESUS MACAQUES. McDermott K, Sinakevitch I, Barnes CA. University of Arizona; Arizona Alzheimer’s Consortium.
34. **EVALUATION OF ONE-CARBON METABOLITE ENZYMES AND RECEPTORS IN BRAIN TISSUE FROM VASCULAR CONTRIBUTION TO COGNITIVE IMPAIRMENT AND DEMENTIA (VCID) PATIENTS.** McKee A, Joshi S, Ille S, Beach TG, Serrano GE, Jadavji NM. Midwestern University; Banner Sun Health Research Institute; Arizona Alzheimer’s Consortium.


40. **AGING WITH TRAUMATIC BRAIN INJURY: PROFILES FOR NEUROPATHOLOGY IN BEHAVIORALLY RELEVANT THALAMOCORTICAL CIRCUITRY OF MALE AND FEMALE RATS.** Mitbander A, Sabetta Z, Krishna G, Curry T, Adelson DP, Currier Thomas T. University of Arizona College of Medicine, Phoenix; Barrow Neurological Institute at Phoenix Children’s Hospital; Midwestern University; Arizona State University; Phoenix VA Healthcare System; Arizona Alzheimer’s Consortium.

41. **BINDING AND DISRUPTION OF AMYLOID BETA AND TAU PLAQUES VIA FOCUSED ULTRASOUND AND TARGETED PHASE-SHIFTED 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.
42. ASSESSMENT OF WHITE MATTER MICROSTRUCTURE AND HYPERINTENSITIES IN ALZHEIMER’S DISEASE USING FREE-WATER DIFFUSION TENSOR IMAGING. Nelson MR, Keeling EG, Bergamino M, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer’s Consortium.

43. APOE GENOTYPE DISCLOSURE: ALZHEIMER’S PREVENTION INITIATIVE GENERATION PROGRAM TRIALS. Oyen E, Langois C, Malek-Ahmadi M, Langbaum JB. Arizona State University; Banner Alzheimer’s Institute; Arizona Alzheimer’s Consortium.

44. THE IMPACT OF RESPIRATORY SYMPTOMS ON COGNITIVE PERFORMANCE FOLLOWING COVID-19 RECOVERY. Palmer JM, Rhodes A, Ryan L. University of Arizona; Arizona Alzheimer’s Consortium.


47. IMPACT OF AGING AFTER 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 CE, Baun J, Zurhellen C, Adelson PD, Thomas TC. University of Arizona College of Medicine, Phoenix; Barrow Neurological Institute; Arizona State University; Neuroscience Associates, Knoxville, TN; Phoenix VA Health Care System; Arizona Alzheimer’s Consortium.


49. CORTICAL THICKNESS PREDICTORS OF MOTOR TASK VARIABILITY IN THE ALZHEIMER’S DISEASE SPECTRUM. Schack K, Malek-Ahmadi M, Duff K, Koppelmans V, King JB, Su Y, Schaefer SY. Arizona State University; University of Arizona College of Medicine – Phoenix; Oregon Health Sciences University; Layton Aging and Alzheimer’s Research Center; University of Utah; Arizona Alzheimer’s Consortium.
50. DEVELOPING A MOTOR LEARNING TEST AS AN EQUITABLE APPROACH TO SCREENING HISPANIC/LATINO OLDER ADULTS FOR PRECLINICAL ALZHEIMER'S DISEASE. Schaefer SY, Hooyman A, Reed A, Ryan L, Huentelman M. Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.


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54. REPRODUCTIVE HORMONE LEVELS AND BRAIN-BASED MARKERS OF NEURODEGENERATION IN ALZHEIMER'S DISEASE. Solis A, Barajas J, Ofori E. University of Texas, El Paso; Arizona State University; Arizona Alzheimer’s Consortium.


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73. **FEASIBILITY AND ACCEPTABILITY OF THE STRENGTHENING SKILLS PROGRAM FOR AGING AUTISTIC ADULTS.** Braden BB, Matthews N, Gallegos S, Hill E, Cortes Coria S, O’Rourke H, Baxter L. Arizona State University; Southwest Autism Research and Resource Center; Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

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76. **FROM ANALYSIS OF ANTIBODIES SELECTION TO ULTRA SENSITIVITY BIOMARKER DETECTION FOR NEUROFILAMENT LIGHT CHAIN (NFL).** Chang T, Chung T, Chen W. Instant Nanobiosensors Co., Ltd; LifeCo Scientific LLC; Arizona Alzheimer’s Consortium.


78. **AMELIORATION OF STREPTOZOTOCIN INDUCED ASTROCYTE MITOCHONDRIAL DYSFUNCTION BY FTO INHIBITOR.** Cockova Z, Honc O, Telensky P, Olsen MJ, Novotny J. Charles University, Czech Republic; St. Anne’s University Hospital Brno; Midwestern University; Arizona Alzheimer’s Consortium.


81. **THE HUMAN BRAIN NUCLEUS INCERTUS: A NEW TARGET IN DEMENTIA?** de Ávila C, Gugula A, Trenk A, Intorcia AJ, Suazo C, Nolz J, Plamondon J, Khatri D, Tallant L, Caron A, Blasiak A, Serrano GE, Beach TG, Gundlach AL, Mastroeni DF. Arizona State University; Jagiellonian University, Krakow, Poland; Arizona Alzheimer’s Consortium; Banner Sun Health Research Institute; Centre de recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec,
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82. **AGE-RELATED BRAIN CHANGES IN EX-VIVO FEMALE BONNET MACAQUE BRAINS: INSIGHTS FROM MULTI-MODAL MRI ANALYSIS.** Dieckhaus L, McDermott KE, Murlikrishnan A, Gray DT, Barnes CA, Hutchinson EB. University of Arizona; Arizona Alzheimer’s Consortium.

83. **DEVELOPMENT AND CHARACTERIZATION OF SINGLE-DOMAIN ANTIBODIES TARGETING AMYLOID-B.** Ding Z, Haug KA, Corzine SW, Dresler SR, Fryer JD. Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.


85. **LOW CLINICAL SENSITIVITY AND UNEXPECTEDLY HIGH INCIDENCE FOR NEUROPATHOLOGICALLY DIAGNOSED PROGRESSIVE SUPRANUCLEAR PALSY.** Driver-Dunkley ED, Zhang N, Serrano GE, Dunkley NA, Sue LI, Shill HA, Mehta SH, Beldn C, Tremblay C, Atri A, Adler CH, Beach TG. Mayo Clinic Arizona; Banner Sun Health Research Institute; Barrow Neurological Institute; Brigham and Women’s Hospital & Harvard Medical School; Arizona Alzheimer’s Consortium.


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96. WHAT MATTERS TO YOU ABOUT YOUR HEALTH AND HEALTH CARE? Johnson K, Chaung M, Berdeja J, Shaw A. Arizona State University; HonorHealth Family Practice; Arizona Alzheimer's Consortium.


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104. MEMORY, AFFECTIVE, AND MOTOR DYSFUNCTION IN PERSONS WITH NEURODEGENERATIVE MEMORY DISORDERS. McElvogue MM, Steffes L, Burke A, Stokes AM, Prigatano GP. Barrow Neurological Institute; Arizona Alzheimer’s Consortium.


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108. AMYLOID BETA ROLE IN TBI AND IMPLICATIONS FOR INCREASED RISK OF ALZHEIMER’S DISEASE. Panayi N, Schulz P, He P, Rowe RK, Sierks MR. Arizona State University; University of Colorado, Boulder; Arizona Alzheimer’s Consortium.


110. DEFAULT MODE NETWORK SPLICING PROTEIN ALTERATIONS IN DOWN SYNDROME WITH ALZHEIMER’S DISEASE-RELATED DEMENTIA. Perez SE, Nadeem M, He B, Malek-Ahmadi M, Mufson EJ. Barrow Neurological Institute; Banner Alzheimer’s Institute; Arizona Alzheimer’s Consortium.

111. POLYGENIC RISK SCORE ANALYSIS SUGGESTS HYPOTHYROIDISM AS A RISK FACTOR FOR ALZHEIMER’S DISEASE. Piras IS, Naymik MA, Don J, Schork N, Saner D, Huentelman MJ. Translational Genomics Research Institute; Banner Health; Arizona Alzheimer’s Consortium.


113. POTENTIAL GREATER RELATIVE REDUCTION OF WHITE MATTER HYPERINTENSITY ACCUMULATION WITH INTENSIVE SYSTOLIC BLOOD PRESSURE CONTROL AT YOUNGER AGES. Pruzin JJ, Reboussin DM, Nassrallah I, Cushman W, Gupta A, Williamson J, Tariot PN, Pajewski NM. Banner Alzheimer’s Institute; Wake Forest University School of Medicine; University of Pennsylvania; University of Tennessee; University of Kansas Medical Center; Arizona Alzheimer’s Consortium.


117. A FLEXIBLE SCHEME FOR TEACHING NEURODEGENERATIVE DISEASE TO GRADUATE STUDENTS: USING THE SPECTRUM OF GENETIC CAUSATION AS AN ORGANIZING PRINCIPLE. Restifo LR. University of Arizona; BIO5 Research Institute; Arizona Alzheimer’s Consortium.


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122. DISSOCIATIVE EFFECTS OF AGE ON NEURAL DIFFERENTIATION AT THE LEVEL OF STIMULUS CATEGORIES AND INDIVIDUAL STIMULUS ITEMS. Srokova S, Aktas ANZ, Koen JD, Rugg MD. University of Arizona; University of Texas, Dallas; University of Notre Dame; Arizona Alzheimer’s Consortium.

123. APOE E4 ASSOCIATED WITH INCREASED ABSTRACT AND NEGATIVE WORD USE DURING NATURALISTIC SPEECH IN COGNITIVELY UNIMPAIRED OLDER ADULTS. Stoica T, Deffner A, Andrews E, Thayer SC, Griffith C, Andrews-Hanna J, Grilli MD. University of Arizona; George Mason University; University of Colorado; Arizona Alzheimer’s Consortium.


128. PREPAREDNESS OF ARIZONA OCCUPATIONAL, PHYSICAL, AND SPEECH THERAPY PRACTITIONERS FOR WORKING WITH CLIENTS WITH ALZHEIMER’S DISEASE AND RELATED DEMENTIAS. Turner T, Ayala P, Christensen S, Venkatesh M. Midwestern University; AT Still University; Arizona Alzheimer’s Consortium.


133. hAPOE INCREASES WEIGHT AND SURVIVAL PROBABILITY IN HAP TRANSGENIC MOUSE MODELS. Wiegand J, Stanley T, Dalton A, Campbell L, Brinton RD. University of Arizona; Arizona Alzheimer’s Consortium.


135. ASSOCIATIONS BETWEEN REPORTED SLEEP AND MEMORY PERFORMANCE IN COGNITIVELY UNIMPAIRED MIDDLE-AGED AND OLDER ADULTS. Youngstedt SD, Chen K, Caselli RJ, Lee-Iannotti J, Reiman EM. Arizona State University; Arizona Alzheimer’s Consortium; Banner Alzheimer’s Institute; Mayo Clinic Arizona; Banner University Medical Center.

136. THE MATHEMATICAL MODEL OF TAUOPATHIES. Sugiyama M, Panagiotou E. University of Tennessee; Arizona State University; Arizona Alzheimer’s Consortium.
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Abstracts
THE DAWN OF A NEW ERA OF ALZHEIMER’S DISEASE THERAPEUTICS: PLAQUE-LOWERING MONOCLONAL ANTIBODIES – BENEFITS, RISKS, CAVEATS AND APPROPRIATE USE CONSIDERATIONS. Atri A. Banner Sun Health Research Institute; Arizona Alzheimer’s Consortium; Brigham and Women’s Hospital; Harvard Medical School.

Our field has entered a new and promising dawn in Alzheimer’s Disease (AD) biomarker-informed “disease-modifying” therapeutics that target lowering or eliminating brain beta-amyloid plaques, a core pathophysiologic and defining feature of AD. A new generation of FDA accelerated or traditionally FDA-approved amyloid-lowering monoclonal antibody AD drugs (AD AL-mAbs) are either clinically available (i.e. lecanemab and aducanumab), or may be on the horizon (i.e. donanemab), bringing with them a completely new paradigm of AD evaluation, diagnosis and treatment; and opportunities for improving autonomy and care.

While a major step forward and a therapeutic stepping stone, the current AD AL-mAb drugs do not provide a clinical cure for AD, nor do they reverse AD symptoms or prevent clinical decline. Expectations for clinically and potentially meaningful benefits demonstrated at the group-level in clinical trials of AD AL-mAbs, including a relative benefit of slowing of clinical progression and clinical trial outcome measures, must be considered along with treatment-related risks, burden and costs.

This presentation will provide brief background and an overview of AD therapeutics and data for AD AL-mAbs; and highlight the opportunities and challenges facing our field as “disease-modifying” AD AL-mAb clinical trial data and protocols are translated to and implemented in the real-world of clinical care. Efficacy expectations; risk and safety considerations, including those related to Amyloid Related Imaging Abnormalities (ARIA); and appropriate use practices, caveats and recommendations will be broadly highlighted.

Conflict of Interest Disclosures (past 5 or more years):

Institutional Research Grants, observational or biomarker studies or clinical trials:
- Alzheimer’s Disease Consortia, Coordinating Research Institutes or Government Funding (ACTC, ADCS, ATRI, NIH), Indiana University (observational cohort), Johns Hopkins (clinical trial), Global Alzheimer’s Platform, Biohaven (with ADCS), Eisai (with ATRI/ACTC), Lilly (with ACTC/NIH), PEACE-AD study (with ADCS), Athira, Alzheon, Vivoryon (with ADCS), NIH
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- At previous institution, served as site PI for the Biogen EMERGE study (clinical trial contract with institution), and at my current institution serve as site PI for ACTC/ATRI/Eisai AHEAD 3-45 AD prevention trial (clinical contract with my institution)
- Scientific, Medical or Data Monitoring Advisory Boards; Consulting; lectures, CME, or disease state education programs; or Work Groups/Committees:
  - AbbVie, Acadia, Allergan, the Alzheimer’s Association, Axovant, AZ Therapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Lundbeck, Merck, Roche/Geneotech, Novo Nordisk, Prothena, Qynapse, Sunovion, Suven, and Synexus.
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Background: The primary goal of the Critical Path for Alzheimer’s Disease (CPAD) Consortium is to develop data-driven tools and methodologies that improve clinical trial design and execution, reduce patient burden, and accelerate the scientific understanding of Alzheimer’s disease (AD). Such tools primarily include disease progression models and clinical trial simulation tools. CPAD acts as a neutral convener, bringing together diverse stakeholders across industry, regulatory agencies, patient advocacy organizations, and academia. The consortium identifies key unmet needs in drug development for AD and provides a pre-competitive space for knowledge sharing to occur. CPAD leverages its aggregated database and core competencies of data management, advanced quantitative analytics, and regulatory science, to 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. The complexity and diversity of CPAD’s data pose a challenge for researchers in terms of data processing. To address this, a user-friendly web-based interface called the "actionable data model" (ADM) tool was developed. This tool allows users to generate analysis-ready data subsets based on participant characteristics filters in a simple, web-based user interface. The ADM tool includes a dashboard with variable lists, summary statistics, and visualization. Users can perform data exploration and visualization using the current version of the application. A collection of users has tested the tool end-to-end, from navigating the user interface to creating relevant analysis subsets and using them to build statistical models for disease progression and clinical trial enrichment. Logistic regression models were initially used to predict the risk of developing AD dementia in patients with mild cognitive impairment (MCI) and positive amyloid status. The analysis utilized data downloaded from the ADM tool based on user-defined characteristics, such as MCI diagnosis, positive amyloid status, baseline cognition, MRI and plasma biomarkers, and longitudinal clinical data.

Results: As of July 2023, CPAD’s clinical trial repository contains 73 studies with 100,812 individual anonymized patient records. A prototype ADM tool was built using the R-Shiny framework, allowing for initial data exploration and analysis subset creation. The ADM tool includes a dashboard with variable lists, summary statistics, and visualization. Users can perform data exploration and visualization using the current version of the application. A collection of users has tested the tool end-to-end, from navigating the user interface to creating relevant analysis subsets and using them to build statistical models for disease progression and clinical trial enrichment. Logistic regression models were initially used to predict the risk of developing AD dementia in patients with mild cognitive impairment (MCI) and positive amyloid status. The analysis utilized data downloaded from the ADM tool based on user-defined characteristics, such as MCI diagnosis, positive amyloid status, baseline cognition, MRI and plasma biomarkers, and longitudinal clinical data.

Conclusions: CPAD provides the necessary legal and regulatory infrastructure that is imperative to stakeholders sharing information and data, as well as for transforming these into actionable tools and solutions to advance the drug development process. We will expand the capabilities of the tool to include tabs for data exploration and analysis subsets. The long-term goal for the ADM tool is to create a user-friendly environment for researchers to efficiently explore datasets and identify interpretable baseline characteristics of subjects across the AD continuum, aiding in disease progression prediction.
Background: Multi-omics data (e.g., whole genome DNA sequencing (WGS), single nucleus RNA sequencing (snRNAseq), proteomics and other molecular data) can be used to provide information about brain networks involved in the development of Alzheimer’s disease (AD) and the molecular drivers that could be targeted in the discovery of disease-modifying and prevention therapies. Here, we capitalized on WGS and snRNAseq data from aged brain donors with and without AD and applied multi-scale data analysis techniques to support this effort.

Methods: In addition to the WGS profile from each participant, we generated snRNAseq profiles from 481,841 nuclei collected from post-mortem superior frontal gyrus (SFG) cortical tissue samples from 101 clinically and neuropathologically well characterized brain donors, including 66 AD cases and 35 unaffected controls, in Banner Sun Health Research Institute’s Brain and Body Donation Program. We used a targeted comparative analysis approach to identify the nuclei associated with glial activation and neurodegeneration in AD and applied multi-scale network modelling approaches to inform the gene regulatory networks that characterize the cell subpopulations.

Results: We observed an AD-associated CD83(+) microglial subtype (AD enrichment (P=2e-47, odds ratio=15.3) with unique molecular networks that encompass many known regulators of AD-relevant microglial biology, including a gain in network connectivity of APOE and the presence of multiple microglial nodes of interest, including TREM2 and complement C1Q complex genes. By integrating WGS data, we also report findings that link a common AD risk variant with CR1 expression in oligodendrocytes as well as alterations in peripheral hematocrit levels.

Conclusions: This study implicates a subset of microglia in the predisposition to AD and illustrates the value of multi-omic data sets from different brain cell types in well characterized brain donors. We plan to provide a shared resource of DNAseq, snRNAseq and laser-capture micro-dissected RNAseq from different brain regions and cell types, and other relevant data within a year.

Background: Physical and cognitive activities are associated with decreased risk of mild cognitive impairment and dementia. However, the longitudinal associations between physical and cognitive activities with trajectories of Alzheimer’s disease (AD) neuroimaging biomarkers among older adults free of dementia remain unclear.

Methods: We conducted a longitudinal study derived from the population-based Mayo Clinic Study of Aging, including individuals aged ≥ 50 years who were free of dementia. Participants had information on physical and cognitive activity engagement in midlife (ages 30-45 for participants aged 50-69; ages 50-65 for participants aged ≥ 70) and late-life (12 months prior to baseline assessment), and AD biomarker assessments. We calculated linear mixed-effect models to examine the association between baseline physical and cognitive activity composite scores for mid- and late-life, and trajectories for individual yearly change in amyloid deposition (measured by PiB-PET), tau burden (measured by Tau-PET), regional glucose hypometabolism (measured by FDG-PET), cortical thickness (measured by MRI), and white matter hyper intensities (WMH, measured by FLAIR-MRI). The models were adjusted for age, sex, and APOE ε4 carrier status.

Results: The sample included 2794 persons (52% males; 2500 cognitively unimpaired, 294 with MCI). The mean [SD] age was 72.6 [9.9] years; 786 participants were APOE ε4 carriers. Although, overall, participants showed an increase in amyloid deposition, tau burden, WMH, and a decrease in glucose metabolism and cortical thickness over time, those with higher late-life physical activity experienced less pronounced increase in Tau-PET SUVR over time [estimate for late-life physical activity with time interaction: -0.002; 95% CI -0.004, -0.001; p = 0.005]. In addition, participants with higher cognitive activities in midlife [est. for midlife cognitive activity with time interaction: 0.001; 95% CI 0.0001, 0.003; p = 0.031] and late-life [est. for late-life cognitive activity with time interaction: 0.002; 95% CI 0.0003, 0.003; p = 0.012] had less pronounced decrease in FDG-PET SUVR over time, and those with higher cognitive activities in midlife also had less pronounced increase in Tau-PET SUVR over time [est. for midlife cognitive activity with time interaction: -0.002; 95% CI -0.003, -0.0002; p = 0.031]. There were no further significant interactions.

Conclusions: Preliminary findings suggest significant associations between 1) late-life physical activity and less tauopathy, and 2) cognitive activities in mid- and late-life with less synaptic dysfunction over time. Further research is needed to validate study findings.
Background: Growing evidence supports that vascular comorbidities (hypertension, diabetes and hyperlipidemia) and vascular diseases (cerebral small vessel disease and carotid artery disease) play a role in Alzheimer’s disease (AD) pathophysiology. However, female versus male risk for these diseases is the opposite; females have an increased risk for AD, and males generally have an increased risk for most cardiovascular diseases. We hypothesized that one or more vascular comorbidities would have a differential effect on men vs. women concerning their AD risk.

Methods: Mariner insurance includes claims data from 2010 through October 2021 that were retrospectively analyzed for this exploratory study. Subjects 45 years of age or older were included. The initial cohort (N=1,783,037) was divided into males or females in the first analysis. Only males and females with asymptomatic extracranial carotid artery disease (aECAD) (N=215,636 subjects) were included in the second analysis. A logistic regression model in each group was performed with the results expressed in Odds Ratio.

Results: We found that DMII and hypertension are associated with higher odds of AD; however the association is stronger in females as compared to males (OR = 1.12, 95% CI:1.09-1.15 vs. OR= 1.05, 95% CI:1.02-1.08 for DMII and OR=1.49, 95% CI:1.42-1.56 vs OR=1.28, 95% CI:1.23-1.34 for hypertension). A similar trend was observed within the aECAD population for females vs males (OR = 1.2, 95% CI:1.13-1.27 vs. OR= 1.02, 95% CI:0.96-1.08 for DMII and OR=1.52, 95% CI:1.33-1.75 vs OR=1.27, 95% CI:1.10-1.47 for hypertension). Age and other cardiovascular comorbidities did not show differential effects on AD with regards to gender.

Conclusions: Although several cardiovascular comorbidities are associated with a similar risk for AD in males and females, DMII and HTN are associated with significantly increased risk for AD in females compared to males. These data suggest that DMII and HTN may have differential physiological effects on AD development in females vs. males. These findings are useful but limited by retrospective study design, and prompt future prospective evaluations.

Background: Alzheimer’s disease (AD) is the most prevalent form of age-related dementia, impacting 6.2 million people aged 65 or older as indicated by CDC data. The presence of amyloid plaques and neurofibrillary tangles are among the earliest signs of Alzheimer’s disease (AD), preceding any cognitive impairment and brain structure alterations. Positron emission tomography (PET) enables direct measurement of brain Aβ and tau pathology, but its limited accessibility and cost have prompted the exploration of alternative diagnosis methods utilizing more widely available magnetic resonance imaging (MRI) or blood-based biomarkers (BBBs).

Methods: We applied our previously developed PASCS-MP framework to extract hippocampal multivariate morphometry statistics (MMS) features from MR images. Together with blood-based biomarker plasma Aβ42/40, we trained a random forest classifier to perform a binary classification of patients’ brain amyloid positivity. The model performance was assessed based on prediction accuracy, precision, recall rate, F1 score and AUC score.

Results: We evaluated the performance of our integrated model on two distinct datasets, one from Alzheimer’s Disease Neuroimaging Initiative (ADNI) database and the other from Banner Alzheimer’s Institute (BAI). In comparison to the two baseline models that solely utilized either MMS features or plasma Aβ42/40 as predictors, our integrated model demonstrated superior performance. The combined model achieved prediction accuracies of 0.85 ± 0.01 on ADNI dataset and 0.90 ± 0.01 on BAI dataset, respectively, which are significantly higher than the baseline models.

Conclusions: In this study, we developed an integrated model that combines features extracted from MR images and blood-based biomarkers to predict brain amyloid positivity of Alzheimer’s disease patients. Our integrated model outperformed the baseline models that relied solely on MRI data or blood-based biomarkers. This approach offers a promising avenue for leveraging more accessible and cost-effective techniques in AD diagnosis, such as MRI and blood-based biomarkers, as alternatives to expensive and less available diagnosis methods like Tau-PET. This study was among the first set of methods to integrate MRI and blood-based biomarkers for AD diagnosis.
Background: White matter hyperintensities (WMH) visualized on magnetic resonance imaging (MRI) likely indicate the presence of small vessel vasculopathy and reduced perfusion. Systolic blood pressure (SBP) is the modifiable risk factor most strongly associated and predictive of future WMH volume (WMHV) accumulation, although advanced age is the strongest overall predictor of greater WMHV. Lowering SBP reduces WMHV accumulation, however it is unknown if age at which SBP begins influences the degree of WMHV reduction. We examined potential distinctive effects of intensive SBP control on WMHV accumulation at different ages.

Methods: We examined the difference in change in log transformed longitudinal WMHV accumulation, adjusted for intracranial volume, in participants from the Systolic Blood Pressure Intervention Trial (SPRINT) MRI sub study at different ages, comparing 251 participants randomized to an SBP goal <120 mm Hg to 201 participants randomized to an SBP goal of <140 mm Hg stratified into three age groups (<65, 65-75, and >75 years old). We then calculated the ratio of WMHV at follow up to that at baseline according to age at randomization by SBP group.

Results: The average SBP during treatment for participants in the goal <120 mm Hg group (intensive treatment) were 120 mm Hg (<65), 121 mm Hg (65-75), and 123 mm Hg (>75). Mean SBP in the goal <140 mm Hg group (standard treatment) were 135 mm Hg (<65), 135 mm Hg (65-75), and 136 mm Hg (>75). The average interval between baseline and follow up MRI was 3.9 years for both groups. The intensive BP group <65 years old had the least WMHv accumulation compared to the standard BP control group, followed by those 65-75 years old, with participants >75 years demonstrating the smallest difference in accumulation. Plotting the ratio of WMHv at follow up MRI to that at baseline according to age at randomization in both groups suggests SBP lowering at younger ages results in a larger proportional effect in reducing WMHv accumulation. These results did not reach statistical significance.

Conclusions: Lower SBP might have a greater effect on WMHV accumulation at younger ages. Large prospective studies that include younger individuals closer to the age at which WMH start to accumulate are needed to determine potential differential effects of SBP lowering across the lifespan.
DIFFUSION MRI-BASED MEASURES OF HIPPOCAMPAL MICROSTRUCTURE ARE ASSOCIATED WITH DELAYED VERBAL MEMORY PERFORMANCE IN COGNITIVELY UNIMPAIRED PERSONS AT GENETIC RISK FOR AD. Lingo VanGilder J, Hooyman A, Schilling KG, Hu LS, Zhou Y, Caselli RJ, Baxter LC, Beeman SC. Arizona State University; Vanderbilt University; Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

**Background:** Early intervention to slow Alzheimer Disease is currently an important treatment strategy, but detecting at-risk individuals before significant disease progression is challenging. Here, we utilized a multi-b-shell, multi-direction diffusion MRI dataset and biophysical modelling of neurite density and complexity (i.e., the neurite orientation and dispersion index – NODDI – model) to investigated if hippocampal microstructural integrity associates with delayed verbal memory performance (DR) in cognitively intact individuals who have an increased risk for AD due to the presence of APOE ε4 allele.

**Methods:** Participants (n = 41 noncarriers, 33 carriers) were over 60 (M/SD: carriers 71/6.6; noncarriers 71/6.4), with no significant differences in gender or DR, and were all scanned on a 3T MRI. Key multi-shell diffusion MRI parameters: b-values = 0.5, 1, and 2 ms/μm² with 6, 38, and 47 diffusion encoding directions, respectively. The microstructure of bilateral hippocampus and its subfields was quantified using the Neurite Orientation Dispersion and Density model and both orientation dispersion (ODI) and neurite density (NDI) indices. Age, APOE status, hippocampal NODDI measures, and their interactions were included as predictors of delayed verbal recall in regression analyses.

**Results:** The left subiculum ODI was significantly related to delayed recall only in the carrier group (FDR-corrected p=0.01); i.e., ODI was less strong with weaker DR scores. Age was significantly correlated for both groups for many of the ODI and NDI measures, bilaterally.

**Conclusions:** ODI, thought to reflect neurite complexity and possibly synaptic density, may be sensitive to early pathological changes while NDI (neurite density) reflected age-related variability in memory performance.

Background: Cerebral white matter rarefaction (CWMR) was considered by Binswanger and Alzheimer to be due to cerebral arteriolosclerosis. Renewed attention came with CT and MR brain imaging, and neuropahtological studies finding a high rate of CWMR in Alzheimer disease (AD). The relative contributions of cerebrovascular disease and AD to CWMR are still uncertain.

Methods: Subjects included in this study were volunteers enrolled in AZSAND and its Brain and Body Donation Program (BBDP; www.brainandbodydonationprogram.org), at Banner Sun Health Research Institute (BSHRI) in metropolitan Phoenix, Arizona. Subjects for the current study were chosen by searching the BBDP database. We selected cases who had an autopsy and were assessed for CWMR scores in all 4 lobes. As we wished to focus this study on CWMR without an obvious cause, we excluded subjects with grossly apparent infarcts at autopsy as well as those with neuropathologically defined acute or subacute infarcts or hemorrhages, traumatic contusions, or history of traumatic head injury, primary or metastatic brain neoplasms, meningitis, or encephalitis. These exclusions effectively restricted our study to those subjects with idiopathic CWMR, i.e. CWMR without an apparent cause other than advanced age. After these exclusions, 1181 subjects remained who were included for the initial analyses.

Results: Almost all neurodegenerative diseases had more severe CWMR than the normal control group. Multivariable logistic regression models indicated that Braak neurofibrillary stage was the strongest predictor of CWMR, with additional independently significant predictors including age, cortical and diencephalic lacunar and microinfarcts, body mass index, and female sex.

Conclusions: It appears that while AD and cerebrovascular pathology may be additive in causing CWMR, both may be solely capable of this. The typical periventricular pattern suggests that CWMR is primarily a distal axonopathy caused by dysfunction of the cell bodies of long-association corticocortical projection neurons. A consequence of these findings is that CWMR should not be viewed simply as “small vessel disease” or as a pathognomonic indicator of vascular cognitive impairment or vascular dementia.
Background: Alzheimer’s disease can result in a progressive and debilitating loss of language function manifesting as the logopenic variant of Primary Progressive Aphasia (lvPPA). In such cases, the neuropathological changes associated with AD accumulate in the left posterior temporo-parietal regions that support language processing, disrupting the dorsal language network that critically supports phonological skills for spoken and written language. The resulting language profile is characterized by reduced and slowed speech production, word retrieval difficulties, and impaired reading and writing. Although treatment research is in its early stages, there is limited, but encouraging, evidence that behavioral treatment directed toward strengthening weakened phonological skills can improve language function. Given the deliberating and progressive nature of the impairment, there is a pressing need to develop targeted interventions that would maximize the function of residual components of critical language networks and potentially slow the language decline. The aim of the present study was to improve language function in PPA by combining speech language therapy with fMRI-targeted transcranial direct current stimulation (tDCS) applied over preserved brain regions in the language processing network.

Methods: In a double-blinded, cross-over design 12 individuals with confirmed diagnosis of lvPPA (3 males; Age: M=70 years, SD =4.6; Edu=18 years, SD=4.6; Post onset=3.3 years, SD=1.9) were randomized to receive 10 sessions of phonological intervention with active tDCS or sham first. Following 2-months rest period, they were crossed over to the other treatment Phase. Response to treatment, generalization and maintenance were evaluated before and after each treatment phase as well as two months after the intervention. Active tDCS was delivered for 20 minutes at 1.5mA using 5x7 cm2 saline-soaked sponge electrodes. The active electrode was positioned over the preserved tissue in either the inferior frontal or posterior brain regions and determined individually for each participant based on the results of structural and functional neuroimaging and computational modeling of tDCS current flow.

Results: For both tDCS and sham groups treatment resulted in significant improvement of phonological skills. However, those receiving active tDCS first showed stronger generalization and maintenance of treatment gains. Functional value of our treatment protocol was evident in the tDCS first group on written narratives which contained more meaningful content with better spelling, and performance at follow-up significantly surpassed pre-treatment levels. These gains occurred in the context of relatively stable performance on other measures of cognition. These findings support the feasibility of our treatment protocol, and strongly support our hypotheses that individuals with lvPPA can improve phonological skills and that this will support language ability.

Conclusions: Our work to date suggests a particularly robust outcome after active tDCS with further consolidation of learning over rest phase, and maintenance at follow-up. Our study is the first to document that improved phonological skills resulted in better functional communication ability (text-level writing) relevant to the everyday lives of individuals living with PPA. Our study contributes to a growing body of evidence demonstrating that tDCS is a safe intervention that has potential to enhance benefits of speech-language treatment.

Background: It is estimated that six million Americans have Alzheimer’s Disease (AD), with two thirds of these individuals being women. There are currently no treatments that halt or attenuate the progressive neurodegeneration, memory loss, and cognitive decline that accompany AD. Only after decades of pathological progression does clinical symptomatology begin to present in patients with probable AD. Animal models can increase our understanding of AD-related pathology and cognitive changes. A transgenic (Tg) rat model of AD, TgF344-AD, expresses the mutant human amyloid precursor protein (APPSW) and presenilin 1 (PS1E9) genes, and includes amyloid beta plaque-like pathology, tau-like pathology, and neuronal loss.

Methods: The current project utilized the TgF344-AD model to systematically assess spatial memory using the water radial arm maze (WRAM) in males and females with or without gonadectomy (the surgical removal of the gonads, GDX). Moreover, we additionally analyzed our data using a novel method to examine detailed navigational strategies, focusing on the precise location in which errors were made relative to the remaining correct choices: near misses or far-away misses relative to the remaining correct spatial locations. One could think of this relative to the process a human uses when traveling from location to location. If the goal were a friend’s house, we contrast missing the goal house only by a near miss and navigating to the next-door neighbor’s house instead, versus a far away miss by going to a house in the wrong city. A total of 80 subjects were tested in this study, split between 8 groups: male and female Tg and Wildtype (WT) rats received either Sham or GDX surgery, followed by WRAM testing.

Results: Female Tg rats, regardless of GDX, showed an overall impairment in spatial navigation, especially when working memory load was highly taxed. They also demonstrated impaired spatial accuracy at a high demand working memory load for near and far away choices relative to the remaining correct choices, as compared to their WT counterparts. Male Tg rats showed Genotype x Surgery interactions for most effects; GDX impaired spatial navigation and induced more near miss and far away errors in only Tg rats, with effects prominent at a high working memory load.

Conclusions: In conclusion, through the arms away analysis we were able to distinguish rats’ navigational accuracy relative to remaining correct choices that would not have been revealed with traditional WRAM scoring measures. For Tg females, they were impaired whether or not they had abrupt surgical ovarian hormone loss, while males needed both abrupt surgical testes hormone loss as well as the Tg genotype to be impaired. This appears to be the case for memory performance at the highest memory load, as well as for accuracy when assessing precise navigation relative to the remaining correct choices.

Background: Psychological Well-Being (PWB) is an adaptive and desired condition across all people. Although definitions can vary slightly, a consistent finding is that age is positively correlated with PWB. Even so, the exact characteristics of age that explain individual differences in PWB are uncertain. Socioemotional Selectivity Theory posits that increased positivity in older adults stems from a tendency to prioritize meaningful relationships and the use of emotion regulation toward the goal of maximizing positive experiences (Carstensen, 1995). Other research has identified the role of conscious thought on variables related to PWB such as less specific thinking being tied to rumination (Andrews-Hanna et al., 2013) and task-unrelated thought being negatively correlated with affective valence (Mills et al., 2021). Given the existing literature, one possible explanation is that, as we age, we have a tendency toward particular patterns of everyday thinking – some of which may contribute to better PWB.

Methods: To facilitate data collection, the Mind Window experience sampling app was developed. Mind Window is a scalable and customizable smartphone app for Android and iOS platforms that gathers both trait and state information from participants and also provides summary feedback to encourage compliance. In our study, Mind Window was used to sample 17 characteristics of thought in everyday life. Data from adult participants across the lifespan (ages 18-80) was collected from 03/2020 to 11/2021. From the complete data set, 500 participants were randomly sampled in order to help balance age and gender.

Results: A multi-variable factor of PWB was defined and used to replicate the finding that age positively predicts the factor. Exploratory factor analysis identified four latent factors for the 17 characteristics of thought – focused/intentional thinking, optimistic/constructive thinking, present-based thinking, and future-based concern. When used in a multiple-mediation analysis, optimistic/constructive thinking and future-based concern were significantly predictive of PWB in a bivariate regression (the latter having an inverse correlation). Additionally, the model indicated that each of the thought factors, aside from future-based concern, was significantly predicted by age. Lastly, optimistic/constructive thinking was a significant partial mediator as this factor mediated approximately 50% of the total effect between age and PWB.

Conclusions: This research demonstrates that a daily, conscious experience of optimistic/constructive thinking explains a large portion of age-related increases in PWB. One use of this finding is as evidence for interventions that target the daily thinking patterns of younger individuals so that these age-related effects can be capitalized on earlier in life. As the direct effect of age was not fully mediated by our measured thought characteristics, future research can also expand upon the influence of thought patterns on PWB by including them as variables with other age-related factors so that the increased PWB we typically see in older adults can be more fully explained.

**Background:** Alzheimer’s disease (AD) is a progressive, neurodegenerative disease with no known cure that eventually leads to death. The first brain region with symptomology is the hippocampus and its associated memory dysfunction. Our goal was to assess memory using a transgenic AD mouse model in both sexes and at two ages to determine whether early memory dysfunction can be identified. In doing so, subsequent studies can be performed at an age before AD symptomology substantially advances for targeted intervention and in collaboration with our Mayo Clinic colleagues.

**Methods:** This study used several types of memory assessment tasks, with the novel object recognition (NOR) and object placement (OP) tasks being the focus of this presentation. Both capitalize upon rodents’ tendency to explore novelty. Male and female mice were bred at the Mayo Clinic and then housed at ASU when they were 2 months old and then they were tested at either 4 to 5 months or 8 to 10 months of age. Brains were collected at both ages and are being processed at the Mayo Clinic. The NOR and OP were performed on different days. Mice were allowed to explore an arena with two objects and then on the next trial, one of the objects was replaced with a different novel object (NOR) or moved to a new location (OP). The time spent exploring both objects was calculated over a 5-minute duration. Choosing to explore a novel object in NOR demonstrates cortex-dependent recognition memory and exploring an object that was moved in OP demonstrates hippocampal-dependent spatial recognition memory.

**Results:** Our data show that both ages perform the NOR task, but the 4-month-old females spend more time discriminating the novel object than their 8 to 10-month-old counterparts. Our analyses also show that 8 to 10-month-old transgenic mice are less likely to explore the moved object on the OP task.

**Conclusions:** These results suggest that these older mice are at the beginning of AD pathology.

Background: Dual specificity tyrosine phosphorylation kinase 1a (DYRK1a) directly phosphorylates tau and amyloid precursor protein and is upregulated in postmortem brain tissue of patients with disorders including Alzheimer’s (AD) and Picks disease (a tauopathy). Our lab has shown that treatment with a DYRK1a inhibitor (DYR219) reduced Aβ plaque deposition and decreased phosphorylated tau at Serine 396 (pTauSer396) in the 3xTg-AD mouse model of AD. Here, we developed and tested a novel DYRK1a inhibitor (DYR533), which has an increased half-life and bioavailability, in 3xTg-AD mice that develop both Aβ and pathological tau, and PS19 mice that develop solely pathological tau.

Methods: We dosed eight-month-old 3xTg-AD and four-month-old PS19 mice daily with either 1.0-, 2.5-, or 5.0-mg/kg DYR533 or a vehicle dose for two or four months respectively per model. Treatment start age occurred at the onset of neuropathology. Mice underwent rotarod testing to assess motor function and water maze testing to assess spatial learning and memory, with testing starting 2 weeks prior to the end of treatment. Blood and brain tissue were collected for neuropathology assessment. We assessed Aβ 40-42 in the 3xTg-AD mice, and pTauSer396 and the pro-inflammatory cytokine tumor necrosis factor (Tnfα) in the hippocampus of both models. Blood plasma was extracted and analyzed for Tnfα levels.

Results: In both 3xTg-AD and PS19 mice, DYR533 reduced soluble and insoluble fractions of pTau Ser396 in a dose dependent manner. Notably, DYR533 in 3xTg-AD mice reduced pTau at threonine 217, which was recently identified as an early marker of AD progression. Soluble cortical Aβ42 levels were significantly reduced in the 1.0 mg/kg and 5.0 mg/kg 3xTg-AD groups. DYR533 significantly reduced the levels of Tnfα in blood plasma and the hippocampus of both 3xTg-AD and PS19 mice.

Conclusions: In conclusion, the DYRK1a inhibitor, DYR533, reduces pTauSer396, as well as blood plasma and hippocampal levels of Tnfα in both 3xTg-AD and PS19 models. Ongoing efforts include testing the effects of DYR533 in a rodent model of Down syndrome (Ts65Dn), which harbors three copies of DYRK1a, and completion of 3xTg-AD and PS19 experiments. Thus far, these results support DYR533 as a potential therapeutic for AD and the tauopathies.
FLORBETAPIR PET UPTAKE IN WHITE MATTER IN AGING AND ALZHEIMER’S DISEASE.
Bhargava V, Luo J, Chen Y, Ghisays V, Malek-Ahmadi MH, Sohankar J, Lee W, Protas HD, Reiman EM, Su Y. University of Arizona College of Medicine, Phoenix; Banner Alzheimer’s Institute; Translational Genomics Research Institute; University of Arizona; Arizona State University; Arizona Alzheimer’s Consortium.

Background: Amyloid PET tracers, typically used to track cerebral amyloid changes in Alzheimer’s Disease (AD) patients, have been recently suggested to measure cerebral white matter (WM) integrity due to structural similarity between myelin and amyloid. We previously reported significant associations of amyloid neuroimaging marker, Pittsburgh Compound B (PiB) PET, with WM hyperintensities as quantified by MRI and FLAIR data, in AD patients (Su et al. 2018, HAI). The goal of this study was to explore the association between Florbetapir (FBP) PET and WM integrity.

Methods: Our study population consisted of 673 participants from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) sorted into the following groups of clinical severity: (1) Normal Controls (NC) participants who are amyloid negative and cognitively normal (CDR=0) (A-CDR-); (2) Preclinical (Pre) who are cognitively normal (CDR=0) and amyloid positive (A+CDR0); (3) Symptomatic AD who are both CDR and amyloid positive (A+CDR+); and (4) Suspected Other Dementia group consisting of cognitively impaired but amyloid negative participants. We analyzed baseline biomarkers as function of stage of AD and age, comparing groups using ANOVA and Scheffe’s Post Hoc Analysis, and linear regression, respectively. Associations between white matter and amyloid FBP uptake were quantified using Pearson correlation with Least Trimmed Square (LTS) regression. Lastly, rate of change of amyloid and white matter uptake of FBP PET were quantified to assess longitudinal biomarker changes using a one sample t-test.

Results: Cross-sectionally, baseline FBP uptake in white matter significantly declines with age (p=0.027) and advancing disease stage with significant differences found between the Preclinical and Symptomatic AD group (p<2.2E-06); and NC and Symptomatic AD group (p<0.003). Significant associations were also observed between baseline FBP uptake in white matter and amyloid (p<0.001).

Longitudinally, rate of change of FBP uptake in white matter progressively declined with advancing disease stage while rate of change of FBP uptake in amyloid increased and plateaued in the Symptomatic group of patients.

Conclusions: Altogether, our results show declining FBP uptake by white matter, both cross-sectionally and longitudinally, through the stages of AD and with age. Our results could have methodological implications on the quantification of amyloid burden using WM as a reference region.

Background: Apolipoprotein E (APOE) ε4 is the strongest genetic risk factor for the development of late-onset Alzheimer’s disease (LOAD). Additionally, females have a 2x greater risk of developing LOAD than males. LOAD patients show brain glucose hypometabolism and severe reduction in hippocampal volume. Hippocampal atrophy has also been linked with plasma ceramide and phosphotidylcholine (PC) levels in these patients. This study explores the effects of sex and genotype on the plasma metabolome and potential correlations to brain imaging metrics in an aged humanized APOE (hAPOE) mouse model.

Methods: Plasma samples from 23–25-month-old hAPOE mice (37M/32F) expressing ε3/3, ε3/4 or ε4/4 genotypes were analyzed via mass spectrometry using the Biocrates MxP® Quant 500 platform. In a subset of these animals (24M/20F), in-vivo FDG-PET and high-resolution ex-vivo MRI were obtained. Cerebral FDG-PET standardized uptake values were normalized to cerebellum (SUVr). Cerebral SUVr and regional volumes were correlated with detected metabolites and metabolic indicators using Pearson correlations. Two-way ANOVAs were used to identify sex and genotype effects with post-hoc t-tests to determine statistical significance.

Results: hAPOE ε3/3 mice had significantly greater cholesteryl ester (54%; p < 0.026) and lysophosphatidylcholine (lysoPC; 27%; p < 0.031) levels compared to ε4/4 mice. Females had lower levels of PCs (93%; p < 0.007), lysoPCs (82%; p < 0.018), triglycerides (62%; p < 0.045), and 1-Met-His (p = 5.84E-25) than males. Significant positive correlations were observed between cerebral SUVr and PCs (45%; p < 0.049) as well as lysoPCs (82%; p <0.017). Total brain volume was negatively correlated with plasma 3-Met-His:creatinine ratio, indicative of muscle protein degradation (r=-0.44; p=0.003) and positively correlated with (LysoPC+ arachidonic acid): PC ratio, indicative of phospholipase A2 activity (r= 0.42; p=0.004). Right hippocampal volume percentage was significantly positively correlated with PCs (64%; p < 0.045) and 1-Met-His (p = 0.00067).

Conclusions: At a comparable human age of ~ 70 years, within the humanized APOE mouse, sex was the major contributing factor to metabolic differences in peripheral blood plasma. Levels of peripheral metabolites correlated with brain volumetrics and glucose metabolism, highlighting potential therapeutic targets for interventions designed to preserve neuronal health in AD.

Background: Alzheimer’s disease (AD) is the most prevalent form of age-related dementia, impacting 6.2 million people aged 65 or older as indicated by CDC data. The presence of amylloid plaques and neurofibrillary tangles are among the earliest signs of Alzheimer’s disease (AD), preceding any cognitive impairment and brain structure alterations. Positron emission tomography (PET) enables direct measurement of brain Aβ and tau pathology, but its limited accessibility and cost have prompted the exploration of alternative diagnosis methods utilizing more widely available magnetic resonance imaging (MRI) or blood-based biomarkers (BBBs).

Methods: We applied our previously developed PASCS-MP framework to extract hippocampal multivariate morphometry statistics (MMS) features from MR images. Together with blood-based biomarker plasma Aβ42/40, we trained a random forest classifier to perform a binary classification of patients’ brain amyloid positivity. The model performance was assessed based on prediction accuracy, precision, recall rate, F1 score and AUC score.

Results: We evaluated the performance of our integrated model on two distinct datasets, one from Alzheimer’s Disease Neuroimaging Initiative (ADNI) database and the other from Banner Alzheimer’s Institute (BAI). In comparison to the two baseline models that solely utilized either MMS features or plasma Aβ42/40 as predictors, our integrated model demonstrated superior performance. The combined model achieved prediction accuracies of 0.85 ± 0.01 on ADNI dataset and 0.90 ± 0.01 on BAI dataset, respectively, which are significantly higher than the baseline models.

Conclusions: In this study, we developed an integrated model that combines featured extracted from MR images and blood-based biomarkers to predict brain amyloid positivity of Alzheimer’s disease patients. Our integrated model outperformed the baseline models that relied solely on MRI data or blood-based biomarkers. This approach offers a promising avenue for leveraging more accessible and cost-effective techniques in AD diagnosis, such as MRI and blood-based biomarkers, as alternatives to expensive and less available diagnosis methods like Tau-PET. This study was among the first set of methods to integrate MRI and blood-based biomarkers for AD diagnosis.
EFFICIENT DIFFUSION MRI MEASUREMENTS OF TISSUE MICROSTRUCTURE WITH SPHERICAL AND PLANAR TENSOR ENCODING. Comrie CJ, Galons JP, Beach TG, Serrano GE, Hutchinson EB. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer’s Consortium.

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

Methods: Imaging was performed on a healthy-aged formalin-fixed post-mortem human temporal lobe, vacuum sealed in a 50 ml falcon tube and Fluorinert. Images were acquired using a 7T Bruker Biospec MRI scanner, the conventional diffusion used a multi-shell acquisition with 201 DWIs over b =0-6,000 s/mm² at an isotropic resolution of 250 microns (~48 hours). Preprocessing and MAP-MRI calculations were performed using TORTOISE 3.2.0 to generate propagator anisotropy (PA), the micro-anisotropic metric, and return-to-origin probability (RTOP), the restriction metric. Continuous waveforms used in the QTI acquisition were developed in the NOW software for spherical tensor encoding (STE) and planar tensor encoding (PTE) both with timings of D=36,30 ms and d=12 ms. Both STE and PTE were acquired at gradient strengths of G=26-166 mT/m over 6 directions for 24 DWIs with an isotropic resolution of 200 microns (~20 minutes per scan). Unprocessed QTI DWIs were averaged with their respective gradient strengths over the 6 directions for both STE and PTE. Histogram analysis was performed in the whole specimen for the PA, RTOP, PTE, and STE images.

Results: Histogram analysis in PA and RTOP were used as “ground truth” references for microscale anisotropy and restriction respectively and revealed two dominant peaks with lower values corresponding with gray matter neurites and the higher values with the white matter myelinated axon bundle pathways. PA demonstrated a third intermediate peak associated with axonal pathways within gray matter regions. Histogram analysis in PTE and STE both showed that as gradient strengths increased, the intensity values decreased. However, PTE was more influenced by higher gradient strengths than STE. While we expected similarities between PA and PTE, the gradient strengths and directional averaging were not able to fully capture the PA distribution. Expectations for resemblance between RTOP and STE was accomplished at the highest gradient strength (166 mT/m) suggesting the isotropic restriction is adequately probed.

Conclusions: The objective to develop QTI waveforms capable of probing similar compartments mapped in the high-order models were successful in the STE waveform, but PTE requires more development to determine the gradient weightings, timings, and angular sampling scheme needed to mimic the PA distribution. Overall future developments and validations will be done for both waveforms, and the methods will be extended to Alzheimer’s Disease.

Background: Subjective cognitive decline (SCD) is the self-reported concern of cognitive decline when objective neuropsychological test scores remain within normal limits, after adjusting for age, sex, and education. SCD has been associated with increased risk for future dementia due to Alzheimer’s disease (AD). Current literature shows mixed associations between SCD and objective minor cognitive difficulties. SCD has also been shown to positively correlate with psychiatric symptoms (i.e., depression; anxiety). The current study investigated (1) the relationship between SCD endorsement and objective neuropsychological test performance across four cognitive domains (i.e., Memory; Language; Visuospatial Functions; Executive Functioning), and (2) the relationship between SCD and psychiatric symptoms.

Methods: Cognitively normal older adult participants dually enrolled in the Longevity Study and Brain and Body Donation Program (n = 39) at Banner Sun Health Research Institute (BSHRI) completed a measure of SCD (Everyday Cognition Scale; ECog). Participants also completed a comprehensive neuropsychological test battery, from which scores were utilized to create indices paralleling those of the ECog. The cognitive domains and tests utilized to create them are as follows: Verbal Episodic Memory (Craft Story/Logical Memory Delayed Recall; AVLT Delayed Recall); Language (Semantic Fluency; Multilingual Naming Test; Boston Naming Test); Visuospatial Functions (Judgment of Line Orientation; Benson Copy); Executive Functioning (Trails B; Stroop Color/Word). Spearman correlational analyses were run to examine the relationship between participants’ SCD levels in four cognitive domains and their performance on associated objective cognitive assessments. The relationships between SCD domains and measures of depression (Center for Epidemiological Studies Depression Scale; CESD) and anxiety (Penn State Worry Questionnaire; PSWQ) were also examined using correlational analyses. All significant analyses included adjustment for age, sex, and education.

Results: ECog Language scores significantly correlated with the Language and Verbal Episodic Memory cognitive domains on neuropsychological testing; however, these associations were not significant after adjusting for age, sex, and education. CESD scores initially significantly correlated with ECog Memory and Executive Functioning domains; however, only the Executive Functioning domain remained significant after demographic adjustment (r = 0.45, p < 0.005); specifically, the Divided Attention subdomain drove this association. No other correlations reached statistical significance.

Conclusions: Endorsement of SCD was not significantly related to performance on neuropsychological testing. Consistent with previous literature, experience of depressive symptoms was associated with SCD; the current study demonstrated this association to be specific to the SCD domain of Executive functioning, particularly related to the subdomain of divided attention. Thus, depressive symptoms should be considered when there is expression of SCD related to executive functioning. Future research may aim to identify the direction of the relationship between SCD in the domain of Executive Functioning and depressive symptoms.

Background: The gut microbiota, the aggregate of all microbial life colonizing the gut, is implicated in Alzheimer’s disease (AD). AD is the most common cause of dementia in elderly populations, characterized by amyloid-β plaques, neurofibrillary tangles, and neuroinflammation. Studies of the gut microbiota in AD patients demonstrate alterations in the gut microbiota that are correlated with disease pathologies. Taxa within the genus Bacteroides are often found upregulated in AD patients and animal models of AD pathologies. Metabolic byproducts of Bacteroides are thought to play an important role in gut-community structure and affect gut integrity in patients with AD. The brain and gut communicate bidirectionally through the gut microbiota-brain axis via pathways such as the vagus nerve and microbial metabolites.

Methods: Our research seeks to evaluate how upregulation of Bacteroides affects gut microbial community structures in mice modeling AD pathologies and their wild-type (WT) cohort. We dosed mice for 5 consecutive days with 1x10^9 CFU of Bacteroides fragilis (Bf) beginning at 8 weeks of age and then once monthly throughout the course of their lives. Mice were raised to 8 weeks [pre-pathology], 24 weeks [plaques modeled], and 52 weeks of age [plaques and tangles modeled].

Results: Results from this study demonstrate that mice modeling AD pathologies have greater abundances of Bf in their fecal microbiome than do their WT, Bf-treated cohorts. WT mice treated with Bf demonstrate an increased abundance of native Bacteroides species in their fecal microbiome. WT mice treated with Bf also exhibit depletion of Lactobacillus in comparison to Bf-treated AD mice and vehicle-control-treated AD and WT mice.

Conclusions: Taken together, these results suggest that treatment with Bf modulates the gut microbiome in a manner unique to mouse strain. Understanding the dynamic microbial community structure of the gut microbiota and the microbes implicated in AD pathogenesis could aid in the development of therapeutics.

Background: Depression has been established as a risk factor for developing Alzheimer’s Disease (AD). Further, depression is a common symptom of the prodromal phase of the disease and acts as an accelerating factor for cognitive decline before and after dementia diagnosis. Based on this association, analyses of real-world medical data were conducted to determine the impact of anti-depressive pharmacological therapy, Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), on risk of AD diagnosis. This study aimed to determine the effect of SNRI therapy on AD incidence, as well as determining responder vs non-responder phenotypes on demographic characteristics, comorbidity burden, and co-treatment profile.

Methods: A retrospective analysis was conducted using the Mariner insurance claims dataset and included patients 60 years of age and older with a diagnosis of depression. To minimize bias, a propensity score matching was conducted to adjust for age, gender, cci and comorbidities. The propensity score matched population was surveyed for a diagnosis of AD after at least 1 year of SNRI drug exposure, and different durations of SNRI therapy were analyzed. Responders were detected through sensitivity analyses based on comorbidities and drug combinations.

Results: The propensity score matched group included 307,671 patients exposed to SNRIs and 307,671 patients with no exposure to any antidepressant therapy. SNRI therapy was associated with a significant decrease in risk of AD diagnosis (RR [95%CI]: 0.73 [0.70–0.76]; P<.0001), with women (RR [95%CI]: 0.66 [0.63–0.70]; P<.0001) exhibiting greater risk reduction compared to men (RR [95%CI]: 0.88 [0.82–0.95]; P<.0001). Long-term SNRI treatment (>6 years) was associated with the greatest AD risk reduction (RR [95%CI]: 0.50 [0.47–0.53]; P<.0001). Responders exhibited higher incidence of obesity and greater use of anti-inflammatories.

Conclusions: SNRI therapy was associated with a significant reduction in AD risk. Furthermore, increased duration of SNRI therapy was associated with greater AD risk reduction. Responders displayed fewer comorbidities and co-treatments although they had a higher incidence of obesity. Clinically, these findings, based on real-world psychiatric care, provide data regarding long-term neurological health outcomes of SNRI anti-depressant therapy. From a mechanistic perspective, data reported herein indicate that sustaining noradrenergic function is a key pathway involved in preventing AD.

Background: The Apolipoprotein E (APOE) ε4 allele has been shown to be heavily associated with late-onset sporadic Alzheimer’s disease. The effect of APOE ε4 on microstructural changes in white matter tracts is less understood, with studies finding either a significant change in the Mean Diffusivity (MD) and Fractional Anisotropy (FA) in regions such as the Superior Longitudinal Fasciculus, and others finding no significant correlation between APOE ε4 and MD or FA values.

Methods: In the present study, we employed Diffusion Tensor Imaging to extract FA values of eight separate white matter tracts within the Corpus Callosum, and tested for effects of APOE ε4 status. Our study consists of 165 eligible participants, 116 older adults and 49 younger adults, with 118 being ε4 non-carriers and 47 ε4 carriers.

Results: Using an ANOVA, we found no statistically significant differences between APOE ε4 status and FA values of callosal white matter tracts. However we did see a significant effect of age group on FA values in these white matter tracts, with younger adults exhibiting significantly higher FA values.

Conclusions: While the literature is still mixed on whether APOE ε4 has a direct effect on white matter microstructure, some have found that the greatest risk to white matter microstructure is presented in those who are homozygous for the ε4 allele, as opposed to the more common ε4 heterozygote. It should also be noted that while we did not observe any evidence of microstructural changes in callosal white matter, other tracts have been shown to be affected by the ε4 allele in previous studies.
DISTINCT IMMUNE SIGNATURES ASSOCIATED WITH SEX AND GENOTYPE IN THE 15M NOVEL hAPP+hAPOE MOUSE RISK MODEL OF ALZHEIMER’S DISEASE. Delatorre N, Van Rossum H, Brinton RD. University of Arizona; Arizona Alzheimer’s Consortium.

Background: Alzheimer’s disease research continues to struggle with the translatability of animal models to human patients. Exploring whole systems is integral to early AD biomarker discovery in the pursuit of therapeutics to delay or prevent AD. Previous finds in our lab indicate sex differences in immune transcription levels in human AD brain and in the humanized apolipoprotein E (APOE) mouse model. Herein we investigated the impact of the APOE genotype in a novel mouse model, humanized amyloid precursor protein (APP), and humanized APOE transgenes (Jackson Laboratory).

Methods: To identify immunophenotypes at late-midlife (15 months: late 40s – early 50s human correlative) a novel hAPP+hAPOE mouse model was utilized: hAPP (5M:5F), hAPP+hAPOE ε3/3 (16M:16F), & hAPP+hAPOE ε4/4 (16M:16F). The brain was hemisected. The left side was processed for multi-color flow cytometry analysis. Peripheral blood was taken via cardiac puncture. The plasma was isolated and ELISA was used to detect levels of Aβ 40-42 and pro-inflammatory cytokines. PBMCs were isolated from the peripheral blood for multi-color flow cytometry analysis. Microglia (CD45, CD11b), microglia reactivity (MHCII, CD68), phagocytosis (pHrodo), and oxidative stress (CellRox) levels were determined in the brain. Lymphocytes (CD3, CD4, CD8, CD19), lymphocyte activity (CD69), and oxidative stress (CellRox) levels were determined in both the brain and peripheral blood. Midlife endocrine status was determined for the female mice by daily lavage.

Results: Female hAPP+hAPOE ε4/4s exhibited increased neuroimmune activity in brain whereas male hAPP+hAPOE ε4/4s exhibited increased activated lymphocytes in the peripheral blood. Significant sex and genotype interactions were apparent in both CNS and peripheral immunophenotypes. Metabolomic analysis indicated significant APOE genotype-driven effects, specifically in plasma glucose, ketone bodies, cholesterol, and triglycerides levels. Females with hAPP+hAPOE ε4/4 genotype exhibited elevated plasma levels of glucose & triglycerides compared to ε3/3s. hAPP+hAPOE ε4/4 female mice exhibited accelerated endocrine aging with fewer number of females cycling regularly compared to hAPP+hAPOE ε3/3 mice.

Conclusions: Outcomes of analyses reported herein indicate that a humanized APP and APOE mouse model revealed significant interactions between APP and APOE genotypes and sex that significantly impacted immune and metabolomic phenotypes in late-midlife. Sex and hAPOE genotype profiles of immune response and activation coupled with metabolic reprogramming provide early evidence in support of potential therapeutic target profiling based on sex and APOE genotype. Our data support the advancement of precision therapeutic strategies to prevent or delay the onset of AD.
STRUCTURAL STUDY ON THE PRONGF-P75NTR-SORTILIN RECEPTOR COMPLEX IMPLICATED IN NEURONAL APOPTOSIS. DeVore K, Nandi P, Poh Y, Chiu P. Arizona State University; Arizona Alzheimer’s Consortium.

Background: p75 neurotrophin receptor protein (p75NTR) has been shown to play a critical role in regulating neuronal growth and apoptosis, and sortilin, a transmembrane co-receptor for p75NTR, has been known to complex with p75NTR and pro-nerve growth factor (proNGF). This formation of the neurotrophin receptor complex, proNGF-p75NTR-sortilin, in the membrane triggers neuronal apoptosis, which has been implicated in neurodegeneration. However, very little structural information about the complex and its formation is currently available.

Methods: This research study aims to gain a complete understanding of the mechanism of this complex formation. Because this receptor complex is driven by their ectodomains, we initially focus on characterizing the protein-protein interaction between these ectodomains. Protein overexpression is currently being optimized using the Bac-to-Bac® Baculovirus Expression System in insect cells (Sf9). Following overexpression, all three proteins will be purified and assembled. The ultimate goal is to use cryogenic electron microscopy to determine the high-resolution structure of the receptor complex and understand the molecular underpinning of the proNGF-triggered neuronal apoptosis.

Conclusions: Continued research on this complex holds the promise of deeper insights into neural development and potential therapeutic targets for neurological conditions.

Background: Animal models serve as a crucial component to translational research pertaining to the human brain. Magnetic Resonance Imaging (MRI) is a powerful non-invasive tool for neurological characterization in both humans and animal models and has been used extensively to understand natural and pathological processes of the brain. In this work we have carried out atlas-based and deformation-based morphometry (ABM and DBM, respectively) to investigate MRI correlates of healthy cognitive aging.

Methods: 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. All rats underwent Morris water maze behavioral task resulting in animals being sub-divided into 3 subgroups of high, average, and low cognition using a corrected integrated pathlength. Following this, high resolution (150 um isotropic) 3D, T2-weighted brain MRI was carried out on all animals. Image Analysis: All images underwent brain extraction and bias correction. ABM utilized a Fischer 344 T2-weighted template image and its co-registered labeled atlas. The template image was registered to the MRI of each individual animal in the study using non-linear registration methods. The transformation matrix was then applied to the labeled atlas. Six ROI’s were considered important to cognition: hippocampal subfields (CA1, CA2, and CA3), dentate gyrus (DG), total hippocampus (CA1, CA2, CA3 and DG), corpus callosum, and fimbria. For DBM, a population template image was first generated from all animals in the study. Individual images were then registered to the template using non-linear registration. Maps of the determinant of the Jacobians from these registrations represent expansions (positive) and contractions (negative) of tissue and were used to assess differences in size on a voxel-wise basis.

Results: Both ABM and DBM analysis showed significant differences in brain with respect to age. In ABM, the cortex showed significant decrease in volume with respect to age whereas deep brain structures such as the total hippocampus, dentate gyrus and fimbria showed significant increases in volume. In DBM, voxels in the cortex demonstrated relative contraction with age while deep brain structures demonstrated relative expansions. No significant differences in brain structure based on cognitive status were seen with ABM or DBM.

Conclusions: Two methods of brain image analysis show similar results in rats, namely that there are region-specific changes in the brain with age, but no detectable changes in the brain with respect to cognition. Most of the changes, whether they be an increase or decrease in volume, occurred from young to middle age, with smaller changes accruing between middle and old age. Lastly, this study shows that ABM and DBM methods provide complementary anatomical analysis and will be compared with microstructural analysis available from diffusion-weighted MRI.
DEEPER DIVING INTO MACHINE LEARNING AND RETINAL COLOR FUNDUS PHOTOGRAPHY FOR ALZHEIMER’S DISEASE SCREENING. Dumitrascu OM, Li X, Sobczak J, Zhu W, Wang Y. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer’s Consortium.

Background: Alzheimer’s disease (AD) has a rising incidence that poses a significant burden on the society and healthcare system. There is a current unmet need to identify biomarkers to diagnose AD in early stages, to allow effective therapeutic interventions. Retinal color fundus photography is a non-invasive and cost-effective tool to study AD. We have previously shown that certain retinal vessel fractal characteristics are associated with AD-specific cognitive decline and neuroimaging measures. To overcome the subjectivity and inefficiency of retinal images manual analysis, we employed a deep neural network approach utilizing weakly supervised localization and Gradient-weighted Class Activation Mapping, to classify and extract AD biomarkers from retinal images. Additionally, we enhanced our automated AD screening tools by comparing the accuracy of neural networks using images from a single eye versus both eyes and employing vessel segmentation versus binary vessel segmentation.

Methods: Our framework consists of two main steps. First, we employed a U-Net-based architecture to segment the retinal fundus images. Second, we input the segmented vessel results and binary vessel segmentation results into the U-Net encoder for feature extraction. We utilized retinal color fundus images from AD patients seen at the Mayo Clinic, along with retinal fundus images from cognitively normal subjects from the Eyepacs database. Each AD patient contributed up to 4 retinal images (macular and optic disc-centered images from both eyes). Each control subject provided macular images from both eyes. Each control subject provided macular images from both eyes.

Results: After data curation, we obtained 318 binary vessel segmentation images from 113 AD patients and 338 vessel segmentation images from 116 AD patients. The control group included 259 images from 129 participants. The overall vessel segmentation group’ accuracy was 95% (120 testing, 476 training images) and binary vessel segmentation group’ accuracy was 88% (116 testing, 460 training images). The accuracy of the segmented images and binary segmented images in the right eye (97.7% and 90.7%) was similar with the left eye (86.4% and 97.7%) in 44 testing and 175 training images. Vessel segmentation images for both eyes (88 testing, 350 training images) had an accuracy of 97.7%, whereas the binary vessel segmentation for both eyes reached 91.8% accuracy. The generated heatmaps pointed-out that our framework primarily focused on vascular changes in the retinal mid-periphery in AD and around the optic disc in healthy individuals.

Conclusions: In a larger dataset of AD-derived retinal images, all our subgroups achieved an accuracy greater than 86%, with the highest accuracy reaching 97.7%, without major differences between single eye versus both eyes, whereas favoring vessel segmentation over binary vessel segmentation. Additionally, our proposed framework successfully identified AD-specific retinal vascular changes. Our distinct sub-group analysis is effectively mitigating the impact of fortuitous occurrences on the results, thereby enhancing our findings’ accuracy.
STUDENT POSTER # 17

APPROACHES TO ALZHEIMER’S DISEASE (AD) DETECTION IN URINE AND FECES THROUGH WASTEWATER-BASED EPIDEMIOLOGY. Ellershaw A, Newell ME, Babbrah A, Driver EM, Aravindan A, Halden RU. Arizona State University; OneWaterOneHealth, Arizona State University Foundation; Arizona Alzheimer’s Consortium.

Background: Incidence of Alzheimer’s Disease (AD) and other dementias have increased 148% globally between 1990 and 2019. However, early detection of AD has been shown to delay progression of the disease and improve patient outcomes. Existing methods are costly, invasive, and utilize diagnostic criteria that are non-specific, which delays diagnosis. Wastewater-based epidemiology (WBE) offers insights into population-level health through detection of biomarkers. The use of human-specific biomarkers may lead to early intervention of AD in at-risk populations.

Methods: AD biomarkers in urine and feces were evaluated using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eligibility criteria included human-specific studies identifying biomarkers through liquid or gas chromatography mass spectrometry (LC-MS, GC-MS) techniques. A geospatial analysis was conducted using ArcGIS Pro 3.0 to determine if a relationship exists between published study locations and geographic regions with higher prevalence of AD.

Results: The PRISMA search of Scopus identified 211 studies published between 2000 and 2022. Of the 24 relevant articles included in this review, 117 biomarkers were identified from 19 distinct categories, including proteins and dicarboxylic acids, with statistically significant differences between AD patients and cognitively healthy patients. The number of studies were primarily isolated to China (n=7), followed by regions in Europe (n=6), the United States (n=3), Japan (n=2), and South Korea (n=2), however the highest age-standardized incidence rates per 100,000 people have been reported in the North Africa and the Middle East (110.2), Asia Pacific (108.9), Central Europe (106.3), and North America (105.8). Regions with the highest incidence rates are not always the locations where AD studies are being performed.

Conclusions: Case-control studies support the potential use of biomarkers found in urine and feces, such as taurine and tryptophan, but have yet to be applied in a clinical setting. Additional research is needed to determine if these biomarkers are present in early onset of the disease. Performing research in countries within higher prevalence regions may lead to improved public health surveillance and subsequent screening. While urine and feces offer a non-invasive matrix for diagnosis, wastewater-based surveillance would establish a population-based approach to help reduce prevalence of disease.
CEREBRAL AMYLOID ANGIOPATHY AND WHITE MATTER RAREFACTION ARE NOT ASSOCIATED WITH FASTER PROGRESSION TO MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER’S DISEASE. Ellsworth B, Malek-Ahmadi M, Arce R, Serrano GE. University of Arizona College of Medicine, Phoenix; Banner Alzheimer’s Institute; Banner Sun Health Research Institute; Arizona Alzheimer’s Consortium.

Background: Cerebral amyloid angiopathy (CAA) and white matter rarefaction (WMR) are cerebrovascular pathologies that commonly occur in cognitively unimpaired (CU), mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients. Previous studies have found mixed results regarding the relationship between CAA, WMR and cognitive decline. The aim of this study was to determine whether CAA and WMR interact with AD-related plaque and tangle pathology to accelerate progression to MCI.

Methods: Cognitive scores and cerebral pathology were evaluated in 324 patients from the brain and body donation program in Sun City, Arizona. All cases were considered cognitively normal at enrollment and progression to MCI was determined through a consensus diagnosis that used clinical and neuropsychological measures to determine cognitive status. Semi-quantitative post-mortem measures of CAA, WMR, neuritic plaque (NP) burden and neurofibrillary tangle (NFT) burden were used to assess pathological severity. Cox proportional hazards models were used to evaluate whether progression to MCI was associated with independent and synergistic effects of CAA and NP/NFT or WMR and NP/NFT were associated with faster progression to MCI. Patients’ age at progression to MCI was used as the time variable with adjustments for years of education and APOE e4 carrier status.

Results: Of the 324 participants, 130 progressed to MCI. The mean length of follow-up for all participants was 7.44±4.61 years. The interactions of CAA with NP and NFT pathology were not statistically significant [CAA/NP interaction: HR = 0.998 (95% CI: 0.984, 1.013), p = 0.834; CAA/NFT interaction: HR = 1.010 (95% CI: 0.990, 1.033), p = 0.412]. The interactions of WMR with NP and NFT pathology also failed to reach statistical significance [WMR/NP interaction: HR = 0.997 (95% CI: 0.984, 1.009), p = 0.601; WMR/NFT interaction: HR = 1.020 (95% CI: 0.998, 1.042), p = 0.072]. In the CAA model, both NFT burden and APOE e4 carrier status independently predicted progression to MCI. [NFT burden: HR = 1.166 (95% CI: 1.045, 1.301), p = 0.0059. APOE e4 status: HR = 1.679 (95% CI: 1.093, 2.579), p = 0.0181], however, NP burden was not significantly associated with progression status [HR: 1.015 (95% CI: 0.970, 1.062), p = 0.521]. Similar findings were noted in the WMR model.

Conclusions: The interactions of CAA and WMR with AD-related plaque and tangle pathology were not associated with an increased likelihood of progression to MCI. Additional analyses are needed to determine whether these interactions are dependent on APOE e4 status.
STUDENT POSTER # 19


Background: Carotid stenosis and other cardiovascular diseases are increasingly recognized as a risk factor for Alzheimer’s disease and related dementias (ADRD). We hypothesize that these diseases could increase risk for ADRD through affecting blood brain barrier (BBB) integrity by various mechanisms including embolic events that are clinical (stroke and TIA) and/or subclinical (microemboli). BBB dysfunction is an early event that increases ADRD risk and is characterized by endothelial activation/inflammation and the disruption of BBB cellular components, including pericytes, astrocytes, endothelial cells, and other cell types. We sought to investigate potential biomarkers of BBB integrity by evaluating whether platelet-derived growth factor receptor-β (PDGFRβ), a marker of pericyte injury, is associated with a history of cerebrovascular accident (CVA) and soluble vascular cell adhesion molecule-1 (sVCAM-1) levels, a biomarker of endothelial inflammation. Such biomarkers could be useful for understanding this pathway of how cardiovascular diseases affect ADRD risk, but could be equally important for studying BBB integrity independent of cardiovascular disease.

Methods: A subset of 88 subjects in the Arizona Study of Aging and Neurodegenerative Diseases (AZSAND) with serum samples obtained at the time of death were included in this cross-sectional study. Enzyme-linked immunosorbent assay (ELISA) was utilized to detect PDGFRβ and sVCAM-1 in the serum, using commercially available test kits. Statistical analyses were performed using Spearman’s rank correlation and Mann Whitney U test.

Results: Our cohort was divided based on their history of CVA. Of note, the group with a history of CVA had a higher occurrence of vascular dementia, hypertension, and coronary artery disease. There was a significant increase in levels of serum PDGFRβ in subjects with a history of CVA compared to individuals without a history of CVA (mean 5869.6 pg/mL vs. 3852.5 pg/mL, P<0.001). This relationship persisted after controlling for the effects of hypertension, vascular dementia, and coronary artery disease. Moreover, PDGFRβ was positively correlated with sVCAM-1 in our cohort (Spearman’s ρ=0.49, P< 0.001).

Conclusions: PDGFRβ, a putative marker of BBB integrity, is elevated in subjects with a history of CVA and is associated with a marker of endothelial inflammation (sVCAM-1). Although exciting because this raises the possibility that PDGFRβ could be used as a blood-based biomarker of CVA physiology affecting the blood-brain barrier and potentially ADRD risk, these data are limited by our small sample size and collection of serum at time of death. Further studies of longitudinal nature in living humans at risk for these disease processes are underway.
BLOOD BRAIN BARRIER INJURY DETECTED IN THE SERUM OF PATIENTS WITH A HISTORY OF STROKE AND TRANSIENT ISCHEMIC ATTACK. French SR, Arias JC, Bolakale-Rufai IK, Serrano GE, Beach TG, Reiman EM, Weinkauf CC. University of Arizona; Sarver Heart Center; Banner Sun Health Research Institute; Banner Alzheimer’s Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.

Introduction: Stroke and transient ischemic attack (TIA) increase risk for cognitive impairment and dementia. Without a lasting infarction, the cause of cognitive decline after TIA remains unknown. We hypothesize that these cerebrovascular accidents (CVAs) have long-term negative effects on the blood brain barrier (BBB) and promote endothelial inflammation (EI), both of which are associated with neurodegeneration. We sought to investigate the effects of CVAs on BBB integrity and EI by evaluating PDGFRβ and VCAM-1 serum levels, respectively.

Methods: A subset of 88 subjects in the Arizona Study of Aging and Neurodegenerative Disorders with postmortem serum samples were available for analysis. Sandwich ELISA was performed to detect PDGFRβ and VCAM-1. Statistical analyses were performed using Spearman’s rank correlation and Mann Whitney U test.

Results: Our subjects were split based on CVA status. Both subjects with stroke and subjects with TIA had increased serum PDGFRβ compared to those without history of CVA (6608.4 pg/mL and 5337.0 pg/mL, P=0.04, and 7849.5 pg/mL vs. 5337.0 pg/mL, P<0.01). No significant differences related to PDGFRβ were observed between subjects with stroke vs. TIA (P=0.25). PDGFRβ was associated with VCAM-1 (Spearman’s r=0.44, P<0.01) and VCAM-1 trends towards being higher in subjects with CVA compared to those without (P=0.13).

Conclusions: PDGFRβ was elevated in subjects who had a history of stroke or TIA compared to matched patients without CVA. These data demonstrate the utility of a serum-based biomarker of BBB integrity, a powerful tool in studying the role of the BBB in various neurodegenerative diseases including Alzheimer’s dementia. These data also raise the possibility that TIA and stroke have lasting effects on BBB integrity and provide insight about their mechanistic role in neurodegeneration. These findings are limited by our small sample size and post-mortem serum collection.

Background: Autosomal-dominant Alzheimer’s disease (ADAD) represents a genetically dominant inherited AD with mutations found in the presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) genes. A case study with an ADAD mutation in the PSEN1 gene, PSEN1 E280A, and a mutation identified in the APOE gene known as the APOE3 Christchurch (APOE R136S) mutation has exhibited no cognitive impairment. The post-mortem brain studies revealed an excess of amyloid plaques and a large decrease in tau pathologies when compared to patients with ADAD. Current advances in cellular models of Alzheimer’s disease 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 APOE R136S mutation has on ADAD.

Methods: To overcome current obstacles in genome editing of hiPSCs, prime editing with a transient reporter for editing enrichment was used to generate cell lines with the APOE R136S mutation and the PSEN1 E280A mutation in diseased and non-demented control (NDC) hiPSC lines. HiPSC lines subject to prime editing were characterized to ensure a normal euploid karyotype, pluripotency, trilineage differentiation potential, and an absence of off-target effects. The clonal cell lines were differentiated into cortical neurons with a scalable microcarrier-based differentiation protocol. Cortical neurons were characterized by immunofluorescence and mutation specific effects were determined through phenotypic assays.

Results: Clonal cell lines with the APOE R136S mutation have been derived in an hiPSC line with a duplication in the APP gene as well as an NDC cell line. The NDC cell line underwent another round of prime editing to introduce the PSEN1 E280A mutation into the genome. All clonal hiPSC lines have been confirmed with sanger sequencing and characterized. Preliminary cortical neuron differentiations revealed phenotypic differences in amyloid plaque and tau burden in a diseased line with the APOE R136S mutation and the NDC cell line with the PSEN1 E280A mutation.

Conclusions: Upon completion of differentiations and phenotypic analysis, this isogenic-approach will create an ideal cellular model to analyze the mechanistic effects that the APOE R136S mutation has on ADAD-related phenotypes and mechanisms. In addition, this study will address the limitations of a single case report of a homozygous APOE3 R136S/PSEN1 E280A mutation carrier and will allow for future studies across various AD-associated mutations. Furthermore, these cell lines and investigations will aid in the design of improved targeted therapies for future treatments of AD.
Background: Alzheimer’s Disease (AD) is a neurodegenerative illness that causes cognitive impairment in affected patients because of atrophy to the patient’s brain. The common consensus is that this atrophy is caused by neuroinflammatory plaques formed from amyloid-β deposits and the hyperphosphorylation of tau proteins. Common detection techniques utilize MRI scans of affected subjects to train machine learning models that can accurately perform the required classification, such as SVM or deep neural networks (DNNs). In our previous study, we used the tetrahedral mesh representation to compute a harmonic field via a volumetric Laplace-Beltrami operator (LBO) based on heat kernel diffusion to then calculate the cortical thickness to a more accurate degree than other methods at the time.

Methods: A number of research has discovered the deep connection between hippocampal atrophy and the AD progression. However, traditional hippocampal shape analyses used hippocampal subregion volumes or approximated the hippocampi with a cylinder shape. Both approaches suffered from the low quality in the approximation and may not be able to capture the subtle hippocampal shape changes induced by AD pathology. Inspired by recent work (Diers et al., NeuroImage, 2023), we applied morphometry operations that connected different hippocampal subregions into a single topologically valid solid and modeled it as a tetrahedral mesh. We applied our recently developed tetrahedral convolutional neural network (TetCNN) to discriminate hippocampal shape differences between different AD clinical groups.

Results: We conducted binary classification experiments on ADNI dataset containing patients who are cognitively unimpaired (CU), patients with mild cognitive impairment (MCI) and Alzheimer’s disease (AD), each group containing 328 patients (N=984 in total). Consequently, we achieved a test accuracy of 0.92 on AD vs CU classification, 0.76 on AD vs MCI classification and 0.62 on MCI vs CU classification.

Conclusions: In this study, we applied the TetCNN approach for AD classification using ADNI dataset and achieved high prediction accuracy on AD vs CU and moderate accuracy on AD vs MCI classifications. The TetCNN’s performance in differentiating MCI samples, however, could potentially be improved by increasing the dataset size and training on a larger training set. In future, we also plan to add a random forest classifier to the architecture to aid in the detection of MCI samples based on volume.
NOVEL MAGNETIC RESONANCE IMAGING SIGNATURES DETECT NEUROINFLAMMATION AFTER EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY.

Giordano KR, Griffiths DR, Hutchinson EB, Lifshitz J. University of Arizona College of Medicine-Phoenix; Phoenix VA Health Care System; University of Arizona; Arizona Alzheimer’s Consortium.

Background: Neuroinflammation and associated microglial activation are pathological features of traumatic brain injury (TBI). After experimental diffuse TBI, we reproducibly report numerous rod microglia aligned along the somatosensory cortex (S1BF). Without specific detection markers, rod microglia investigations are limited to post-mortem observation. Conventional imaging techniques (CT, MRI) lack sensitivity to detect microscale changes associated with microglia morphology. New imaging tools can be applied to detect rod microglia, if not evaluate their role in diagnosis, prognosis, or therapy post-injury. Our objective was to detect activated microglia morphologies after diffuse TBI, hypothesizing that discrete sequences of diffusion magnetic resonance imaging (dMRI) could detect rod microglia.

Methods: Male and female rats received midline fluid percussion or sham injury. Brains were harvested at 7 days post-injury and fixed for high resolution ex vivo dMRI, including diffusion tensor imaging and mean apparent propagator imaging, followed by patho-anatomical validation with immunohistochemistry.

Results: An imaging signature of increased restriction, especially in the direction of the rod microglia long axis, was detected in brain-injured S1BF. Immunohistochemistry revealed increased density of Iba-1+ activated microglia in brain-injured S1BF registered to the dMRI signature. Rod microglia were present around the perimeter of the brain-injured S1BF, whereas abundant activated microglia occupied the areas identified by dMRI. Uninjured brains were devoid of dMRI signal and activated microglia.

Conclusions: While not specific to rod microglia, we identified an imaging signature associated with neuroinflammation after diffuse TBI. Non-invasive detection of activated microglia could improve diagnosis, prognosis, and therapeutic monitoring in the care of TBI survivors. Funding: NINDS-F31NS113408, AAC, BIAA.

Background: We use advanced diffusion MRI (dMRI) and biophysical modelling, applied to cognitively intact cohorts of APOE e4 carriers and non-carriers, as a non-biased metric to test the hypothesis that deficits to striatal microstructure play a role on the earliest stages of AD pathogenesis.

Methods: Multi-shell dMRI data were collected from cohorts of APOE e4 carriers (n=41) and non-carriers (n=50) using a 3T scanner at the Mayo Clinic in Arizona. Diffusion MRI acquisition parameters: b-values = 1000, 2000 s/mm² (85 total diffusion weighted directions) and nine interleaved b = 0 s/mm² values. Raw diffusion data were preprocessed to correct for susceptibility artifact and motion distortion using the synthesized b0 for diffusion distortion correction (Synb0-DISCO) algorithm and softwares including FSL and MRtrix. NODDI model parameters, including the “neurite density” and “orientation dispersion” indices (NDI and ODI, respectively), were then calculated for all datasets. In an effort to validate our results against an external dataset, multi-shell dMRI data were acquired from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database containing APOE e4 carriers (n=22) and non-carriers (n=39) using the ADNI-3 advanced protocol on a 3T scanner with three shells: b = 500,1000, 2000 s/mm² (112 total diffusion weighted directions) and thirteen interleaved b = 0 s/mm² values.

Results: In the first study, significant APOE e4-specific differences in NDI were identified in left striatum (β = 0.72, 95% CI = [0.33; 1.11], adj p = 0.01), left caudate (β = 0.58, 95% CI = [0.18; 0.97], adj p = 0.04), left putamen (β = 0.66, 95% CI = [0.25; 1.06], adj p = 0.03) and right ventral striatum (β = 0.6, 95% CI = [0.19; 1.00], adj p = 0.04). In each region carriers demonstrated a lower magnitude of NDI, but not ODI, than non-carriers. In the second study, we observed similar (not significant) trends in NDI as the first study in the left striatum (β = 0.23, 95% CI = [-.31; .77], p = 0.4), left caudate (β = 0.29, 95% CI = [-0.26; 0.84], p = 0.3) and right ventral striatum (β = 0.18, 95% CI = [-0.32; 0.68], p = 0.46) but not the left putamen (β = -0.04, 95% CI = [-0.58; 0.51], p = 0.9).

Conclusions: This study provides evidence of reduced striatal microstructure integrity in cognitively intact APOE e4 carriers relative to their non-carrier counterparts. These results are supported, but not yet validated to the level of statistical significance, by the smaller external ADNI-3 dataset. Future efforts will focus on: (i) associating dMRI-based measures of striatal microstructure to pre-MCI neuropsychological decline and (ii) bolstering the external dataset to improve external validation studies. Broadly speaking, these results suggest that striatal microstructure and striatum-related behaviors, including motor learning, may be early targets of AD pathogenesis.
APOE ε4 PREDICTS ACCELERATED COGNITIVE AND BRAIN AGING OUTCOMES IN OLDER AUTISTIC ADULTS. Harker SA, Al-Hassan L, Lewis CR, Braden BB. Arizona State University; Arizona Alzheimer’s Consortium.

Background: Autism spectrum disorder (ASD) is a developmental and social communication disorder affecting over 75 million individuals worldwide. Recent research evidence suggests that middle-aged and older autistic adults are 2.6 times more likely to be diagnosed with early onset Alzheimer’s disease compared to neurotypical (NT) adults and by 2030, there will be roughly 700,000 older autistic adults in the United States. Thus, this research aims to test the hypothesis that Alzheimer’s related genes (APOE ε4), contribute to accelerated cognitive and brain aging outcomes in older autistic adults. APOE is polymorphic, and the APOE ε4-allele is one of the strongest indicators of developing Alzheimer’s disease (NIH 2021). Exploring this field bridges a vast knowledge gap surrounding autistic adults, allowing for increased understanding, resources, and integration of precision medicine.

Methods: To assess whether the Alzheimer’s risk allele (APOE ε4) contributes to accelerated cognitive and brain aging outcomes in older autistic adults, we hypothesized that middle-aged and older autistic adults that are ε4-allele carriers may have exacerbated declines in short term verbal memory and learning reduction as they age. Verbal learning and memory was assessed using the Auditory Verbal Learning Test. Short-term memory was measured via the immediate recall of the first trial. Long-term memory was measured via the twenty-minute delayed trial. Total words (A1-A5) measured learning. DNA was extracted from saliva and was used to conduct APOE genotyping and assessed via TapeStation methods. Data was analyzed using SPSS with a general linear model evaluating the main effects of ASD, age, and their interaction, controlling for sex.

Results: Our findings suggest that the APOE ε4-allele may have the greatest negative impact on autistic males. Short-term verbal memory (A1) showed a main effect of the ε4-allele with carriers remembering fewer words. Total learning showed a main effect of the ε4-allele with carriers learning fewer words.

Conclusions: Higher prevalence of the APOE ε4-allele may be an important factor in the increased risk of Alzheimer’s disease for autistic adults. Thus, aging and autism may lead to verbal learning discrepancies that are evident when compared to neurotypical controls. To fully elucidate cognitive related changes, it is paramount to replicate this study using a larger sample size with longitudinal data. Currently, DNA genotyping is being performed on Illumina Global Diversity Array (>1.8 million markers).
AGE-RELATED DIFFERENCES IN THE MIND’S MIND AND MIND’S EYE: A NOVEL SCORING PROTOCOL APPLIED TO AUTOBIOGRAPHICAL PAST AND FUTURE THINKING.

**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. Despite imagination’s diverse applications, the cognitive processes underlying imagination remain unclear, as does the effect of older age on the construction of imaginative thoughts. In the present study, we evaluate our proposal that imaginative thinking is composed of two broad cognitive processes, namely the mind’s eye and the mind’s mind (Andrews-Hanna & Grilli, 2021; Raffaelli et al., 2020), and that the balance between these two cognitive processes shifts with typical older age.

**Methods:** Here, we developed a novel scoring protocol based on the mind’s eye and mind’s mind to test this idea. In study 1, we applied this protocol to the autobiographical memories of young and older adults. In study 2, a separate cohort of only older adults retrieved unique autobiographical events and imagined novel future events.

**Results:** Our study produced three main findings. First, we demonstrate that the use of mind’s eye and mind’s mind details are consistent with the framework we proposed. Second, our novel scoring protocol demonstrated high inter-rater reliability for both studies. Third, we found significant age-related shifts in the balance of mind’s eye and mind’s mind between young adults and healthy older adults, such that older adults showed a bias to use the mind’s mind.

**Conclusions:** These results suggest that imaginative thinking is captured by the mind’s eye and mind’s mind and changes with age. More broadly, this novel scoring procedure enables quantitative insight into the ways in which imaginative thinking varies across individuals, as well as clinical populations whose pathology targets the neural underpinnings of imagination, such as Alzheimer’s disease.
Background: The logopenic variant of primary progressive aphasia (lvPPA) is an atypical presentation of Alzheimer's disease characterized by impaired naming that results from underlying deficit in phonological processing and impaired verbal working memory. Confrontation naming tasks are commonly used to assess naming difficulties by asking participants to name preselected sets of objects or drawings. However, verbal fluency tasks, that involve generation of words based on specific criteria, allow for a more comprehensive examination of naming mechanisms. Importantly, stimulus-level investigations have shown that words’ psycholinguistic properties can impact naming accuracy through the influence of phonological and semantic abilities. The present study aimed to characterize performance patterns in a verbal fluency task (animal fluency) among individuals with lvPPA versus controls, investigate the relationship between generated words and their psycholinguistic properties, evaluate the contributions of phonological and semantic abilities and their mediating role on the relationship between generated words and their psycholinguistic characteristics.

Methods: 15 participants with lvPPA and 20 matched controls completed the animal fluency task and a comprehensive assessment battery that characterized phonological and semantic skills. We recorded the total number of correct words generated and eight psycholinguistic properties for each word. Group differences were examined with independent samples t-tests and analysis of covariance. Stepwise and multiple linear regression analyses were used to investigate the contribution of psycholinguistic properties on word generation and the relative contributions of phonology and semantic abilities on performance patterns, respectively. Mediation analyses explored the simultaneous influence of phonological and semantic abilities on the relationship between relevant psycholinguistic properties and the number of correct words produced.

Results: Compared to controls, individuals with lvPPA produced fewer correct responses and words with earlier age of acquisition. The number of correctly generated words was predicted by age of acquisition, such that individuals who generated more responses, produced words that were acquired significantly later in life. The regression analyses revealed that higher phonological and semantic skills predicted greater number of correct words generated and the production of words acquired later in life, of lower frequency, and had fewer semantic neighbors. Also, higher semantic skills predicted production of words that are less familiar and less arousing. Phonology, but not semantics, was a significant partial mediator of the relationship between age of acquisition and total number of correct words generated in lvPPA.

Conclusions: These results indicate that phonological ability is a significant predictor of word generation in lvPPA. Our findings contribute to the understanding of the language processes that underlie word retrieval performance patterns in the context of animal fluency in lvPPA and may inform assessment and treatment strategies for individuals with lvPPA.
CHARACTERIZATION OF MACROVASCULAR AND MICROVASCULAR PERFUSION IN ALZHEIMER’S DISEASE AND VASCULAR DEMENTIA. Keeling EG, McElvogue MM, Ott LR, Sabbagh M, Burke A, Bakkar N, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer’s Consortium.

Background: Cerebrovascular co-morbidities are common in Alzheimer’s disease (AD), and vascular dementia (VaD) is often diagnosed alongside AD. MRI studies have found that cerebral perfusion decreases with dementia compared to healthy aging. Moreover, blood brain barrier (BBB) permeability increases in dementia, which can enable further neuropathology in the brain. Perfusion and BBB changes occur prior to symptomatic onset, providing an opportunity to detect early changes and prevent further cerebrovascular decline in people at-risk for dementia. Advanced MRI biomarkers sensitive to neurovascular characteristics of the brain may be able to detect such changes and distinguish between different types of dementia. In the present study, we propose the use of an advanced MRI acquisition to assess perfusion on complementary macrovascular and microvascular scales and further characterize the cerebrovascular profiles of AD and VaD. We hypothesize that there will be differences in the perfusion metrics (such as cerebral blood flow (CBF) and relative cerebral blood volume (rCBV)) between the macrovascular and microvascular analyses, providing complementary information. Additionally, we hypothesize that macrovascular and microvascular perfusion will be lower in AD and VaD cohorts compared to healthy controls, with VaD patients having the most reduced perfusion.

Methods: Dynamic susceptibility contrast MRI (DSC-MRI) data were acquired at 3T (Ingenia, Philips) in three cohorts: (1) non-cognitively impaired cohort (HC, n=2, 69.0±8.0 years old, 2 females), (2) AD (n=2, 77.0±12.0 years old, 1 female), and (3) VaD (n=3, 74.7±9.1 years old, 2 females). Data were acquired with a multi-echo, multi-contrast (SAGE) acquisition (5 echoes with TE1-5=7.7/26/56/74/92 ms), before, during, and after injection of gadolinium-based contrast agent. Additional acquisition parameters were as follows: repetition time (TR) = 1.5 s, voxel size = 2.75×2.75×5 mm, 200 volumes, acquisition time = 5 min. SAGE-DSC data underwent standard pre-processing. Macro- and microvascular CBF and rCBV were calculated as previously described. A region-of-interest (ROI) analysis was performed to assess perfusion metrics within normal-appearing gray matter (NAGM) and normal-appearing white matter (NAWM). White matter hyperintensities WMH, common to aging and dementia, were segmented and subsequently removed from NAWM analysis using the SPM12 LST toolbox’s LGA algorithm. Data were checked for normal distribution using the Shapiro-Wilk test in R. Kruskal-Wallis and Dunn tests were performed to assess group differences.

Results: Macrovacular CBF was lower for AD and VaD compared to HC in NAGM and NAWM, while there was no difference in macrovascular CBF between AD and VaD. Similarly, microvascular CBF was lower for AD and VaD compared to HC in NAGM and NAWM, while there was no difference in microvascular CBF between AD and VaD. As expected, microvascular CBF was lower than macrovascular CBF for all groups. Similar group-wise trends were observed for rCBV. Microvascular rCBV was also lower than macrovascular rCBV.

Conclusions: Preliminary results show that macrovascular and microvascular perfusion decreases with AD and VaD. Microvascular perfusion metrics were lower for all groups compared to macrovascular perfusion metrics. Enrollment is ongoing, and future directions for this work include analysis of perfusion metrics within cortical and subcortical ROIs, correlation of neuroimaging findings with cognitive testing, and assessment of cerebrovascular reactivity.

The consideration of sex as a biological variable was formally mandated by the National Institutes of Health in 2016, thus requiring strong justification for exclusion of one sex in research designs in submitted grant proposals. However, marked inattention to sex- and gender-inclusive research persists, obscuring understanding of the influence of sex and gender diversity on health outcomes. Regarding the neuroscience domain specifically, fewer than three percent of research studies are dedicated to factors unique to females, such as menopause and ovarian cycle related influences. Empirical evidence has demonstrated some molecular differences between the sexes, and in these cases, they prove to be important for implications in drug pathways; for example, studies indicate that women are nearly two times more likely than men to develop an adverse drug reaction, and in a 2023 study of 400 pharmaceutical substances, 20% showed clinically relevant sex and gender differences, especially for efficacy and adverse events. Including sex and gender factors into experimental research paradigms will begin to close the gap in knowledge between the sexes. Increased participation of women in science has led to greater inclusion of sex and gender variables in the scientific literature. Indeed, there are robust and repeated effects showing that in medical science, women scientists and diverse research teams are more likely to focus upon sex, gender, and diversity within disease-related research domains. Sex and gender difference analyses are more likely to be performed in papers that include women as authors, and principal investigators who identify as women are more likely than men to explicitly include sex in grant proposals. The dearth in knowledge of female disease-related trajectories and profiles yields consequences for female individuals, which can include incomplete and inadequate characterization of disease symptomology, leading to a lack of information for appropriate diagnosis and treatments. This is especially noteworthy in diseases where females have a higher prevalence than males, such as with Alzheimer’s Disease. Achieving excellence in academic science and medicine requires that we eliminate the knowledge gap for how sex and gender diversity impact health and disease. Given the long-apparent differences between the lifespans of males and females, studying sexually differentiated factors during aging is especially pertinent.

Background: Brain-derived neurotrophic factor (BDNF) contributes to learning and memory by affecting neuroplasticity in the brain. A single-nucleotide polymorphism in the BDNF gene causes a valine to methionine substitution at codon 66 of the BDNF protein (Val66Met). There are inconsistent results regarding whether this polymorphism has a significant effect on hippocampal volume, as some studies have reported smaller hippocampal volume in individuals with at least one Met allele while other studies have reported no genotype effect.

Methods: In order to help clarify the question of whether the Met allele impacts hippocampal volume, we analyzed a sample of 169 cognitively unimpaired younger and older adults. Following genotyping, participants were considered a Met carrier if at least one Met allele was present (n=68). Using Freesurfer, we derived volume estimates for the following hippocampal subfields: cornu ammonis of the body and head (CA1 body, CA3 body, CA4 body, CA1 head, CA3 head, CA4 head), dentate gyrus of the body and head, subiculum of the body and head, and tail. We tested for interactions between age group and BDNF Met allele carrier status on hippocampal subfield volumes using ANOVAs.

Results: We found significant age group by Met status interactions for both the head and body of the CA1, dentate gyrus, and subiculum, as well as the CA4 body and tail subfield volumes. Older adults carrying a Met allele appeared to have smaller volumes than younger Met carriers for all these subfields, whereas older non-Met carriers only showed smaller volumes than younger non-Met carriers for the dentate gyrus head. Furthermore, older Met carriers had smaller volumes than older non-Met carriers for the CA4 body, dentate gyrus body, subiculum body, CA1 head, dentate gyrus head, and tail. In contrast, younger Met carriers did not differ from younger non-Met carriers for any subfields.

Conclusions: The present results indicate that the BDNF Met allele is associated with decreased hippocampal volume among older adults, but not younger adults. Several previous studies on younger adults have not found an effect of BDNF Met status on hippocampal volume, in line with the current findings. BDNF Met may have a selective effect on hippocampal volume among older adults, perhaps interacting with aging processes to exacerbate atrophy.
ACCELERATED DEEP-LEARNING FOR MODEL-FREE AND MULTI-SHELL (ATLAS) DWI.
Martin P, Altbach M, Bilgin A. University of Arizona; Arizona Alzheimer's Consortium.

Background: Diffusion-weighted magnetic resonance imaging (dMRI) is a prominent technique for qualitatively and quantitatively assessing microstructural characteristics of tissues. dMRI techniques such as Diffusion Tensor Imaging (DTI) have been utilized to study a wide range of structural and pathological processes. One of the major challenges of dMRI is the long data acquisition times required to obtain and leverage a large number of diffusion-weighted images (DWIs) for accurate estimation of the various diffusion metrics obtained from different models across multiple shells. In this work, we present a novel deep-learning (DL) technique, AcceleraTed deep-LeArning for model-free and multi-Shell (ATLAS), in predicting unacquired DWIs over multiple shells, given an accelerated acquisition in one shell.

Methods: Our ATLAS DL process was carried out using a Unet, comprising contracting and expansive paths and channel attention. Overlapping patches were utilized for improved estimation. Experiments were conducted with k=6,9, and 12 as input to the network to represent different acceleration ratios. DWI datasets were acquired from the Human Connectome Project (HCP) public database. 50 subjects were used for training, 10 for validation, and 10 for testing. The proposed ATLAS pipeline comprised two trained models: The first model used k acquired DWIs at b = 1000 s/mm² as input to predict N = 90 DWIs at b = 3000 s/mm². The second model performed an intra-shell prediction, using the same k inputs and predicting N = 90 DWIs at b = 1000 s/mm². Tensor-derived metrics, such as Fractional Anisotropy (FA) and Mean Diffusivity (MD), were calculated. The metrics derived from N=90 DWIs were used as reference values in subsequent analysis and metrics derived from using only k DWIs at each shell were also calculated for comparison.

Results: Overall, the results show that ATLAS is able to effectively predict fully-acquired DWIs and obtain high-quality tensor metrics over multiple shells, when given an accelerated input of DWIs for b = 1000 s/mm². Although ATLAS is in early development, it demonstrates good performance and the benefits from relaxing the need for full acquisitions of DWIs acquired across multiple shells. Moreover, without being constrained to a diffusion model, it can potentially be adapted to diffusion models other than DTI.

Conclusions: We developed a novel DL technique, ATLAS, which can predict DWIs over multiple shells from accelerated single-shell data, enabling high-accuracy predictions of DTI metrics, and significantly reducing the requirements of acquiring large DWI datasets over multiple shells. ATLAS also has the potential to be used with various diffusion models, such as Diffusion Kurtosis Imaging and Constrained Spherical Deconvolution.
UTILIZING SHORT STORIES TO UNDERSTAND THE IMPACT OF CONTEXT ON PATTERN SEPARATION AMONG OLDER AND YOUNGER ADULTS. Martinez AC, Karnafel MJ, Palmer JM, Ryan L. University of Arizona; Arizona Alzheimer’s Consortium.

Background: Pattern separation serves to create discrete representations of similar memories in the brain so that they do not overlap with one another. Typically this is tested by using a continuous object recognition task whereby participants identify if objects are the same, similar, or different compared to objects previously seen in the task. These objects are usually embedded on white backgrounds or semantically related scenes to evaluate the effect of context on pattern separation. Our lab and others have shown an age-related effect on the ability to distinguish similar objects; older participants tend to classify similar objects as objects they have previously seen more than younger adults. This effect is exacerbated in older adults when these similar objects are shown on repeated scenes. Although this effect is interesting, it is difficult to generalize these findings to everyday function. For example, having to recall the subtle perceptual details of two similar lamps (objects) may not translate to recalling the details between two similar memories of going out to dinner with your family (events). Designing a task that allows us to test the memory of short stories, filled with episodic details, rather than recalling perceptual differences of objects may better relate to pattern separation in the real world.

Methods: A cohort of 33 undergraduate students at the University of Arizona, along with an ongoing cohort of 4 older adults (65 years and older) were recruited to participate in the study. Participants were asked to listen to a series of 20 unique short stories in succession. Each story contained four target details for the participant to remember. An example of a story that a participant may listen to is, “Amelia was knitting a hat while enjoying a latte. She was working on it for her newborn granddaughter. A barista accidentally bumped into her table while walking by, causing Amelia’s drink to spill. The barista was apologetic and brought Amelia a free blueberry scone.” The objects “hat”, “granddaughter”, “table”, and “blueberry scone” were the target details for the presented story. Each story took place in either a coffee shop or library and a picture of where the story took place would appear on screen for the participant to look at while listening. Participants were asked to imagine that the story they were hearing was taking place in the picture being shown and were told they would be asked questions about the stories later on. Approximately 15 minutes later, participants answered 160 yes/no questions 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 consistent picture (i.e., a different library or coffee shop picture), (3) an inconsistent 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 a same or similar detail from the story. Using Amelia’s story, an example of a similar detail question would be, “Was Amelia knitting a sweater” while a same detail question would be “Was Amelia knitting a hat?” Prior to starting the actual task, participants listened to practice stories and answered practice questions. However, concerns about ceiling effects may have interfered with the validity of those results. The data presented here had participants complete the task without the practice session.

Results: A 4 x 2 repeated measures ANOVA analyzed accuracy in this study. There was no significant main effect of detail, F(1,32) = 0.69, or context, F(3,96) = 1.21. However, an interaction between detail and context was found F(3,96) = 3.30, p < 0.05. Follow-up paired t-tests revealed significant differences between the same and similar details in the inconsistent condition t(32) =
2.70, $p < 0.05$ and between same and similar details in the same context condition, $t(32) = -2.10$, $p < 0.05$.

**Conclusions:** In line with the pattern separation literature, participants were more accurate when answering questions about the same details compared to answering questions about the similar detail when the same context was used. However, interestingly, the opposite pattern was also observed when an inconsistent context was used when answering questions. When participants were provided with an inconsistent context, accuracy for similar details was better than the accuracy of same details. As of this writing, data for the older adult cohort is still being collected. We hypothesize the interaction between detail and context that was observed with the young to also be present in older adults. In addition, we predict a main effect of age such that younger adults will perform better than older adults on this task.
STABILITY IN LOCUS COERULEUS CELL POPULATIONS IN COGNITIVELY IMPAIRED RHESUS MACAQUES. McDermott K, Sinakevitch I, Barnes CA. University of Arizona; Arizona Alzheimer’s Consortium.

Background: The Locus Coeruleus (LC) is a brainstem nucleus best known for being the primary central nervous system site of noradrenaline production and is critical for the modulation and optimization of numerous behaviors. The LC appears to be especially vulnerable to pathological changes associated with Alzheimer’s disease (AD). It is unclear, however, whether neurodegeneration of the LC is specific to diseases such as AD, or if LC cell composition changes are part of the normative aging process. We have established three distinct subregions in the macaque LC: a medial and a lateral nucleus, and a compact area. It is unclear whether any of these subregions of the LC are more susceptible to cell loss.

Methods: Our research utilizes coronal brainstem sections from a colony of 30 cognitively assessed rhesus macaques ranging in age from 7 to 32 years (human equivalent ~21 – 96 years). All monkeys underwent tests of spatial short-term memory (delayed response), object recognition memory (delayed nonmatching-to-sample), and object discrimination. We used immunofluorescence techniques to identify neuronal nuclei (NeuN), catecholaminergic neurons (TH), vasculature (STL), and astrocytes (GFAP). The entirety of the LC region was imaged at 40X on a confocal microscope. These same immunolabeled sections, along with adjacent Nissl stained-brainstem sections, were also imaged at 5x on a fluorescence microscope. Neuron, glia, and vascular populations were determined for the whole LC using unbiased stereological techniques. For the subregion analysis, Nissl and immunolabeled brainstem sections are first aligned with MRIs using AMIRA software. We then define and assess the volume of each subregion of the LC. Older monkeys tended to have smaller volumes in the medial LC subregion compared to younger monkeys.

Results: Despite these volume differences, preliminary results from the ventral LC indicate that TH+ and total neuron cell counts remained stable across age. Furthermore, vascular and GFAP staining densities were not different between the adult and aged animals.

Conclusions: Our preliminary results indicate there is no broad loss of neurons or supporting cells in the LC with age; however, we are currently investigating whether there are age-related changes in the LC’s postsynaptic targets.
EVALUATION OF ONE-CARBON METABOLITE ENZYMES AND RECEPTORS IN BRAIN TISSUE FROM VASCULAR CONTRIBUTION TO COGNITIVE IMPAIRMENT AND DEMENTIA (VCID) PATIENTS. McKee A, Joshi S, Ille S, Beach TG, Serrano GE, Jadavji NM. Midwestern University; Banner Sun Health Research Institute; Arizona Alzheimer’s Consortium.

Background: Vascular Contribution to Cognitive Impairment and Dementia (VCID) is a form of dementia that is projected to double in prevalence within the next three decades, placing it at the forefront of health service priorities. Deficiencies in one-carbon (1C) metabolites, such as dietary deficiencies in folic acid, result in elevated levels of homocysteine and have been linked to cognitive dysfunction and VCID in the aging population. However, the understanding of the role of 1C metabolism in VCID remains limited, necessitating further research in this area. This study aims to investigate the levels of 1C enzymes and receptors in post-mortem brain tissue from female and male patients diagnosed with VCID.

Methods: Post-mortem cerebral cortex tissue from controls and VCID-diagnosed patients have been obtained from the Brain and Body Donation Program at Banner Health. Immunofluorescence staining was performed to visualize enzymes involved in 1C metabolism. Both male and female patient samples were used. Brain tissue is stained with methylenetetrahydrofolate reductase (MTHFR), Folic Acid Receptor (FR), Methylenetetrahydrofolate dehydrogenase (MTHFD), Serine hydroxymethyltransferase (SHMT), cystathionine B reductase (CBS), Thymidylate synthase (TS), Choline Acetyltransferase (ChAT), and Acetylcholine Esterase (AchE). All staining is colocalized with a neuronal marker, NeuN, to ensure that the staining is specific to neurons, as well as DAPI. Co-localization of the staining with neuronal nuclei (NeuN) is quantified using microscopy imaging.

Results: Preliminary findings suggest alterations in choline metabolism in VCID patients, and additional data will be collected by staining for other 1C enzymes and receptors. The gathered data will provide valuable insights into the involvement of 1C metabolism in VCID, potentially contributing to the development of novel diagnostic tools and therapeutic approaches for this debilitating condition.

Conclusions: The gathered data will provide valuable insights into the involvement of 1C metabolism in VCID, potentially contributing to the development of novel diagnostic tools and therapeutic approaches for this debilitating condition.

Background: Apolipoprotein E (APOE) plays a critical metabolic role by facilitating the binding of lipid complexes to cell surface receptors, providing tissues with energy substrates. The APOE-E4 (APOE4) polymorphism is the predominant genetic risk factor for late-onset Alzheimer’s Disease (LOAD), while APOE3 is considered risk-neutral. Female biological sex also nearly doubles LOAD risk. This study utilizes the JAX humanized APOE knock-in mouse model to investigate the contributions of chromosomal sex and APOE genotype to plasma metabolic profiles, along with potential correlates to cognitive performance in a novel objection recognition (NOR) task.

Methods: Male and female mice aged 23-25 months old (37M/32F) with humanized APOE3/3, APOE3/4, and APOE4/4 genotypes underwent blood plasma extraction and subsequent metabolic profiling via mass spectrometry using the Biocrates MxP® Quant 500 platform. A subset of animals (34M/28F) additionally performed an NOR paradigm prior to metabolic profiling. Two-way ANOVA and post-hoc t-tests were utilized to determine data significance.

Results: Metabolomic analyses indicated that male mice exhibited relatively higher levels of glucogenic amino acids, including glycine, asparagine, and histidine. In contrast, female mice had higher levels of TMAO and ADMA along with lower levels of phosphatidylcholines, cholesteryl esters (CE), and triglycerides. In males, APOE3/4 and APOE4/4 genotypes were associated with lowered CE levels. APOE3/4 female mice had the lowest CE plasma concentrations. Female APOE4/4 mice had increased concentrations of several diglyceride and triglyceride species, relative to APOE3/3 and APOE3/4 female mice. Behavioral correlates indicated that triglyceride levels negatively correlated with locomotion throughout the NOR paradigm. Memory performance, as determined by the discrimination index, positively correlated with plasma concentrations of glycine and negatively correlated with hydroxy acylcarnitine levels.

Conclusions: In mice aged to resemble a ~70-year-old human population, these results suggest that biological sex affects peripheral metabolic profiles greater than APOE genotype. Male metabolism was characterized by elevated glucogenic amino acid levels; female metabolic profiles demonstrated increased TMAO and lower phosphatidylcholines and triglycerides, suggesting differences in lipid metabolism. APOE3/4 genotype was associated with lowered CE in both sexes while APOE4/4 females had higher triglycerides, indicating potential sex-genotype interactions upon metabolism that may confer elevated LOAD risk and influence behavior.

Background: Autobiographical memory narratives (memories of personal events) elicited from structured interviews are believed to provide insight into how memories are retrieved in daily life. Despite this assumption, to our knowledge, no study has tested whether structured interview episodic specificity predicts how elaborately autobiographical memories are shared in natural, daily environments. To close this gap in knowledge, we conducted a novel study designed to objectively measure episodic specificity in both structured interviews and in “day-to-day life” in the same group of participants.

Methods: We conducted preliminary analyses on 42 healthy, cognitively unimpaired young and older adults (ages 19-80, M = 62.05, SD = 1782). Participants completed the Autobiographical Interview (AI), with their memory narratives transcribed and scored using the established AI protocol to parse internal (episodic) and external (semantic and other) details. We then had participants use the Electronically Activated Recorder (EAR) for 10 days to unobtrusively capture audio recordings of real-life, everyday instances of their autobiographical thought sharing. Recordings containing autobiographical thoughts were scored using a modified version of the AI protocol. Using linear regression, we examined whether the proportion of internal details shared in structured interviews predicted the proportion of internal details shared in the real-world, accounting for age, gender, and education.

Results: The overall regression model was statistically significant (R2 = 0.39, F(4,37) = 6.02, p = 0.008). The proportion of internal details shared in structured interviews significantly predicted the proportion of internal details shared in the real-world (β = 0.31, p = 0.002), while age (β = 0.0003, p = 0.65), gender (β = -0.01, p = 0.64), and education (β = -0.002, p = 0.62) did not.

Conclusions: To our knowledge, these analyses provide the first evidence that autobiographical memory episodic specificity, derived from structured interviews, is a significant, moderate-strength predictor of natural memory sharing in daily life. The fact that the structured interview measure predicts 28% (partial Pearson’s correlation; r = 0.53, p < 0.01) of the variance in naturalistic episodic specificity both supports the validity of structured interview testing and hints at the need for future research identifying additional sources of variance in naturalistic cognition.

Background: Alzheimer’s disease (AD) is the most common type of dementia, affecting 1 out of every 9 older adults in the US. However, primary care providers (PCPs) miss almost half of all cases, even though nearly over 90% of older adults see their PCP on an annual basis. Thus, there is an urgent need for tools and tests to assist PCPs in detecting AD in its preclinical stage, when emerging therapies are most effective. Previously, a brief motor test in humans was developed that involves anticipatory dexterity. This test is simple and short enough to be feasibly administered in primary care. Prior clinical research in older adults with and without cognitive impairment have shown that motor tests can predict the extent of AD progression over one year (Schaefer et al., 2020), and is sensitive and specific to brain amyloid (measured with PET) (Schaefer et al., 2022a) and hippocampal atrophy (Schaefer et al., 2022b; Malek-Ahmadi et al., 2023). By measuring learning over multiple trials, rather than performance on a single trial, scores are independent of patient symptoms (pain, weakness, or tremor). At this time, however, the exact mechanisms of AD that our motor test detects remain unknown. The overall objective of this research was to develop and validate a rat version of our motor test to identify plausible mechanisms of how the motor test is associated with preclinical AD.

Methods: Fisher CDF rats at 3 months of age (n = 6, males) underwent food restriction and were maintained at 90% body weight. Rats were trained in a clear Plexiglass chamber to reach through a shutter and take a sucrose pellet dispensed on a ridged bowl attached to a spring. The amount of successful pellet retrievals were recorded, and the timing of the task was analyzed from high-speed video capture (>100 Hz). The time to acquire a pellet and the number of successful retrievals over time were recorded.

Results: Our results demonstrate that rats learn to reach within 5 days. Although animals were initially hesitant to reach through the shutter, a 3D printed pellet tray modification to train animals allowed for increased reaches. Reaches and consumption of sucrose pellets increased with time in training and increased food restriction.

Conclusions: Pilot tests have demonstrated that structural modifications were necessary to improve task learning and overall performance. Future work includes comparing performance in wildtype compared to mutant TgF344-AD rats, which have biomarkers of AD. The task will be adjusted to increase in difficulty by changing the tension to high, medium, and low spring constants on the bowl. We will also evaluate the kinematics of arm and digit movement during the task to study trajectory of approach and pellet grab using SLEAP, a machine-learning pose tracking software. This work is significant as it will generate a preclinical model to understand the relationship between performance on the motor test and AD brain pathology. The long-term goal of this research will be to develop an objective, motor-based clinical assessment to assist PCPs in identifying signs of preclinical AD.
SEX AND APOE DIFFERENCES IN ALZHEIMER’S DISEASE-ON-RAMP RISK FACTOR PROFILES: ARE ALL RISK FACTORS FOR ALZHEIMER’S DISEASE CREATED EQUAL?

Background: Obesity, diabetes (T2D), hypertension (HTN) and hyperlipidemia (HLP) are relevant Alzheimer’s Disease (AD)-on-ramp modifiable risk factors (RFs). However, it remains unclear whether the risk conferred by these conditions is modified in time by other unmodifiable AD risk factors, such as chromosomal sex and APOE genotype. In this study, we conducted a retrospective analysis using the UK Biobank to evaluate age-specific effect of AD-on-ramp RFs, in combination with sex and APOEε4 carrier status.

Methods: Inclusion criteria were age older than 55 years old, no prior history of neurodegenerative disease, neurosurgery, or cancer, and enrollment with at least 3 years of follow-up. Propensity score matching was performed based on age at recruitment, educational level, center, and Charlson comorbidity index. Stratified Cox proportional hazard models (CPHMs) with counting process formulation were used to examine the association between each time-depending modifiable RFs and AD onset, adjusted for sex and APOE genotype. Age stratification was evaluated when violation of hazard ratio (HR) proportionality assumption occurred during aging. Finally, we performed extended stratified CPHM for recurrent event to estimate AD onset based on the development of multiple RFs in time.

Results: Preliminary findings revealed RF-specific differences in AD on-set based on the RF’s age diagnosis. The risk of developing AD is significantly greater than APOEε4 effect if HTN is diagnosed before 63yo, while if diagnosed after 72yo, APOEε4 is the major contributor of an increased AD risk. Similarly, HLP was associated with higher risk of AD if diagnosed before 65yo or in the 65-72 age group, while T2D in the <64 or 64-72 age groups, and obesity in the <70 age group. Again, the age-stratum-specific decline of RFs’ effects on AD on set were modulated by a substantial increased effect of APOEε4 carrier status with the age-strata. Additionally, when considering a CPHM with all the RFs together, higher risk of developing AD was consistently associated with earlier RF diagnosis (<62), while APOEε4 carriers exhibited higher risk of AD onset in the older age.

Conclusions: This study identified critical tipping points indicating a decline in the HRs of the modifiable RFs with aging and a considerably stronger association of APOEε4 with the late-onset AD. Age stratification within CPHMs provided valuable insights into age-specific HRs and identifies age-dependent RFs. Furthermore, our study highlights the assessment of interactions between age, sex, and APOE genotype, aiding in targeted interventions and personalized medicine approaches for AD prevention.
GENERATION OF FUNCTIONAL GABAERGIC INTERNEURONS FROM HUMAN-INDUCED PLURIPOTENT STEM CELLS WITH EARLY EXPRESSION OF PARVALBUMIN. Mintah AE, Brafman D, Amini N, Fang X, Jansen J, Dwyer S. Arizona State University; Trailhead Biosystems; Biogen, Inc.; Arizona Alzheimer’s Consortium.

Background: Gama-Aminobutyric Acid (GABA) is the principal inhibitory neurotransmitter in the mammalian central nervous system (CNS), produced by GABAergic interneurons. Impairment in the development or function of these cells has been linked to neurological disorders like autism, schizophrenia and recently Alzheimer’s disease. Alzheimer’s disease (AD) is characterized by amyloid beta (Aβ) plaque formation, neuronal loss, and neurofibrillary tangles. Recent studies suggest that abnormal Aβ production interferes with GABAergic interneuron function, contributing to cognitive decline in AD mice. Phosphorylated tau, crucial in AD progression, accumulates in GABAergic interneurons in hippocampal regions of AD patients and mice. However, generating GABAergic interneurons from human pluripotent stem cells (hPSCs) is time-consuming and costly.

Methods: Here, we present a novel High-Dimensional design of experiment-based method for differentiating GABAergic interneurons expressing Parvalbumin by day 26.

Results: RNA Seq and RT-PCR showed increased expression of GABAergic markers, indicating successful differentiation. Viability studies demonstrated high cell viability post-thaw. Calcium transient studies revealed high-spiking Parvalbumin cells, and Elisa quantification demonstrated elevated intracellular GABA with decreased extracellular GABA, indicating a pure differentiation.

Conclusions: This rapid method holds promise for modelling GABA-associated diseases and drug screening.
AGING WITH TRAUMATIC BRAIN INJURY: PROFILES FOR NEUROPATHOLOGY IN BEHAVIORALLY RELEVANT THALAMOCORTICAL CIRCUITRY OF MALE AND FEMALE RATS. Mitbander A, Sabetta Z, Krishna G, Curry T, Adelson DP, Currier Thomas T. University of Arizona College of Medicine, Phoenix; Barrow Neurological Institute at Phoenix Children’s Hospital; Midwestern University; Arizona State University; Phoenix VA Healthcare System; Arizona Alzheimer’s Consortium.

**Background:** Traumatic brain injury (TBI) continues to be one of the most complex brain injuries with long-term consequences that can lead to persistent and late-onset symptoms and increased risk for developing age-associated neurodegenerative disorders. Furthermore, while aging is an associated risk factor for neurodegenerative conditions, little is known regarding how the brain compensates for aging after TBI, where TBI is implicated in accelerating brain aging or exacerbating neurodegenerative pathology. Moreover, while reported TBI is higher in males than females, clinical evidence is conflicting concerning sex-dependent recovery after TBI. Therefore, we hypothesize that the neuropathological manifestations in rat brains after experiencing TBI may vary based on time post-TBI and biological sex.

**Methods:** A total of 64 young adult age-matched male and naturally cycling female Sprague-Dawley rats underwent craniectomy and midline fluid percussion injury (FPI) (moderate severity; 1.7–1.9 atm for females and 1.8-2.0 for males) or sham surgery. Brains were collected at 7, 56, and 168 days post-injury, placed in Multibrain (R) blocks, and stained with aminocupric silver stain by Neuroscience Associates. Silver stain histological analysis was conducted to evaluate neuropathology in the ventral posteromedial nucleus of the thalamus (VPM), primary somatosensory barrel cortex (S1BF), and thalamic reticular nucleus (TRN) where pixel density of staining was quantified using ImageJ to determine the temporal profile of neuropathology. Data were analyzed using a three-way ANOVA as a function of injury, time post-injury, and sex with a Tukey’s post-hoc comparison (p>0.05).

**Results:** FPI induced significant neuropathology in all brain regions at 7 DPI. At 168 DPI, neuropathology remained significantly elevated in the VPM and TRN, but returned to sham levels in the S1BF. No sex differences or sex interactions were detected in any of the brain regions.

**Conclusions:** Our data provide evidence of chronic neuropathological after a single diffuse TBI in both sexes as well as age and injury-related interactions. By elucidating the interactions between age, sex, and injury in shaping neuropathological outcomes, our findings contribute to a deeper comprehension of the underlying mechanisms and potential avenues for specific treatment strategies.
BINDING AND DISRUPTION OF AMYLOID BETA AND TAU PLAQUES VIA FOCUSED ULTRASOUND AND TARGETED PHASE-SHIFTED 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 (Abeta) 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 to, and possibly 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 microbubble 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. 3XFAD and 5XFAD transgenic (TG) mice were used once a protocol was established. 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 low power. 15 minutes after sonication, mice were given an IV injection of PSMBs, followed by a second sonication for 2 minutes at a higher power. The mice then underwent MRI and were perfused 1 hour-post PSMB injection. Tissue was sliced into 5 micron sections and stained for H&E and Abeta using anti-amyloid beta 1-16.

Results: Results indicate that the BBB can reversibly be disrupted in WT and TG mice using a combination of MVT-100 MB and FUS at a low power setting. The experiments also demonstrated that the PSMBs and FUS are well-tolerated, with minimal tissue damage in the area of sonication in WT and TG mice. Fluorescence microscopy indicates 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. Preliminary IHC results indicate that AB accumulates in the region of sonication in TG mice that received FUS with and without PSMB intervention.

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 in-depth analysis of IHC staining and blood analyses for the treatment groups, as well as IHC and MRI co-registration analysis.
ASSESSMENT OF WHITE MATTER MICROSTRUCTURE AND HYPERINTENSITIES IN ALZHEIMER’S DISEASE USING FREE-WATER DIFFUSION TENSOR IMAGING. Nelson MR, Keeling EG, Bergamino M, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer’s Consortium.

Background: Alzheimer’s disease (AD) can be characterized by a decline in white matter integrity measured with diffusion MRI, where white matter microstructural decline has been seen in both healthy aging and AD populations. Furthermore, a decrease in white matter integrity is associated with the development of white matter hyperintensities (WMH), which are brain lesions that result from the accumulation of water molecules in myelin sheaths. In the present study, an advanced diffusion MRI method was implemented to remove the effect of extracellular free water (FW) from the diffusion images. Previous studies have shown that FW-corrected diffusion tensor imaging (FW-DTI) images yield more robust differences in white matter integrity in AD patients, compared to standard DTI processing. This study investigates changes in white matter microstructure and WMH in AD, mild cognitive impairment (MCI), and healthy controls using FW-DTI. We hypothesize that participants with MCI and AD will have a larger WMH burden compared to healthy controls. Participants with MCI and AD will also have decreased fractional anisotropy (FA), which corresponds to a decline in white matter microstructural integrity.

Methods: Data was downloaded from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database. ADNI subjects were included if they had at least one visit with multi-shell DTI data to perform the FW-DTI analysis. A total of 28 subjects are included in the present analysis (Healthy Controls (HC): 77.34 ±9.00 years of age, Cognitively Impaired (CI, consists of AD and MCI): 74.00 ±6.95 years of age). DTI images were preprocessed with FSL from the FMRIB software library, and FW correction was performed with the DiPy model in python. Then, b0 images were coregistered to a group template using advanced normalization tools (ANTS). The SPM12 lesion segmentation toolbox (LST) was implemented for the calculation of the volume and number of WMHs using the lesion growth algorithm, and WMH volume was normalized to each subject’s total white matter volume. The average FA and FW in both normal appearing white matter (NAWM) and WMH was also calculated. A voxel-wise analysis was conducted with an independent samples t-test corrected for multiple comparisons (FDR <0.05). A region of interest (ROI) analysis was done with the JHU White-Matter Tractography Atlas.

Results: Voxel-wise analysis of FW-FA found healthy control participants had higher FA compared to participants with MCI or AD. Healthy controls also had higher FA in the ROI analysis. Significant FW-FA differences were found in the right uncinate fasciculus, as well as the bilateral anterior thalamic radiation, corticospinal tract, forceps major, forceps minor, inferior frontal-occipital fasciculus, and the inferior longitudinal fasciculus. The normalized WMH volume, number of WMH, and average FA and FW in both NAWM and WMH was calculated in each participant, but no significant differences were found between groups in this preliminary analysis.

Conclusions: Significant differences in prominent white matter tracts support their established role in neurodegeneration. Future directions of this work include increasing group size, assessment of sex differences, and comparison of results using FW-DTI to standard DTI.
Background: Apolipoprotein E (APOE) is the most well-established genetic risk factor for developing late-onset Alzheimer’s disease (AD). APOE e4 homozygotes have a 30-55% risk of developing AD through age 85. APOE genotype disclosure is not a part of routine clinical practice and is currently advised against for cognitively unimpaired individuals. However, this is likely to change due to advances in preclinical AD research as well as requirements for clinical trial enrollment. We are testing whether APOE disclosure results in short- or long-term psychological or emotional distress. The Generation Program trials are the first to examine the safety and efficacy of returning APOE genotype results on a large scale to individuals close to their estimated age of onset for developing symptoms of dementia due to AD.

Methods: The Alzheimer’s Preventative Generation Studies 1 and 2 both enroll cognitively normal adults ages 60-75 who are APOE e4 homozygotes, and Generation Study 2 also enrolls APOE e4 heterozygotes who have elevated amyloid PET scan results. The Alzheimer’s Preventative Initiative (API) Genetic Counseling and Disclosure (GCD) Process is implemented for all participants to learn their APOE genotype. For participants screening for Generation Study 1, the impact of APOE disclosure is examined at several time points prior up to 12 months following disclosure including measures for psychological well-being, health behaviors, genetic knowledge, satisfaction with disclosure, and impact of disclosure.

Results: Of the participants screening for Generation Study 1, 213 were APOE4 homozygotes, 861 were heterozygotes. Prior to genetic disclosure, participants were assessed for distress, depression, anxiety, perceived risk and threat of AD, and knowledge of disease. Minimal changes in mean scores were observed on these measures up to 12 months following APOE disclosure.

Discussion: Initial descriptive analyses indicate that APOE disclosure is safe and well-tolerated in participants screening for the API Generation Study 1. Future analyses will explore differences in measures by APOE genotype. Given the recent advancements in disease modifying therapies for AD, additional work is needed to develop efficient, scalable platforms for returning APOE results to participants in a safe and effective manner.
THE IMPACT OF RESPIRATORY SYMPTOMS ON COGNITIVE PERFORMANCE FOLLOWING COVID-19 RECOVERY. Palmer JM, Rhodes A, Ryan L. University of Arizona; Arizona Alzheimer’s Consortium.

Background: The long-term effects of cognitive function following COVID-19 infection is still poorly understood with many individuals reporting persistent physical and neurologic symptoms after the acute infection. Acute respiratory distress syndrome (ARDS) is a common severe symptom in individuals with COVID-19. Potentially, individuals with more severe respiratory symptoms, such as ARDS, may experience a high prevalence of cognitive impairment in areas of executive functioning and memory that interfere with daily life. We investigated how the severity of respiratory symptoms impacted cognitive performance on two hippocampally-mediated tasks.

Methods: Participants were divided into groups based on a self-report measure of symptom severity at the time of infection. Group 1 included COVID-19 negative controls (n=18). Group 2 included COVID-19 positive individuals without reported respiratory symptoms (n=34), Group 3 included COVID-19 positive individuals with respiratory symptoms (e.g., labored breathing/shortness of breath) (n=27), and Group 4 included hospitalized COVID-19 patients (n=18). Participants were tested on a thorough battery of cognitive tests, which included the Mnemonic Similarity Task (MST) to assess 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. The FNAME shows twelve different faces one at a time, each with a different name and occupation. Participants are then given a surprise memory test where they identify identical and perceptually similar objects. The FNAME shows twelve different faces 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.

Results: A total of 98 participants completed the cognitive battery. Of the total sample, 66 participants (67.3%) were females and 32 (32.7%) were males. Group 1 controls had an average age of 61.68 and education of 17.16 years. Group 2 had an average age of 57.26 and education of 16.07 years. Group 3 had an average age of 54.00 and education of 15.96 years. Group 4 had an average age of 59.44 and education of 13.61 years. The proportion of correct identification of similar objects after accounting for false alarms from the MST was analyzed using a one-way ANOVA between the four groups. A main effect of group, F(3,96)=2.94, p<0.05, was found, and follow up independent samples t-test revealed significant differences between the hospitalized group and all other groups. However, the proportion of correctly identifying old objects corrected for false alarms (i.e., recognition) was not significant, F(3,96)=0.01, ns. The total correct names recalled on the FNAME between the four groups was analyzed using a one-way ANOVA. A significant effect of group, F(3,96)=2.77, p<0.05, and follow up independent samples t-test revealed significant differences between the hospitalized group and all other groups as well. Interestingly, the total correct occupations recalled between the four groups were not significant, F(3,96)=0.57, ns.

Conclusions: The most severe cases of COVID-19 resulted in poorer performance on a measure of pattern separation and associative memory. However, the impairment appeared to be domain-specific as hospitalized COVID-19 participants performed just as well as all other groups on object recognition. Additionally, the data may suggest that recall of the names on the FNAME task is a more sensitive measure of memory performance post-COVID-19 than the recall of the occupations. Interestingly, no differences were observed between the COVID-19 groups that had no respiratory symptoms and respiratory symptoms. Potentially, the greater variability in the COVID-19 group without respiratory symptoms can explain null results.

Background: Alzheimer’s disease (AD) is the most common progressive form of dementia and is the fifth most common cause of death in the United States for those over the age of 65. Approximately 6.5 million people are currently diagnosed in America alone, a number which will only grow in the future due to aging populations. Biologically, AD is defined specifically by the presence of extracellular β-amyloid deposition (Aβ), otherwise known as neuritic plaques, and hyperphosphorylated TAU protein aggregates, including intraneuronal neurofibrillary tangles (NFTs) and dystrophic neurites. The progression of symptoms correlates with accumulation of localized proteinopathies, particularly TAU. Intriguingly, TDP-43 proteinopathy also occurs in up to 57% of AD patients. TDP-43 proteinopathy is known to have profound effects on the transcriptome and RNA metabolism pathways in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), however the impacts in the contexts of AD is critically understudied.

Methods: Fluorescence Activated Cell Sorting (FACS). I used 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. Nuclei will be stained with Alexa Fluor 488 conjugated to NeuN, and Alexa Fluor 647 conjugated to TDP-43. Stained nuclei will be sorted based on NeuN and TDP-43 fluorescence directly into Qiagen RLT lysis buffer with 1% β-mercaptoethanol for RNA isolation.

RNA Isolation. FACS sorted nuclei will be collected directly into Qiagen RLTplus lysis buffer with 1% β-mercaptoethanol for RNA isolation. The samples will be vortexed to ensure complete lysis and passed through a Qiashredder homogenizer column. RNA will be isolated from the homogenate by following the protocol of the Qiagen RNeasy Plus Mini kit and eluting into 30μl RNase-free water.

Results: Nuclei isolation and FACS methodology has been optimized to produce the necessary nuclei populations for RNA sequencing.

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 and LCM. 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.
EXPLORING INTERACTIONS BETWEEN AMYLOID AND ALPHA-SYNucleIN PROTEINOPATHIES USING KNOCK-IN AND VIRAL-MEDIATED GENETIC APPROACHES.


Background: Neurodegenerative diseases are associated with the accumulation of one or more pathological features in the brain. Lewy body dementia (LBD) is a prime example of a disease that is characterized by a mixture of pathologies, namely extracellular plaques of amyloid-beta and neuronal Lewy bodies of aggregated alpha-synuclein (α-syn). Exploring the pathophysiological relationship between amyloid and alpha-synuclein may be crucial to understanding LBD and other clinicopathologically related dementias.

Methods: We systemically administered adeno-associated virus (AAV) to drive neuronal overexpression (using the hSynapsin promoter) of human wild-type (WT) α-syn (N=11), disease-linked mutant α-syn(E46K; N=12), or EGFP (control; N=11), in aged heterozygous APPNL-G-F/MAPT double KI mice that develop robust, age-dependent amyloid pathology in the context of human tau expression. At 3- and 12-weeks post AAV administration (N= ~4 per group per timepoint), we harvested central nervous system (CNS) tissue to characterize AAV-transgene expression and associated pathological hallmarks. We assessed relative protein levels and localization by western blotting and immunostaining, respectively, with antibodies against human alpha-synuclein (Syn211), total alpha-synuclein (Syn1-Clone42), and EGFP. We also assessed early pathology by staining for amyloid plaques (X-34) and phosphorylated alpha-synuclein (pS129-α-syn), and sequentially extracting detergent insoluble and soluble protein fractions to measure insoluble synuclein accumulation.

Results: We find that transgene expression is robust, stable, and brain-wide by 3 weeks post AAV-injection (p.i.), with limited increases between 3- and 12-weeks. At 12-weeks p.i. we see that transgene expression is also robust throughout the spinal cord, as expected. Interestingly, the data suggest mutant α-syn(E46K) treated groups may accumulate and phosphorylate α-syn earlier than WT α-syn treated groups. By 12-weeks, both AAV-α-syn groups exhibit accumulation of insoluble α-syn, widespread α-syn phosphorylation, and potential interactions with amyloid plaques.

Conclusions: Here, we validate a novel mixed-model of amyloid and alpha-synuclein pathology, that leverages an established knock-in mouse in combination with custom viral constructs. In a larger scale study, our approach will help us understand disease-relevant amyloid and alpha-synuclein interactions in vivo by studying their impact on pathology, behavior, and transcriptional signatures.
IMPACT OF AGING AFTER 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 CE, Baun J, Zurhellen C, Adelson PD, Thomas TC. University of Arizona College of Medicine, Phoenix; Barrow Neurological Institute; Arizona State University; Neuroscience Associates, Knoxville, TN; Phoenix VA Health Care System; Arizona Alzheimer’s Consortium.

Background: Aging after traumatic brain injury (TBI) is commonly associated with developing chronic post-traumatic symptoms characterized by complex pathophysiological events that are hypothesized to increase risk or early-onset of neurodegeneration.

Methods: Injury induced by midline fluid percussion (FPI), we evaluated markers of neuropathology (amino cupric-silver stain), axonal damage (APP), astrocyte activation (GFAP), microglial activation (Iba-1), autophagy (neutral red), and phospho-tau (AT8) in the dentate gyrus (DG) of the hippocampus in age-matched male and female Sprague Dawley rats (n=5-6/group). Pathology was quantified using ImageJ for pixel density or skeleton analysis and compared using a Student's t-test.

Results: Silver staining was present in FPI and age-matched shams; however, the organization, localization, and degree of neuropathology differed within the regions of the DG. Overall, pathology in FPI was greater than sham (p<0.05). Positive APP pathology was present in white matter tracts of sham and FPI rats. GFAP density decreased in FPI compared to sham (p<0.05). A 45% increase in neutral red staining pixel density was observed in FPI group compared to shams (p<0.05), and often co-localized with silver pathology. No differences were detected in microglial activity. No AT8 staining was present in the DG. No sex differences were detected.

Conclusions: These data indicate novel differences between age-related and TBI-related neuropathological processes that require further investigation.

Background: Treatment of menopause with hormone replacement therapy (HRT), including subtypes of estrogen and testosterone, has been found to positively impact aspects of cognition and blood pressure, factors that are vulnerable to decreased estrogen. Most research concerning HRT utilizes a population younger than sixty years old as there is a critical period after which prolonged use of HRT has been shown to exert negative cognitive effects. To further investigate this relationship, the current study compared performance on measures of verbal memory and executive functioning, as well as meant arterial pressure (MAP) and pulse pressures, between cognitively normal, normotensive post-menopausal women who were or were not using HRT.

Methods: Data was obtained from the Banner Sun Health Research (BSHRI) Brain and Body Donation Program (BBDP) database. Two-hundred and eleven cognitively unimpaired female participants between the ages of 50 and 85 completed measures of verbal memory (Rey Auditory Verbal Learning Test version II [AVLT] and WMS Logical Memory) and executive functioning (Trail Making Test Part B [TMT-B]) as part of their annual neuropsychological testing visit. Participants were grouped based on whether they reported use of estrogen or testosterone treatment (HRT, n=68) or "no HRT" (n=143). Further, the sample was mainly White (>96%). The Mann-Whitney u-test was used to analyze group differences on each verbal memory and executive functioning measures as well as on MAP and pulse pressure. Spearman's rho was used to assess the associations between MAP, age, and cognitive measures.

Results: Age (M=73.27, SD=7.05) and education (M=15.37, SD=2.45) did not differ significantly between the HRT groups. There was no significant difference between those on or not on HRT in verbal memory and executive functioning abilities (p=0.30-0.97). The HRT group had significantly lower MAP values (p=0.002), and there was no correlation between MAP and age (p=0.11). MAP did not correlate with measures of verbal memory and executive functioning (p=0.10-0.97).

Conclusions: HRT status was not associated with verbal memory or executive functioning, however those in the HRT group did have significantly lower MAP levels. This is consistent with other studies that suggest HRT may protect the arterial wall function (Wharton et al., 2014). While this study did not show an association between HRT and cognition, it is possible that HRT's cardio-protective effect may have indirect benefits toward maintaining cognitive function.

The current study has noteworthy limitations. First, the sample size was limited and lacked generalizability. Additionally, the potential correlation of initiation and duration of HRT and its effect on cognition was unknown. Future research should examine the effect of duration of HRT on other aspects of cognition and cardiovascular health with a larger, more diverse sample.
CORTICAL THICKNESS PREDICTORS OF MOTOR TASK VARIABILITY IN THE ALZHEIMER’S DISEASE SPECTRUM. Schack K, Malek-Ahmadi M, Duff K, Koppelmans V, King JB, Su Y, Schaefer SY. Arizona State University; University of Arizona College of Medicine – Phoenix; Oregon Health Sciences University; Layton Aging and Alzheimer’s Research Center; University of Utah; Arizona Alzheimer’s Consortium.

Background: Volumetric magnetic resonance imaging (MRI) data has been associated with motor task performance for cognitively unimpaired (CU), Mild Cognitive Impairment (MCI), or probable mild Alzheimer’s Disease (AD) individuals. The current study expanded on these findings by determining how regional measures of cortical thickness predict motor task performance.

Methods: One hundred and six older adults were recruited from a cognitive disorders clinic or through the community in the Salt Lake City, UT metropolitan area between 2018 and 2022. Participants were classified as either CU, MCI, or mild AD based on ADNI criteria. Structural MRI measures were obtained using the ADNI protocol, and cortical thickness measures were obtained using FreeSurfer 6.0. All participants completed a complex motor task that required them to use their non-dominant hand to sequentially place beans into a series of cups using a spoon. Task performance was recorded as trial time (seconds) where lower values indicate better performance and the intrasubject standard deviation (ISD) of performance from four trials was used as the primary measure for each subject. Regression tree analysis was used to derive a constellation of cortical gray matter thickness measures that best predicted age-adjusted motor task ISD. Receiver operator characteristic (ROC) analyses were also used to determine how well the MCI and AD cases could be differentiated from the CU cases.

Results: The regression tree model yielded cortical thickness measures from temporal(fusiform gyrus, entorhinal cortex), parietal (rostral anterior cingulate), frontal (frontal pole, isthmus cingulate), and occipital (lateral occipital) regions that best predicted the motor task ISD. ROC analyses yielded AUC = 0.65 (CI = 0.53 - 0.77) for CU vs. MCI, AUC = 0.78 (CI = 0.67 - 0.90) for CU vs. AD, and AUC = 0.70 (CI = 0.60 - 0.80) for CU vs. MCI + AD.

Conclusions: These findings were consistent with those previously found, which suggest that cortical regions associated with learning (temporal), executive function (frontal), and visuospatial (parietal and occipital) function may underlie motor task performance in the AD spectrum. In particular, the fusiform gyrus features prominently in these and our prior results which may indicate an important role in mediating motor task performance. Further studies using function imaging methods are needed in order to better characterize the network.
DEVELOPING A MOTOR LEARNING TEST AS AN EQUITABLE APPROACH TO SCREENING HISPANIC/LATINO OLDER ADULTS FOR PRECLINICAL ALZHEIMER’S DISEASE. Schaefer SY, Hooyman A, Reed A, Ryan L, Huentelman M. Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.

Background: In the United States, Hispanic/Latino older adults are 1.5 times more likely to develop Alzheimer’s disease (AD) than non-Hispanic White older adults, yet they are excluded from AD preclinical/prevention trials at nearly twice the rate of non-Hispanic White participants, often for failing to meet the cognitive inclusion criteria. Notably, ~95% of participants in AD drug trials are non-Hispanic White. The disproportionate rate of excluding Hispanic/Latinos from AD trials is consistent with the fact that many cognitive tests show worse diagnostic accuracy of Mild Cognitive Impairment (MCI) and dementia for Hispanic/Latinos, even with normative data. Thus, there is an urgent need for equitable and appropriate tools for early AD screening. To meet this need, we have developed a simple procedural test of motor learning that generalizes across patient demographics. Unlike other cognitive tests, it is not affected by sex and educational attainment. Our prior work has validated our test in patients with MCI and AD, showing that less motor learning is associated with greater cortical amyloid burden and hippocampal atrophy. Our test can discriminate AD dementia from MCI, and can predict functional decline over one year in patients with MCI. The purpose of this preliminary study was to test for differences between Hispanic/Latino and non-Hispanic White participants to ensure equity across ethnicities.

Methods: 93 non-Hispanic White participants (mean±SD age: 63±8.3; 81 F) and 12 Latino participants (mean±SD age: 62±5.9; 12 F) completed our motor learning test, a verbal memory test (paired associates learning) and a simple visual reaction time test (svRT). We leveraged the ongoing MindCrowd online cohort for this study; thus all participants completed all tests remotely and unsupervised. To examine if there were differences in test performance based on ethnicity, Hispanic/Latino participants were matched with eligible non-Hispanic White participants from the sample based on age, sex, and highest level of education completed. Separate linear models for motor learning, memory and attention tests were used with the independent variable of ethnicity. Effect sizes (calculated as Cohen’s d) for each outcome were then reported for each test.

Results: Matching between Hispanic/Latino and non-Latino White participants was successful. In this pilot sample, there was no statistically significant difference for either the motor learning (p = .85) or paired associates learning (p = .86) between groups. There was, however, a significant difference between groups for the svRT (p = .0008). Effect size estimates for the motor learning and paired associates learning task were near zero (motor learning d = .08 and PAL d = .07). The effect size estimate for the svRT was 1.58, which is generally accepted as “very large.”

Conclusions: We acknowledge that these results are very preliminary, but they provide initial evidence that our motor learning test may be stable across ethnicities. We are underpowered, however, and more data are needed to test our hypotheses. We are encouraged by the fact that 12% of participants with motor learning test data identify as Hispanic/Latino, providing promising recruitment as the latest MindCrowd cohort continues to grow. Our long-term goal is to develop tools to improve minority health and eliminate health disparities in preclinical AD screening.

Background: Age-related changes in human brain may contribute to the development of age-related neurodegenerative diseases. It may be possible to estimate “brain age” from magnetic resonance imaging (MRI) and the difference between a person’s brain and chronological age, \( \Delta \text{age} \), reflecting whether a person’s brain has been aging faster or slower than their chronological age. Deep Learning Models typically regress age on imaging features, leading to systematic biases associated with regression to the mean (RTM), including overestimation of brain age in younger persons and underestimation in older persons. We estimate brain age from a person’s MRI as a multi-class classification problem and developed deep learning model to estimate brain age free from RTM bias.

Methods: Two 3D ResNet-18 models were implemented: regression and multi-class classification. We transform the task of predicting age as continuous variable to predicting probabilities of discrete age values where age is discretized to closest integer values. Both models were trained on 7,372 T1-weighted MRI scans of 5,848 cognitively normal participants (age: 8-95 years) from public data sources (IXI, ICBM, ABIDE, NACC and OASIS). We create train, validation, and test set in ratio 80:10:10 with matching age distribution. Mean squared error is used as loss function in training regression model. Whereas in the classification model, we introduce two loss terms in addition to standard cross-entropy loss: (1) minimizing the difference between mean (\( \Sigma c \cdot pc \)) of expected age and the actual age, and (2) minimizing variance (\( \Sigma (c\text{-mean})^2 \cdot pc \)), where \( pc \) is probability sample belonging to class \( c \).

Results: The regression model achieved MAE=3.93 years and \( R^2=0.90 \) on unseen test set whereas classification model achieved MAE=2.41 and \( R^2=0.96 \) on same test set. We observe significant decrease in systematic bias using the classification model - for younger (age<30) and older (age>70) subsets, average \( \Delta \text{age} \) improved from 3.17 to 0.2, and from -2.49 to -0.97 respectively (Figure1).

Conclusions: Our proposed classification model with improved loss function to predict brain age from imaging features eliminates systemic bias present in traditional regression approaches and also improves performance by a significant margin. This model can be used more reliably to study age-related alterations in brain and AD-related deviations from natural aging.

**Background:** Multiple amyloid tracers with varying characteristics pose a significant challenge to standardized interpretation and quantification of amyloid PET measurements. We previously demonstrated that a deep learning based 2D residual inception encoder-decoder network (RIED-Net) architecture improved harmonization of florbetapir (FBP) and PiB PET. However, 2D networks fail to capture spatial information among image slices and 3D networks with more parameters require larger datasets and powerful computation for training. Here, we investigate the performance of a 2.5D approach to further improve harmonization preserving spatial information.

**Methods:** 92 PiB-FBP image pairs from Open Access Series of Imaging Studies (OASIS) were processed using established pipelines to extract regional standard uptake value ratios (SUVRs), mean cortical SUVRs (mcSUVRs), and SUVR images. A 2.5D U-Net model with residual connections was implemented to learn the nonlinear mappings from the image pairs. Input to the network is a stack of 3 adjacent FBP slices along a particular view, providing extra spatial information about volumetric data. The output of network is a stack of corresponding 3 PiB slices. Multi-slice output avoids averaging/blurry effects common in traditional 2.5D approaches. 10-fold cross-validation was implemented on axial, coronal and sagittal views separately to generate synthetic PiB SUVR imaging from FBP data. The average synthetic PiB image from axial, coronal and sagittal views was used for performance evaluation. Correlation was evaluated between the virtual PiB mcSUVR derived from imputed PiB vs. the real PiB mcSUVR and voxel-wise between the imputed vs. real PiB SUVR images.

**Results:** The agreement of mcSUVR improved from r=0.90 between PiB and FBP to r=0.95 between synthetic and real PiB SUVR images (p<0.0001) in cross-validation dataset. Additionally, imputed PiB SUVR images were visually more similar to real PiB SUVR images than FBP. Voxel-wise correlation improved from 0.88 to 0.93 (p<0.0001).

**Conclusions:** Our proposed 2.5D Residual U-Net for synthetic imaging was able to learn voxel-wise nonlinear associations between FBP and PiB images. The model trained in 2.5D approach with additional spatial information, was able to significantly improve agreements of amyloid burden measurement from two tracers and generate PiB SUVR images that are visually more similar to real PiB SUVR images than FBP.
ASSOCIATIONS BETWEEN NEUROPSYCHIATRIC SYMPTOMS AND PATHOLOGY IN
NEUROPATHOLOGICAL COHORTS OF ALZHEIMER’S DISEASE, ALZHEIMER’S DISEASE
WITH LEWY BODIES, AND DEMENTIA WITH LEWY BODIES. Shakir N, Tremblay C, Zhang N,
Adler CH, Belden CM, Mehta S, Shill HA, Driver-Dunckley E, Atri A, Beach TG, Serrano G,
Choudhury P. Banner Sun Health Research Institute, University of Arizona; Mayo Clinic College
of Medicine; Banner Alzheimer's Institute; Barrow Neurological Institute; Brigham and Women's
Hospital; Harvard Medical School; Arizona Alzheimer’s Consortium.

Background: Neuropsychiatric symptoms (NPS) are frequent in Alzheimer’s Disease dementia
(ADD), but a higher NPS burden is found in dementia with Lewy bodies (DLB). Lewy body (LB)
pathology frequently co-occurs with AD pathology and may not meet neuropathological criteria
for DLB (ADLB). Previous studies have shown that both ADLB and DLB cases have faster
cognitive and/or functional decline compared to AD. However, the difference in NPS severity over
disease course and survival in these pathological subgroups is not well understood. We
investigated changes in NPS severity over time using the Neuropsychiatric Inventory-
Questionnaire (NPI-Q), comparing neuropathologically defined cohorts of AD (without LB), ADLB,
DLB, and controls.

Methods: Cases from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND)
with a final neuropathologic diagnosis of DLB (+/- AD co-pathology; n=65), ADLB (n=89), AD
(without LB; n=140), and controls (no neuropathological diagnosis; n=82) were included.
Total NPI-Q (scores ranging from 0-36) at time of enrollment and within 2.5 years of death were
calculated for all groups. Statistical analysis utilizing ANCOVA (adjusting for age, sex, baseline
MMSE, and cognitive symptom duration) with pairwise comparisons and Kaplan-Meier curves
were completed.

Results: Age at onset of cognitive symptoms was not different between pathological groups. NPI-
Q scores at enrollment were highest in ADLB (7.33 +/- 4.85), higher (p<0.001) than DLB (5.10 +/- 3.37),
AD (4.54 +/- 3.63), and controls (1.78 +/- 1.70). At final evaluation, NPI-Q scores were
highest in DLB (10.04 +/- 6.28), followed by ADLB (8.0 +/- 4.68) and ADD (7.61 +/- 5.05) when
compared to controls (2.78 +/- 3.97) (all p<0.001). DLB and AD demonstrated significant
increases in NPI-Q severity during follow up (p<0.001). AD had longer survival times (5.8 years)
compared to ADLB (4.0 years) and DLB (3.9 years). Subjects with NPS had a shorter median
survival time (3.4 years) compared to subjects without NPS (6.5 years; p=0.002).

Conclusions: The presence of Lewy body co-pathology in Alzheimer’s disease, in ADLB cases
that do not meet neuropathological criteria for DLB, results in more severe NPS earlier in the
disease course, while DLB show more severe NPS prior to death. This suggests that diffuse
neocortical LB pathology is not the major driver of either NPS.
REPRODUCTIVE HORMONE LEVELS AND BRAIN-BASED MARKERS OF NEURODEGENERATION IN ALZHEIMER'S DISEASE. Solis A, Barajas J, Ofori E. University of Texas, El Paso; Arizona State University; Arizona Alzheimer’s Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in older adults. With the aging population, the number of Americans living with AD is projected to rise dramatically in the coming decades. Identifying early markers of AD pathophysiology is crucial for developing preventive interventions. Reproductive aging and hormonal changes have been proposed as potential risk factors for AD. This study examined associations between levels of reproductive hormones implicated in reproductive senescence, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and pregnancy-associated plasma protein A (PAPP-A), and early AD neuroimaging measures, such as hippocampal and entorhinal volumes in older men and women.

Methods: Data were analyzed from 470 participants in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) study aged 65 years and older (mean 75.1 years, 179 women and 291 men). Quantitative proteomic data on plasma samples collected from ADNI participants of FSH, LH, and PAPP-A were measured at baseline along with structural MRI, cognitive testing using the MMSE, and cerebrospinal fluid (CSF) tau and Aβ levels. Multiple regression analyses were performed to examine associations between each hormone and AD biomarkers, adjusting for age, sex, education, and APOE-ε4 genotype. Multivariate ANOVA were also computed to examine gender x disease interaction on each hormone.

Results: In adjusted models, higher FSH levels were significantly associated with smaller hippocampal volumes (p<0.001) and entorhinal cortex (p<0.001) volumes, worse MMSE scores (p=0.002), and higher CSF tau (p=0.012). No significant associations were observed for LH or PAPP-A after covariate adjustment. Disease by gender interaction revealed significant linear increase FSH in women, whereas a significant nonlinear relationship was revealed in mean where FSH levels were the highest in subjective memory complaints.

Conclusions: These findings suggest high FSH may be an early marker of AD pathophysiology, demonstrated by its associations with key early neuroimaging measure markers of neurodegeneration and CSF biomarkers. The reproductive aging process could promote AD neurodegeneration through complex hormonal changes. Additional research is warranted to further characterize the role of the hypothalamic-pituitary-gonadal axis in AD pathogenesis.

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

Methods: To investigate these questions, we delivered a single biphasic electrical pulse (pulse width: 0.5 ms) of varied intensities (100-600uA) with a 30s interval between pulses to the CA1 layer in iHC and vHC of anesthetized male F344 young (9 months, n = 1) and old (27 months, n = 1) rats. We simultaneously recorded evoked neural activity along the dorsoventral length of the mPFC using Neuropixels probes. Recordings were obtained from neurons spanning 3.84 mm along the mPFC, including the prelimbic and infralimbic regions (areas 24b and 25). As iHC and vHC projections vary across the different layers of the mPFC, we also compare evoked neural responses across different layers of mPFC in response to HC stimulation – by recording first from layer II/III and then from layer V in mPFC. Stimulating both the iHC and vHC, we observed responses in the mPFC at only very specific depths across all stimulation magnitudes for a given rat.

Results: The magnitude of LFP, however, was higher with vHC compared to iHC stimulation at the same stimulus intensity. Furthermore, the slope of the maximum LFP response increased and the response time decreased with increasing magnitude of stimulus Our preliminary findings allow for a comparison of the effect of hippocampal axonal input, monosynaptic or otherwise, along the dorsoventral length of the mPFC and connectivity changes with respect to age.

Conclusions: The increased LFP response time from stimulus in aging suggests a differential effect of anesthesia with age on the HC to mPFC synaptic connectivity. Our future analysis will further investigate layer and regional differences within the mPFC on LFP and single-unit activity with respect to HC stimulation.

Background: Down Syndrome (DS) and Alzheimer’s disease (AD) include cholinergic neurodegeneration which parallels cognitive decline. Triplicated genes in DS are thought to play a role in basal forebrain cholinergic neuron (BFCN) pathology; one avenue to assess triplicated genes’ role is to normalize their expression in DS mouse models by stereotaxic injection of adeno-associated viruses (AAVs) carrying silencing constructs such as short hairpin mRNA (shRNA). However, stereotaxic surgeries have drawbacks particularly when targeting areas lying deep within the brain. The introduction of the AAV-PHP.eB serotype, which can cross the blood-brain-barrier when introduced into peripheral vasculature, has been shown to vary in efficiency depending on mouse background. Here, we investigated tropism of the AAV-PHP.eB serotype in the Ts65Dn mouse, the most commonly used DS mouse model (Jax #005252). We then used AAV-PHP.eB to assess our ability to globally modulate expression of intersectin 1 (ITSN1), a protein triplicated in DS that may relate to BFCN dysfunction and memory impairments.

Methods: We retro-orbitally injected three-month-old trisomic Ts65Dn mice (3n; n = 14-16, balanced for sex) and disomic littermate controls (2n; n = 18-20, balanced for sex) with 2.9x10^10 vg of either AAV-PHP.eB-U6-scramble-GFP (AAV-scrmb; control) or AAV-PHP.eB-U6-shITSN1-GFP (AAV-shITSN1). Mice were behaviorally tested at 7 months and euthanized at 8 months followed by tissue collection. Reporter expression was visualized with anti-GFP antibody in 50μm coronal sections, and we assessed knockdown of ITSN1 via immunoblot.

Results: Mice injected AAV-shITSN1 showed significant effects of ITSN1 knockdown, including increased resting tremors, decreased motor performance in trisomic mice, increased latency in the radial arm water maze – suggesting impaired spatial reference learning and memory – and decreased brain weight. However, knockdown efficiency varied by brain region assessed at the tissue level, with the cerebellum appearing to be most affected.

Conclusions: We demonstrated successful CNS tropism of AAV-PHP.eB into the Ts65Dn mouse model, with 2.9x10^10 vg of intravenous AAV leading to expression throughout key brain regions affected in DS and AD five months following injection. As this expression appears variable, further optimization of virus titer and cell-specific targeting using less ubiquitous promoters is warranted. Overall, the AAV-PHP.eB serotype remains an intriguing alternative to viruses needing stereotaxic surgery for delivery, allowing modulation of genes triplicated in DS to investigate their mechanistic role in neurodegeneration both molecularly and behaviorally.
Background: Cholesterol dysregulation is a well-documented factor involved in the pathophysiology of Alzheimer’s Disease (AD). APOE4, which is involved in cholesterol transport, is recognized as the strongest genetic risk factor for late-onset AD. In a previous study using clinical data, we showed that exposure to statins, a first-line cholesterol lowering therapeutic, was associated with a reduced risk of developing AD. Another study showed the risk reduction associated with statins was greater in APOE4 carriers. Although the effects of statins in the periphery are well documented, the mechanisms by which statins act in the brain remain poorly understood.

Methods: This study aimed to identify potential mechanisms by which statins impact AD pathology at a cellular level and the different response by APOE genotype. Humanized APP/APOE3 and APOE4 mouse neurons and astrocytes were co-cultured and treated with vehicle or atorvastatin at clinically relevant concentrations. Metabolic flux analysis was used to determine the impact of statins on mitochondrial bioenergetics and dynamics. Multi-electrode array (MEA) was used to conduct electrophysiological recordings on hippocampal neurons. Lipid droplet burden in astrocytic cells was determined using LipidTOX staining and confocal microscopy. qPCR and Western Blot were used to determine the expression of key proteins involved in cholesterol transport.

Results: In this study, hippocampal neurons treated with atorvastatin in the presence of astrocytic cells induced a significant increase in the number of spikes and spike frequency, as well as the number of bursts and number of spikes within a burst. In contrast, in the absence of astrocytes atorvastatin exposure in neurons did not exhibit a significant difference compared to vehicle. Electrophysiological properties were increased in a dose-dependent manner and the effect was greater 24-hours following treatment. Atorvastatin also increased astrocyte mitochondrial respiration whereas it did not in neurons or in neurons co-cultured with astrocytes.

Conclusions: Outcomes of these analyses indicated that atorvastatin acts primarily on astrocytes. Specifically, atorvastatin increased mitochondrial respiration in astrocytes and increased synaptic activity on neurons which was astrocyte dependent. These results provide evidence of a neuroprotective role of atorvastatin by regulating lipid metabolism deficits in a cell-specific manner.
JUVENILE FEMALE MICE DEMONSTRATE INCREASED MOTIVATION AND ATTENTION COMPARED TO MIDDLE-AGED ANIMALS IN A PAIRWISE VISUAL DISCRIMINATION TASK.
Truong V, Bowser S, Verpeut J. Arizona State University; Arizona Alzheimer’s Consortium.

Background: Dementia-related illnesses are a proliferating concern for the healthcare industry as the population ages. While many studies track the rate of cognitive decline in later stages of dementia, there has been little research on rates of decline during early dementia. Determining differences in early cognitive decline between males and females will allow for better individualized healthcare and increased understanding of how cognition wanes across the lifespan. Additionally, focusing on sex differences is imperative to confirm whether neuroprotective hormones, such as estrogens and androgens, affect cognitive decline before and during the onset of dementia (Bimonte-Nelson, et al., 2021). We hypothesized that juvenile, postnatal day 21 (P21) female mice would exhibit equal performance to males, but would undergo less drastic cognitive decline than males into middle-age.

Methods: To test cognition changes across the lifespan, both male and female C57Bl/6J juvenile (P21) and middle-aged (10 months old) mice (n = 12 per group) were assessed using a pairwise visual discrimination task. During this task, animals learn to associate the choice of one shape with a reward of sweetened condensed milk. After 10 days, the correct shape is switched to analyze reversal learning. Animals were recorded during all components of the task to assess locomotion, latency, and non-task related behaviors. To analyze possible relationships between cognitive-related neural structure and cognitive behavior, a subset of mice (n = 3 per group) were assessed for changes in dendritic structure complexity and spine number.

Results: We found that while juvenile male and female mice were able to discriminate between two shapes equally, female mice, regardless of age, were faster to initiate each trial (p < 0.01) and choose an image (p < 0.001). Juveniles initiated and responded faster to trials during the early stages of shaping (p< 0.05). In addition, juveniles demonstrated significantly more correct choices during visual discrimination (p < 0.05), but no age differences were found for reversal learning.

Conclusions: This current work establishes age-related changes in both males and females on the visual discrimination task, a translatable task to humans, which will be used to quantify changes in neural pathology and brain structure in future studies.

Background: Dysregulation of inflammatory processes is a hallmark feature of Alzheimer’s disease (AD). Previous findings from our group demonstrated upregulated immune transcripts in the humanized APOE (hAPOE) mouse model that were related to T lymphocyte expression, microglial activation, and interferon signaling. These findings were translationally validated in the human AD brain and identified sex differences in inflammatory regulators during midlife aging. Based on this, we hypothesized that 1) increased peripheral expression of the pleiotropic cytokine interferon gamma (IFN-γ) during female midlife aging may induce CNS neuroinflammation 2) IFN-γ driven neuroinflammation is modulated by APOE genotype. With this study we test if intraperitoneal administration of peripheral IFN-γ induces genotype-dependent neuroinflammatory events in the hAPOE ε3/3 and hAPOE ε4/4 mouse brain.

Methods: To evaluate the role of IFN-γ in female midlife aging and AD risk, female hAPOE mice were intraperitoneally treated with recombinant IFN-γ for 9 days during midlife. Inflammatory profiles were obtained using 1) multi-color flow cytometry to assess microglial reactivity, phagocytosis, oxidative stress, and the presence of lymphocytes 2) Meso-scale Discovery ELISA assays to quantify β-Amyloid (Aβ) 40, Aβ-42, and inflammatory cytokine levels in plasma and cortex 3) targeted quantitative RT-PCR to determine immune RNA transcript levels in hippocampus.

Results: IFN-γ treated animals exhibited upregulation of markers that perpetuate inflammation including plasma cytokine expression of TNF-α (p=0.003), IL-2 (p=0.0.045), IL-10 (p=0.001), and IFN-γ (p=0.010). APOE genotype-dependent immune response was detected in brain T lymphocytes (p=0.020) and activated microglial phagocytosis (p=0.040). Plasma Aβ-40 levels were increased in hAPOEε4/4 (p=0.013) and a reduction in the Aβ 42:40 ratio was identified in IFN-γ treated mice (p=0.006) consistent with the human AD prodrome. IFN-γ treated mice exhibited a hippocampal transcriptomic profile consistent with inflammatory aging.

Conclusions: Activation of interferon-γ signaling during midlife induced APOE genotype-dependent response in the CNS. These results support further investigation of the interaction between APOE genotype and exacerbation of neuroinflammation in female midlife aging. Precision immune therapeutic strategies that target peripheral inflammation during early midlife aging have the potential to reduce risk of AD.

**Background:** The hippocampus is identified as crucial for declarative memory and is an early site for pathologic changes related to AD. Most prior work has focused on assessing volume changes in the hippocampus in T1-weighted MR images as an early marker for dementia. There are molecular and cellular changes that are expected to precede volume loss that are not captured with conventional volumetric MRI techniques.

In recent years, there has been an increased interest in incorporating quantitative imaging into clinical and research MRI protocols to map parameters associated with molecular or cellular changes in tissue due to pathology. A major limitation of this approach is the need for acquisition of data at several time points for accurate parameter estimation, resulting in unacceptable scan times (sometimes hours) when spatial and temporal resolution are paramount.

In this work we leverage on quantitative MRI technology for rapid T1 and T2 mapping developed at the University of Arizona to obtain high-resolution parameter maps of the hippocampus. The goal is to detect changes in the white and gray matter in the hippocampus in subjects with, or at risk of, cognitive impairment.

**Methods:** Two novel pulse sequences, developed at the University of Arizona, RADTSE and IR-RADGRE, were adapted for high-resolution T2 and T1 mapping of the hippocampus at 3T. These yielded high resolution (0.47x0.47x2 mm) anatomical images and corresponding T2 or T1 maps in 6-7 min per sequence. Conventional MPRAGE (1mm isotropic) and 2D high-resolution T2-weighted (0.47x0.47x2 mm) anatomical imaging data as well as T2 (RADTSE) and T1 (IR-RADGRE) mapping data covering the left and right hippocampus were acquired in 12 subjects. In 10 of the subjects, data were acquired at two time points to assess reproducibility of the T2 and T1 mapping techniques. Cognitive testing was also performed in the subjects. RADTSE and IR-RADGRE data were processed offline using an iterative algorithm developed in-house to generate contrast images (TE or TI images) from which T1 and T2 maps were generated. ROIs analysis is used to assess reproducibility and to compare data between subjects.

**Results:** The RADTSE and IR-RADGRE pulse sequences yielded high-resolution images at multiple contrast (12 TE time points for RADTSE and 32 TI images for IR-RADGRE). The quality of the contrast images and maps was excellent and allowed depiction of the hippocampus anatomical features.

Our initial analysis shows promising results in identifying differences in T2 and T1 between a subject with pathology (e.g. carotid artery disease) compared to normal volunteers. While the differences between the subject with pathology and normal volunteers were not seen in the anatomical images, the quantitative maps exhibited remarkable differences. This shows the promise of the T2 and T1 mapping techniques to quantify pathological changes beyond volume loss. Analysis of the 12 subject data set is underway.

**Conclusions:** We are presenting two novel techniques for high-resolution in-vivo T2 and T1 mapping of the hippocampus. Our preliminary results show the potential of these quantitative techniques to characterize changes in the hippocampus that may precede changes in volume. Analysis is underway to assess the reproducibility of the quantitative techniques and to compare results between normal and subjects with, or at risk of, cognitive impairment.
TRANSMEMBRANE PROTEIN 184B (TMEM184B) PROMOTES EXPRESSION OF SYNAPTIC GENE NETWORKS IN THE MOUSE HIPPOCAMPUS. Wright EB*, Larsen EG*, Hart HR, Roessle CM, Bhattacharya MRC. University of Arizona; Arizona Alzheimer’s Consortium.

**Background:** In Alzheimer’s Disease (AD) and other dementias, hippocampal synaptic dysfunction and loss contribute to the progression of memory impairment. Recent analysis of human AD transcriptomes has provided a list of gene candidates that may serve as drivers of disease. One such candidate is the membrane protein TMEM184B. To evaluate whether TMEM184B contributes to neurological impairment, we asked whether loss of TMEM184B in mice causes gene expression, focusing on the hippocampus.

**Methods:** Because one major risk factor for AD is age, we compared young adult (5-month-old) and aged (15-month-old) wild type and Tmem184b-mutant mice to assess the dual contributions of age and genotype.

**Results:** TMEM184B loss altered expression of pre- and post-synaptic transcripts by 5 months and continued through 15 months, specifically affecting genes involved in synapse assembly and neural development. Wnt-activated enhancer elements were enriched among differentially expressed genes, suggesting an intersection with this pathway. Few differences existed between young adult and aged mutants, suggesting that transcriptional effects of TMEM184B loss are relatively constant.

**Conclusions:** Taken together, our data suggest that TMEM184B is required for proper synaptic gene expression and anxiety-related behavior and is more likely to be linked to neurodevelopmental disorders than to dementia.
EFFECT OF APOE ON WHITE MATTER MICROSTRUCTURE USING DTI IN COGNITIVELY NORMAL OLDER ADULTS. Yamada N, Goradia D, Malek-Ahmadi M, Devadas V, Protas H, Sohankar J, Luo J, Reiman EM, Su Y. Banner Alzheimer’s Institute; Arizona State University; University of Arizona College of Medicine, Phoenix; University of Arizona; Arizona Alzheimer’s Consortium.

Background: Alzheimer's disease (AD) susceptibility has been linked to the Apolipoprotein E (APOE) gene which primarily deals with lipid transportation in the brain and is thought to impact white matter (WM) tract integrity. The presence of the APOE4 allele is thought to increase the risk of Alzheimer’s disease development, while APOE2 is thought to provide protection against the disease. Previous studies utilizing diffusion tensor imaging (DTI) have revealed a widespread lower Fractional Anisotropy (FA) in the brains of individuals with the APOE4 allele. Despite these findings, the mechanism behind APOE’s influence on white matter is not well understood, and there has been limited research investigating the WM microstructure in APOE2 populations. Here we investigate the effects of APOE2 and APOE4 alleles on WM tracts using DTI and Tract-Based Spatial Statistics (TBSS).

Methods: In this study, we examine a cohort of cognitively normal adults (n=281) divided into 5 groups based on the presence of APOE alleles: 4/4 n=54, 3/4 n=66, 2/4 n=17, 2/3 n=46, 3/3 n=98. Homozygous APOE2 group comparisons were not included due to low numbers of scans. DTI protocol: Scanner: GE Discovery 750, Head coil: 32 ch, TR: 9050 ms, TE: 57.2 ms, Resolution: 1.37x1.37x2.7 mm, Direction 46, B-Values: 0 and 1000. Preprocessing was performed using DTIPrep, a software package designed for the preprocessing and quality assessment of DTI data by detecting and correcting artifacts, improving the reliability and accuracy of subsequent scan analyses. DTI data was fit using weighted-linear fitting using FSL-FDT. To perform analysis, voxelwise comparisons of the genetic groups were carried out using Tract-Based Spatial Statistics (TBSS) which projects all subjects’ FA data onto a mean FA tract skeleton before applying voxelwise cross-subject statistics.

Results: The results of the 8 TBSS comparisons of FA are as follows: APOE2/3 > APOE3/3, APOE2/3 > APOE3/4, APOE2/3 > APOE4/4, APOE2/4 > APOE3/3, APOE2/4 > APOE3/4, APOE2/4 > APOE4/4, and APOE3/4 > APOE4/4. We noted that widespread lower FA values were found in APOE4 carrier comparisons. In addition, the results showed higher FA values in carriers of APOE2 allele relative to non APOE2 carriers. All group comparisons resulted in a p < 0.05 before correcting for multiple comparisons. After correction, the comparison APOE2/3 (n=48) > APOE4/4 (n=54) remained significant.

Conclusions: Our results suggest that the presents of APOE4 allele has a detrimental effect on WM microstructure integrity. Our findings also suggest that the presence of the APOE2 allele may confer a protective effect on tract integrity, as evidenced by higher FA values found in the APOE 2/3 cohort when compared to both the APOE 4/4 and 3/3 groups. Previously, this relationship has only been shown using multi-shell diffusion imaging models and not with DTI. Additionally, with future evaluations of measures such as mean, radial, and axial diffusivity, as well as T1/T2 ratio may strengthen the relationship of the effect of APOE on WM tracks of the brain.

Background: Progranulin (PGRN) deficiency and lysosomal dysfunction have been independently linked to Alzheimer disease. Several lines of evidence suggest that there is a link between PGRN and lysosomal function. PGRN is a pleiotropic signaling molecule whose activity depends upon differential proteolytic processing. Depending on how PGRN is processed, the resulting products generated can regulate inflammation, lysosomal function, and/or growth. Not only is the lysosome a site of PGRN processing, the resulting PGRN subunits promote the function of several lysosomal proteases. In addition, in models of PGRN insufficiency, increasing the levels of PGRN restores lysosomal function and reduces inflammation. Thus, this work investigates the link between lysosomal function and PGRN synthesis and processing.

Methods: Experiments utilized the SW13 human adrenal carcinoma cell line that exists in two epigenetically distinct subtypes. PGRN processing and production were analyzed by both ELISA and immunoblotting using antibodies that bind to characterized epitopes. Live cell measurements of pH were performed using the ratio metric DND 160 fluorescent dye. Lysosomal proteolytic assays were performed by measuring fluorescent intensity produced after proteolysis of an endocytosed substrate. Lysosomes, purified by ultracentrifugation, were analyzed by lipidomic and proteomic mass spectrometry.

Results: Results suggest that differential processing of PGRN occurring within each SW13 subtype is correlated to both differences in rate of growth and lysosomal pH. Specifically, the slow-growing, metastatic subtype produces higher levels of PGRN and expresses increased levels of matrix metalloproteinases (MMP) 2/9, compared to the more proliferative subtype. Interestingly, when PGRN is exogenously added to the culture medium, the proteases expressed by each subtype influences whether PGRN will be processed into a product(s) promoting growth or a product(s) promoting inflammation. We also show that the pH of lysosomes in each subtype differs, with the slowly growing, metastatic subtype having a significantly higher pH than the proliferative subtype. This result suggests that lysosomal proteases, which have increased activity at a more acidic pH, may be responsible for producing a PGRN product(s) that promotes growth in the proliferative subtype, while the more alkaline lysosomal pH of the slowly growing subtype does not.

Conclusions: Ongoing experiments address the possibility that decreasing lysosomal pH may shift the processing of PGRN, influencing the biological activities associated with this versatile signaling molecule. As mutations in the PGRN gene are implicated both in dysfunctional lysosomal pH and a variety of neurodegenerative diseases, these results may provide a novel approach to regulate proper intracellular functions to slow or prevent development of disease.

Background: Biomarkers are one of the primary diagnostic tools to facilitate the early detection of Alzheimer's disease. The accumulation of beta-amyloid (Ab) plaques in the human brain is one of the presymptomatic hallmarks of AD. However, current methods to detect Ab pathology are either invasive (lumbar puncture), quite costly, and not widely available (amyloid positron emission tomography - PET) or largely under development (blood-based biomarkers - BBBM). Thus a less invasive and cost-effective approach is demanded.

Methods: Magnetic resonance imaging (MRI) which has been used widely in preclinical AD, has recently shown the capability to predict brain Ab positivity. This motivates us to develop a method, pre-training graph attention convolution, taking MRI to predict Ab positivity. The proposed self-supervised learning architecture refines feature extraction from mesh representation via pre-training and fine-tuning, resulting in more powerful biomarkers for Ab identification. We obtain subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and use our method to discriminate Ab positivity.

Results: Theoretically, we provide analysis toward the understanding of what the network has learned. Empirically, it shows strong performance on par or even better than state of the art.

Conclusions: In summary, our work is the first to use a graph-attention-based deep neural network combined with pre-training and fine-tuning to identify brain amyloid burdens.

Graph attention convolution and pre-training provide a new way of analyzing brain images.

Our method exhibits the robustness and generalizability of a trained model compared with directly training models for classification tasks.

With more data being collected, the gap between direct classification and pre-training could become larger, and the performance drop between validation and test accuracy could be smaller.

Background: Alzheimer's Disease (AD) is characterized by age-dependent cognitive decline and neurodegeneration and is the most common form of dementia in the 65+ aging population in the United States. The pathological hallmarks of AD include the formation and aggregation of amyloid beta plaques and hyperphosphorylated tau proteins leading to failure of critical brain circuit function. Increasing evidence shows that the dorsal hippocampus and medial prefrontal cortex (mPFC) are among the brain regions that are most susceptible to AD pathology. These regions are crucial for learning, memory and spatial navigation and show significant impairment during progression of AD. A novel model of AD was developed by Cohen et al. in 2013 in Fischer 344 rats that express the familial AD human mutant genes: Swedish amyloid cursor protein (APPsw) and presenilin-1 delta E9 (PS1ΔE9).

Methods: The TgF344-AD model results in a comprehensive set of AD-like phenotypes including: 1) progressive amyloid plaque aggregation and formation, 2) endogenous rather than engineered tauopathy leading to the formation of neurofibrillary tangles (NFTs), 3) cognitive decline and 4) gliosis and neuronal loss.

Results: While there has been some characterization of the behavioral status of the TgF344-AD rats, the onset of the behavioral deficit has been roughly determined to be around 9 months in both cross sectional (Cohen et al 2013) and in longitudinal (Berkowitz et al 2018) studies. A more fine-grained month by month analysis of when the behavior begins to change in the TgF344-AD male and female rats has yet to be determined.

Conclusions: The purpose of this study was to identify this transition across several behavioral domains including the hippocampus-dependent spatial version of the Morris water maze task, the medial prefrontal cortex (mPFC)-hippocampus-dependent temporal order recognition (TOR) memory task, and the amygdala-midbrain-dependent elevated zero (EZ) maze task. Six groups (n=65) of male and female TgF344-AD and wildtype (WT) rats at ages 4 months, 5 months, 6 months, 8 months, 9 months, and 10 months of age were tested on the tasks discussed above. Both male and female TgF344-AD rats were comparable in performance to their age-matched WT controls at 4 months, 5 months, 6 months of age on the spatial version of the Morris water maze, the TOR task and on the EZ maze task.

Ongoing testing of male and female TgF344-AD rats at 8 months, 9 months, and 10 months will determine the precise age-of-onset of impairment due to AD pathology across the listed behavioral domains of this study.
Arizona Alzheimer’s Consortium
24th Annual Scientific Conference

Poster Presentation
Abstracts
Background: Alzheimer's disease, a neurodegenerative disorder, is characterized by progressive memory loss, cognitive decline, and impaired communication skills. One significant source of distress for both patients and their loved ones is the loss of personal connections due to the degradation of the patient's unique conversational characteristics. This research project was initiated to create a chatbot with the ability to mimic the conversational style of a specific individual, acting as a digital surrogate, thereby mitigating the impact of Alzheimer's on personal relationships.

The presentation at the conference will offer a more in-depth look at the chatbot demonstration, discussing the intricacies of our methods, the implications of our preliminary results, and the challenges and goals for future stages of this ground-breaking research.

Methods: In this detailed feasibility study, we employed robust machine learning algorithms and natural language processing tools based on the GPT-4 architecture to train and develop a personalized chatbot. The model was trained on a comprehensive dataset comprising one individual's writings, speeches, and other forms of digital communication. This data served as the groundwork for the chatbot's understanding of the individual's specific linguistic patterns, commonly used phrases, perspectives, and known factual information. In addition, the chatbot was designed to consider context and sentiment to create a more authentic conversational experience.

Results: The personalized chatbot successfully simulated the chosen individual's conversational style in our controlled testing environment. Unbiased observers, during blind tests, reported impressive verisimilitude in the chatbot's responses when compared to real conversations with the individual. Notably, the personalized chatbot elicited higher emotional responses and engagement from the observers compared to standard AI conversational models. These results, while promising, represent preliminary findings and require further validation in broader, real-world scenarios.

Conclusions: The preliminary results of our feasibility study and simulation suggest that personalized chatbots may have the potential to alleviate some of the emotional distress associated with Alzheimer's disease for both patients and their families. By preserving the essence of individual communication, these chatbots may provide a sense of familiarity and comfort to those affected. However, there is a clear need for more research and refinement of this model, specifically its testing and validation in larger, real-life family settings. Additionally, ethical concerns around the usage of personal data and the potential psychological implications of these chatbot interactions warrant close scrutiny in future phases of the project.
TOLERABILITY, LIKEABILITY & EFFICACY OF A COGNITIVE TRAINING PROGRAM. Ashish D. Banner Alzheimer’s Institute, Tucson; University of Arizona; Arizona Alzheimer’s Consortium.

**Background:** Patients with mild cognitive impairment (MCI) or early stages of dementia often search for treatments to improve their cognitive and daily functioning or help with managing their deficits. Research suggests that multi-component non-pharmacological interventions provided to patients with caregivers have similar benefits as pharmacological treatments but without any side effects. Previously, we presented about developing a Multicomponent Comprehensive Intervention with Care-partners (MCI-Care) at Banner Alzheimer’s Institute. Here, we present the information about the tolerability, likability, and efficacy of the cognitive intervention.

**Methods:** The cognitive training consists of approximately 20 sessions provided to dyads of patients with MCI or early stages of dementia and their care-partners. The cognitive training program includes three main components:

- Psychoeducation, training, and problem-solving for healthy brain behaviors.
- Psychoeducation, training, and problem-solving for compensatory strategies.
- Psychoeducation and cognitive training addressing attention, processing speed, executive functioning, and memory domains.

A total of 14 patients started the treatment (male=7; female=7) that ranged 49 to 85 years of age. Diagnoses included MCI due to TBI (n=2), Alzheimer’s (n=2), Vascular (n=1), or unclear (n=5) etiologies; or dementia due to Alzheimer’s (n=2), Dementia with Lewy Bodies (n=1), or mixed (n=1) etiologies. At the end of the training, patients completed a brief survey about their experiences.

**Results:** Nine out of 14 patients completed the training. Patients demonstrated improvements in self-reported mood symptoms, quality of life, and self-efficacy. The care-partner reported improvement in patients’ complaints of cognitive dysfunction and functional difficulties, and their own caregiver burden. All patients who completed the treatment found it informative and helped in their daily functioning and patients rated the treatment 4 out of 4, where 4 stands for "very likely" they would recommend this training.

Three patients with MCI did not complete the training after their mood improvement. Two patients with dementia needed more support with caregiving resources.

**Conclusions:** The MCI-Care is best tolerated by patients who do not have significant mood issues or significant need of caregiving resources. The patients liked the intervention and found it helpful. There is some evidence of the efficacy of the intervention. Further research will establish statistical and clinical significance.
BIOINFORMATICS AND MACHINE LEARNING BASED IDENTIFICATION OF POTENTIAL
OXIDATIVE STRESS AND GLUCOSE METABOLISM-RELATED DIAGNOSTIC
BIOMARKERS IN ALZHEIMER DISEASE. Aslam S, Beach T, Serrano G. Banner Sun Health
Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer’s disease (AD) is a devastated neurodegenerative disease, accounting
for 60 to 80% of dementia cases. We do not fully understand AD etiology and pathogenesis but
oxidative stress plays key roles in AD pathogenesis. Glucose metabolism is the main source of
energy for brain and any trouble in its metabolism could lead to neuronal dysfunction. Many
studies described the interplay between glucose metabolism and oxidative stress in AD. We
aimed to find an oxidative stress and glucose metabolism related gene (OSGMG) based
diagnostic feature biomarkers for AD.

Methods: RNA seq data (GSE125583) generated from Brain and Body donation program (BBDP)
cases is retrieved from GEO database (219 AD cases and 70 controls). Glucose metabolism and
oxidative stress genes are collected from MSigDb database and performed the Pearson
correlation analysis to find the common genes of glucose metabolism and oxidative stress related
genes (OSGMGs) with cutoff |R| > 0.3, P < 0.05. Limma package was used to identify the
differentially expressed genes (DEGs) in AD which meet the following criterion: adj.P-value <
0.05. Differentially expressed oxidative stress and glucose metabolism related genes (DE
OSGMGs) were screened by the intersection of DEGs and OSGMGs in R. Kyoto Encyclopedia
of Genes and Genomes (KEGG) pathway enrichment analyses of DE-OSGMGs was run using R
(clusterProfiler). WGCNA algorithm was used to find the co-expressed DE-OSGMGs. Machine
learning algorithms (XGBoost and LASSO) were used to find the diagnostic feature biomarkers
for AD. ROC curve analysis was employed to assess the discriminatory power of diagnostic
feature biomarkers using pROC package of R.

Results: Hundred common genes between oxidative stress and glucose metabolism were
identified as OSGMGs, while 13982 DEGs were found upon the analysis of RNA-seq data
(GSE125583). Then, a total of 57 DE-OSGMGs were identified from the overlapping analysis of
OSGMGs and DEGS, which were further used for downstream analysis. KEGG analysis showed
that the DE-OSGMGs were largely enriched in, glycolysis/gluconeogenesis and carbon
metabolism. Furthermore, 11 candidate co-expressed DE-OSGMGs were found upon the
WGCNA analysis. Finally, five candidate genes (ARPP19, SLC25A12, IGF1, PPARGC1A, PDK1
) were recognized as diagnostic feature biomarkers for AD employing the XGBoost and LASSO
algorithms and ROC analysis (value > 0.7) also showed the discriminatory power of these
biomarkers.

Conclusions: Our study identified molecular mechanisms affected by OSGMGs of AD subjects;
and key genes that could serve as potential diagnostic biomarkers for AD. In the future, we will
validate these biomarkers in biofluids to assess their clinical utility.
THE HUMAN RAP1 AND GFAPε PROTEINS INCREASE γ-SECRETASE ACTIVITY IN A YEAST MODEL SYSTEM. Bae NS, Lewis KN, Carpenter R, Whetzel A, Swanson MJ. Midwestern University; Arizona Alzheimer’s Consortium.

Background: Alzheimer’s disease (AD) is an age-related disorder that results in progressive cognitive impairment and memory loss. Deposition of amyloid β (Aβ) peptides in senile plaques is a hallmark of AD. γ-secretase produces Aβ peptides, mostly as the soluble Aβ40 with fewer insoluble Aβ42 peptides. The rare, early-onset AD (EOAD) occurs in individuals under 60 years of age. Most of the EOAD cases are due to unknown genetic causes, but a subset is known to be due to mutations in the genes encoding the amyloid precursor protein that is processed into Aβ peptides or the presenilins (PS1 and PS2) that process APP. RAP1(TERF2IP) is a telomeric protein that is responsible for maintaining genome stability. As cells replicate/age, its level decreases. It is found in cytoplasm as well as in nucleus. Its role in cytoplasm is unknown. Our study was designed to identify the interacting proteins of RAP1 and investigate its possible role in age-related diseases.

Methods: Identifying the interacting protein of RAP1 was done utilizing a yeast 2-hybrid screen. Interactions of various proteins were verified using in vitro co-immunoprecipitation. We modified and improved a reconstituted γ-secretase system in Saccharomyces cerevisiae to measure the γ-secretase activity levels. Aβ peptide production was measured using ELISA. All interactions were verified by using immunoblotting along with immunofluorescence microscopy techniques.

Results: We have identified GFAPε (glial fibrillary acidic protein-ε) as a protein that interacts with the telomere protection factor RAP1. RAP1 can also interact with PS1 alone or with both PS1 and GFAPε together in vitro. GFAPε coprecipitated with RAP1 from human cell extracts. RAP1, GFAPε and PS1 all colocalized in human SH-SY5Y cells. Using a γ-secretase system reconstituted in yeast, we found that RAP1 increased γ-secretase activity, and this was further increased by the co-expression of GFAPε. However, expression of GFAPε alone was not able to significantly affect γ-secretase activity.

Conclusions: Our data show that the nuclear protein RAP1 has an extratelomeric role in the cytoplasm through its interactions with GFAPε and PS1. RAP1 increased γ-secretase activity, and this was potentiated by GFAPε. Our studies are the first to connect RAP1 with an age-related disorder.

Background: Cerebral white matter rarefaction (CWMR) was considered by Binswanger and Alzheimer to be due to cerebral arteriolosclerosis. Renewed attention came with CT and MR brain imaging, and neuropathological studies finding a high rate of CWMR in Alzheimer disease (AD). The relative contributions of cerebrovascular disease and AD to CWMR are still uncertain.

Methods: Subjects included in this study were volunteers enrolled in AZSAND and its Brain and Body Donation Program ([BBDP]; www.brainandbodydonationprogram.org), at Banner Sun Health Research Institute (BSHRI) in metropolitan Phoenix, Arizona. Subjects for the current study were chosen by searching the BBDP database. We selected cases who had an autopsy and were assessed for CWMR scores in all 4 lobes. As we wished to focus this study on CWMR without an obvious cause, we excluded subjects with grossly apparent infarcts at autopsy as well as those with neuropathologically defined acute or subacute infarcts or hemorrhages, traumatic contusions, or history of traumatic head injury, primary or metastatic brain neoplasms, meningitis, or encephalitis. These exclusions effectively restricted our study to those subjects with idiopathic CWMR, i.e. CWMR without an apparent cause other than advanced age. After these exclusions, 1181 subjects remained who were included for the initial analyses.

Results: Almost all neurodegenerative diseases had more severe CWMR than the normal control group. Multivariable logistic regression models indicated that Braak neurofibrillary stage was the strongest predictor of CWMR, with additional independently significant predictors including age, cortical and diencephalic lacunar and microinfarcts, body mass index, and female sex.

Conclusions: It appears that while AD and cerebrovascular pathology may be additive in causing CWMR, both may be solely capable of this. The typical periventricular pattern suggests that CWMR is primarily a distal axonopathy caused by dysfunction of the cell bodies of long-association corticocortical projection neurons. A consequence of these findings is that CWMR should not be viewed simply as “small vessel disease” or as a pathognomonic indicator of vascular cognitive impairment or vascular dementia.
USING CO-ACTIVATION PATTERN (CAP) ANALYSIS TO STUDY THE DYNAMICS OF RESTING-STATE NETWORKS IN PATIENTS WITH COGNITIVE IMPAIRMENT. Bergamino M, Baxter LC, Caselli RJ, Sabbagh MN, Burke A, Stokes AM. Barrow Neurological Institute; Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

Background: Functional magnetic resonance imaging (fMRI) techniques offer a means to assess connectivity by examining correlations in the temporal patterns of brain activity across different regions. In recent studies, a novel approach called co-activation pattern (CAP) analysis has been proposed to track changes in functional connectivity within specific timeframes during rest. Building upon the methodology outlined by Zhuang et al. (doi: 10.1016/j.neuroimage.2018.01.019), a dominant CAP (d-CAP) set can be generated from multiple clustering runs for each group under the constraint of low spatial similarity between d-CAPS. We applied this method in healthy controls (HCs) and subjects with cognitive impairment (CI).

Methods: This study included 15 HC (age: 74.3±6.5 years; MoCA: 26.0±2.4) and 23 CI (age: 76.9±6.8 years; MoCA: 15.6±6.3). The default mode network (DMN), visual network (VN), and frontoparietal network (FPN) were analyzed by both independent components analysis (ICA) and d-CAPs analysis. ICA was performed by MELODIC (FSL). For the d-CAPs analysis, we employed a custom script developed in R. This analysis involved synthesizing the d-CAPs for each study group and evaluating the switching probability and spatial consistency.

Results: Using ICA, statistical differences in functional connectivity for each network were found between groups. For both DMN and VN, functional connectivity was higher in HC than CI in clusters in the right hemisphere. For the FPN, clusters of lower connectivity in CI were associated with interhemispheric regions. For both groups, the number of d-CAPS was 3 for DMN and 2 for FPN, while 5 and 3 d-CAPS were observed in the VN for HC and CI, respectively. Increased co-activation was observed in HC compared to CI in all three networks, while a small cluster of decreased co-activation was also observed in the VN. Across all three networks, lower switching probabilities were observed in CI compared to HC, while spatial consistency was similar across networks, dCAPs, and groups.

Conclusions: The results of our study revealed significant differences in functional connectivity between HC and CI groups. Specifically, the CI group exhibited lower connectivity compared to the HC group, which is consistent with previous reports of decreased functional connectivity in individuals with AD and MCI. In the HC group, we observed increased co-activation, indicated by large effect sizes, in various brain regions. This finding suggests stronger and more widespread network engagement in the HC participants. In contrast, the CI group exhibited fewer d-CAPs within the VN, indicating a potentially less dynamic network in individuals with CI. Moreover, the reduced switching probability observed in the CI group further supports the notion of decreased network dynamics in this population. Importantly, the spatial consistency and reliability of the identified networks were generally preserved in both the HC and CI groups. This finding suggests that the identified network patterns were consistent within each group and can be reliably detected using resting-state fMRI data.
ASSOCIATIONS BETWEEN BLOOD-BASED BIOMARKERS AND AMYLOID PET MEASUREMENTS IN COGNITIVELY UNIMPAIRED PRESENLIN 1 E280A MUTATION AND NON-MUTATION CARRIERS FROM THE API AUTOSOMAL DOMINANT ALZHEIMER’S DISEASE COLOMBIA PREVENTION TRIAL. Bhargava V, Malek-Ahmadi M, Lopera F, Rios-Romenets S, Londoño N, Aponte C, Quiroz YT, Langbaum J, Tariot P, Su Y, Chen K, Wittner T, Clayton D, Doody R, Reiman EM. University of Arizona College of Medicine, Phoenix; Banner Alzheimer’s Institute; Arizona State University; Translational Genomics Research Institute; Universidad de Antioquia, Medellin, Colombia; Massachusetts General Hospital; Harvard Medical School; Genentech; Arizona Alzheimer’s Consortium.

Background: Blood-based biomarkers have promise in the detection, tracking, and study of preclinical Alzheimer’s disease (AD) and the evaluation of putative prevention therapies. Presenilin 1 (PSEN1) E280A mutation carriers from the world’s largest autosomal dominant AD (ADAD) kindred are virtually certain to develop early-onset dementia in their 40s. Here, we sought to characterize the extent to which baseline plasma pTau181 and pTau217 (indicators of amyloid-mediated tau pathophysiology and tau tangles), glial fibrillary acidic protein (GFAP, an indicator of astrogliosis), and neurofilament light (NFL, an indicator of neurodegeneration) are related to PET measurements of amyloid plaque burden in cognitively unimpaired (CU) PSEN1 E280A mutation carriers from the recently completed Alzheimer’s Prevention Initiative Autosomal Dominant AD (API ADAD) Colombia Trial.

Methods: Baseline data from 249 CU kindred members (166 PSEN1 mutation carriers with average age 37 +/- 5.8 years old and 83 noncarriers with average age 43 +/- 7.5 years old) were included in this analysis. Plasma pTau181, pTau217, GFAP and NFL plasma measurements were characterized on the Elecsys platform using Roche NeuroToolKit immunoassays. Mean cortical-to-cerebellar florbetapir PET standardized uptake value ratios (SUVRs) were used to characterize amyloid plaque burden. Relationships between log-transformed plasma biomarker measurements and PET measurements were characterized using Spearman correlation with and without adjustment for age, sex, and presence or absence of the APOE4 allele. Mediator analysis was further performed to test if the relationships between neuroimaging and plasma biomarkers were mediated by other plasma biomarkers.

Results: Log-transformed plasma pTau181, pTau217, GFAP, and NFL measurements were correlated with PET measurements of amyloid plaque burden (r=0.48, p<0.001; r = 0.17, p = 0.03; r=0.45, p<0.001, and r=0.24, p=0.002; respectively) in PSEN1 mutation carriers. None of the associations was significant in the non-carriers. Correlations remained significant for plasma pTau181 and GFAP after adjustment for age, sex, and APOE4 (p>0.001). Mediation analysis revealed that the relationship between amyloid PET SUVR and GFAP was mediated by ptau181.

Conclusions: Plasma amyloid-mediated tau (pTau181) and neuroinflammatory biomarker (GFAP) measures correlate well with PET measurements of amyloid plaque in CU ADAD mutation carriers. The relationship between PET amyloid SUVR and plasma GFAP is at least partially mediated by plasma phosphorylated tau (ptau181).
FEASIBILITY AND ACCEPTABILITY OF THE STRENGTHENING SKILLS PROGRAM FOR AGING AUTISTIC ADULTS. Braden BB, Matthews N, Gallegos S, Hill E, Cortes Coria S, O'Rourke H, Baxter L. Arizona State University; Southwest Autism Research and Resource Center; Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

Background: Research suggests that autistic adults are vulnerable to age-related cognitive decline, co-occurring mood conditions, and ongoing social challenges. Despite this, supports for autistic adults beyond young adulthood are exceptionally limited. The objectives of this study were to: 1) develop the Strengthening Skills Program (SSP), a multi-component program for autistic adults of all ages to address persistent or worsening cognition, mood, and social challenges, and 2) examine and compare feasibility and acceptability of the SSP to an adapted version of an established adult autism social communication intervention.

Methods: Development was based on focused interviews (5 autistic adults, 30-68 years, 3 male; 4 family/friends selected by the autistic adults), and adaptations from the Mayo Clinic Healthy Action to Benefit Independence and Thinking (HABIT) program for cognitive compensation strategies, Mindfulness-Based Stress Reduction for mood regulation, and the Program for the Education and Enrichment of Relational Skills (PEERS) for social communication. Pilot RCT participants included 42 adults (Age=41.43±13.99 years; 59.5% male) who met criteria on the Autism Diagnostic Observation Schedule 2 and up to one program partner of each participant (i.e., family/friend). Across two cohorts, participants were randomly assigned to three groups: SSP (n = 14), PEERS only (active comparator; n = 14), or delayed treatment control (DTC; n = 14). Random assignment was stratified by age, gender, and presence of a program partner. Both programs were delivered through Zoom. The SSP participants attended 16 weekly 3-hour group meetings that included discussion of cognitive compensation (e.g., habit formation), mindfulness, and social communication strategies adapted from the established PEERS program for young adults. PEERS participants attended 16 weekly 90-minute group meetings with the same adapted social communication strategies as the SSP group. Feasibility was assessed by via attrition and fidelity of implementation. Acceptability was compared between SSP and PEERS via a post-program satisfaction questionnaire.

Results: Fidelity of implementation ranged from 94-100% for SSP (M=99%) and 85-100% (M=97%) for PEERS only, which was not statistically different. Attrition in the SSP group was 36%, and attrition in the PEERS only group was 14%, which was also not statistically different. Composite acceptability scores on the participant satisfaction survey for the SSP were significantly higher than PEERS only [t(19) = 2.21, p = .04]. Themes identified from qualitative responses identified unique benefits of the SSP noting that anyone could benefit from the program and the program facilitated understanding of autism and autistic identity. Both programs had themes of enjoyment/thankfulness, supportive environment, and connection with other group members. Limitations of PEERS only were related to program content and method, whereas limitations of SSP were related to program format.

Conclusions: The SSP for autistic adults across the lifespan has promising feasibility and acceptability as compared to an established program for autistic young-adults. These findings suggest that cognitive compensation and mindfulness strategies that have been used in other aging populations provide added benefit for aging autistic adults. Furthermore, the multi-component approach of the SSP may be beneficial for other aging populations in addition to autistic adults.
EARLY-STAGE PARTNERS IN CARE (EPIC) LIVING ALONE: A VIRTUAL PILOT FOR PEOPLE LIVING ALONE WITH EARLY-STAGE MEMORY PROBLEMS.  


Background: In 2023, 6.7 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: Thirty-one percent (31%) of participants were male and 85% lived outside the state of Arizona spanning from Hawaii to Massachusetts. Their ages ranged from 60 to 87 years (mean=71.3, SD=8.5) and 61.5% had a diagnosis of Alzheimer’s Disease. Preliminary feasibility and acceptability data show that thirteen participants completed all seven sessions and project assessments, and post-intervention perception of benefit and satisfaction survey responses completed by participants showed overall benefit from the intervention. Participants reported EPIC Living Alone helped make them feel more confident in dealing with problems related to memory loss (100%); better prepared to take care of their future care needs (100%); made their life easier (85%); helped them better understand memory loss and its effects (85%); and enhanced their ability to care for themselves (85%). Participants also reported their communication skills had improved (85%), and they acknowledged they felt more confident in communicating with family and friends leading to more fruitful conversations related to future care needs and preferences. Moreover, the intervention helped them feel “less alone” and better able to relate with others who were in a similar situation. 

Conclusions: Findings from this preliminary study of EPIC Living Alone were very promising with participants reporting they benefitted in multiple ways including feeling better prepared for the future. Additional analyses of pre-post outcomes are underway; however, 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).
A MALPIGHIAN TUBULE PHENOTYPE IN PARKIN MUTANT DROSOPHILA MELANOGASTER. Chagolla SM, Pearman K, Call GB. Midwestern University; Arizona Alzheimer’s Consortium.

Background: Parkinson’s Disease (PD) is an age-related neurodegenerative disease that affects millions worldwide. Although the most noticeable symptoms are associated with dysregulation of motor function, non-motor function symptoms are also present and can be debilitating. Mutation of the parkin (park) gene, the Drosophila melanogaster ortholog of the human PRKN gene, can cause many phenotypes that are similar to PD symptoms, including selective loss of dopaminergic neurons, decreased lifespan, and mitochondrial dysfunction. Here, we report a new phenotype in homozygous park25 (a null allele) flies in the Malpighian tubule (MT). The MT is the excretory organ of the fly and thus considered analogous to the kidney. These simple tubules are very small, being essentially cellular monolayers and typically only 3mm in length. The MT is made up of three known cell types, principal cells (PCs), stellate cells and renal stem cells (RSCs).

Methods: MTs from homozygous park25 and control (w1118) Drosophila were dissected in phosphate buffered saline (PBS) at various ages. All samples were fixed with 4% paraformaldehyde (20 min). Stone analysis: Once fixed, MTs were washed 3 times in PBS, 10 min each. MTs were then mounted on a slide in 50% glycerol with a coverslip and imaged using Zeiss Discovery.V8 and Keyence BZ-X700 microscopes. Cell analysis: Once fixed, MTs were washed 3 times in PBS with 0.1% triton X100 (PBT), 10 min each, then blocked in 5% normal goat serum in PBT (1 hr). Once blocked, MTs were incubated in 6.25 μg/ml DAPI (nuclei) and 0.05 units phalloidin-568 (f-actin) in PBT (10 min). MTs were washed 2 times in PBT, 10 min each, mounted on a slide in Vectashield with a coverslip, and imaged using a Leica TCS SPE confocal microscope.

Results: The data indicate that park25 flies have larger MT areas compared to controls in 15- and 20-day-old flies. The MTs in park25 flies also have concretions that may be similar to kidney stones, while control flies do not. Based on the nuclei in park25 flies, it appears that the RSCs have exited their normal quiescent state and have produced a number of replacement PCs.

Conclusions: We hypothesize that the well-characterized mitochondrial dysfunction in the park25 flies prevents appropriate solute transport processes from happening, leading to the development of stones. We believe that the RSC differentiation is in response to damage induced by the stones, similar to that observed by others.
FROM ANALYSIS OF ANTIBODIES SELECTION TO ULTRA SENSITIVITY BIOMARKER DETECTION FOR NEUROFILAMENT LIGHT CHAIN (NFL). Chang T, Chung T, Chen W. Instant Nanobiosensors Co., Ltd; LifeCo Scientific LLC; Arizona Alzheimer’s Consortium.

**Background:** In the field of neurological diseases, the identification and quantification of axonal damage from peripheral blood have become crucial for diagnostic and prognostic assessments of various neuropsychiatric conditions. Neurofilament light chain (NFL) has emerged as a stable biomarker released from neuro-axonal damage in different neurological disorders. However, current methods for analyzing blood NFL levels rely on less specific enzyme-linked immunosorbent assay (ELISA) techniques or more expensive single-molecule array (SIMOA) methods.

**Methods:** Six monoclonal antibodies and three polyclonal antibodies were purchased from 4 different sources. Affinity and kinetic properties of each antibody were determined using INB FOPPR system INB-D200. The epitope binning tests were performed in the tandem format. The Nfl protein is initially immobilized on the fiber. Subsequently, the first antibody is injected, followed by a wash step. Finally, the second antibody is injected. If the second antibody against the same epitope of the target it will be blocked by the first antibody then there will be no signal change in the sensorgram. However, if the two antibodies do not block each other, there will be a noticeable change in the signal.

**Results:** Based on the affinity analysis results, there were five antibodies exhibiting better affinity constants, with values smaller than 10 nM. Among these five antibodies, Abcam (1) and IReal (2) demonstrated better stability. We then eliminated Uman (1) and Uman (2) because they are antibodies with application patents owned by another company.

The epitope binning tests were performed on the remaining four antibodies in a tandem manner on the same chip. It is observed that GeneTex (2) shares an epitope with one of the IReal (2) antibodies. On the other hand, IReal (1) antibodies have epitopes that are distinct from both IReal (2) and GeneTex (2). Additionally, GeneTex (3) shares the same epitope as GeneTex (2) and one of the IReal (1) antibodies.

By integrating the results of the affinity analysis and epitope binning, it is determined that Abcam (1) and IReal (2) antibodies are the suitable antibody pairs for the assay development. Although Abcam (1) antibody has the second-best affinity constant, it demonstrates superior stability. Moreover, it is a monoclonal antibody. On the other hand, IReal (2) antibody exhibits the best affinity constant, despite being a polyclonal antibody. Based on the results, Abcam (1) was picked to serve as the capture antibody, and IReal (2) antibody was selected as the detection antibody for the development of a sandwich based FOLINSA assays. The standard curve was generated with a duplicated test. The standard curve suggests a linear range of 0.04 pg/mL to 125 pg/mL, covering a dynamic range of four orders of magnitude. The limit of detection (LOD) for the Nfl assay was determined to be 3.4 fg/mL.

**Conclusions:** We were able to utilize FOPPR system (INB-D200) to perform antibody analysis and selection of the best capture and detection antibodies for the development of an ultra sensitive FONLISA assay for the detection of neurofilament light chain (NFL) in biological samples.

Background: In neurological diseases, the identification and quantification of axonal damage from peripheral blood allows for diagnostic and prognostic assessment of various neuropsychiatric illnesses. Neurofilament light chain (NFL) has been reported as a stable biomarker release from neuro-axonal damage of various neurological disorders. Currently, all blood NFL analyses methods have relied on less specificity enzyme-linked immunosorbent assay (ELISA) and more expensive single-molecule array (SIMOA) methods. In this study, a novel method called fiber optic nanogold-linked immunosorbent assay (FONLISA) of fiber optic particle plasmon resonance (FOPPR™) technique was developed to measure the peripheral blood NFL concentrations.

Methods: FONLISA has coated NFL capture antibody on the fiber surface and immobilized the NFL detector antibody on the surface of a gold nanoparticles (AuNPs). The binding of serum NFL protein with these antibodies may yield sufficient changes of nanoplasmonic absorption of evanescent wave that meet the required detection enhancements for sensitivity and for specificity in NFL measurement.

Results: The method provided a wide linear detection range from 0.04 pg/mL to 125 pg/mL (~4 orders) for NFL. The low limit of detection (LOD) was 3.39 fg/mL. This analytical method has been validated with both intra-day CV < 7% and inter-day CV < 20% analyses. Two techniques of SIMOA and FOPPR were used to compare and verify the concentrations of serum NFL levels in 8 subjects. A correlation coefficient of 0.886 was observed between the method of SIMOA and FOPPR in the same subjects of NFL.

Conclusions: We successfully developed a FOPPR technique called FONLISA for the quantitative measurement of neurotoxic indicator neurofilament light chain with a wide linear detection range and a very low LOD. This technology obtained comparable results as that by SIMOA which is several times more expensive than our FOPPR system.
AMELIORATION OF STREPTOZOTOCIN INDUCED ASTROCYTE MITOCHONDRIAL DYSFUNCTION BY FTO INHIBITOR. Cockova Z, Honc O, Telensky P, Olsen MJ, Novotny J. Charles University, Czech Republic; St. Anne’s University Hospital Brno; Midwestern University; Arizona Alzheimer’s Consortium.

Background: Alzheimer's Disease (AD) pathogenesis includes perturbed cerebral bioenergetics and neuroinflammation that may contribute to compromised cognitive function. The mRNA modification N6-methyladenosine (m6A) has been implicated in neurodegeneration. Streptozotocin (STZ) treated astrocytes express significantly higher levels of a m6A eraser, the Fat Mass and Obesity protein (FTO). Inhibition of FTO enhanced survival of STZ exposed astrocytes, suppressed oxidative stress, mitochondrial dysfunction and bioenergetic disturbances.

Methods: Cell viability was performed using the MTT assay. Cell cytotoxicity was measured using LDH. Apoptosis was estimated by Annexin V/Hoechst 33258 staining. Mitochondrial membrane potential and mass were determined by MitoTracker Red and Green. Intracellular ROS generation was measured by DHE. m6A was quantified using the EpiQuick m6A quantification kit. Mitochondrial respiration was evaluated in whole cells using MitoXpress Xtra Oxygen Consumption Assay. Intracellular ATP was measured using the ATP Bioluminescence Assay Kit CLS II with modifications. Gel electrophoresis, Western blot, protein determination and cell culture were performed using standard protocols.

Results: STZ reduced astrocyte viability in a concentration dependent manner. FTO Inhibition increases astrocyte survival due to STZ treatment. STZ induced apoptotic signaling is diminished by FTO inhibition. FTO inhibition elicits a protective effect against STZ induced oxidative stress and GFAP elevation. STZ and FTO inhibitors affect mitochondria and cellular bioenergetics.

Conclusions: The STZ model of AD results in oxidative stress, impaired energy metabolism and astrocyte activation. FTO is upregulated by astrocyte STZ treatment, perturbing m6A signaling. FTO inhibition mitigates STZ toxicity in astrocytes, and mitigates the altered bioenergetic state induced by STZ. These observations are being applied to evaluate increased mitochondrial biogenesis and cellular respiration, and in in vivo models of AD to reverse cerebral hypometabolism and spatial memory deficits.

Background: It is now known that the expression of more than a thousand genes is affected in Alzheimer’s disease. These multiple changes in gene expression involve over 90% of the known biological pathways. This raises the question of what cell/molecular mechanism may be responsible for such large numbers of changes in gene expression in Alzheimer’s disease.

Methods: We have explored and analyzed gene expression data from many data bases using bio mathematical and statistical algorithms.

Results: On the basis of our analyses of gene expression data we propose a model of Alzheimer pathobiology that starts with a cellular response to stress manifested by stress granules, which sequester major components of the mechanism for exchange of molecules between the cell nucleus and the cell cytoplasm. This leads to ectopic localization of many intracellular molecules, including epigenetic molecules. This, as well as additional effects, lead to altered expression of genes that leads to the clinical phenotype of Alzheimer’s disease.

Conclusions: It is time to shift focus away from specific phenomena in Alzheimer's disease, such as tau, Abeta, inflammation, cell death, metabolism, protein processing, etc. to phenomena that encompass the entire complex set of changes in Alzheimer's disease. This can be done by considering the entire pattern of changes in gene expression in Alzheimer's disease - as well as other neurodegenerative diseases.

Background: The primary goal of the Critical Path for Alzheimer’s Disease (CPAD) Consortium is to develop data-driven tools and methodologies that improve clinical trial design and execution, reduce patient burden, and accelerate the scientific understanding of Alzheimer’s disease (AD). Such tools primarily include disease progression models and clinical trial simulation tools. CPAD acts as a neutral convener, bringing together diverse stakeholders across industry, regulatory agencies, patient advocacy organizations, and academia. The consortium identifies key unmet needs in drug development for AD and provides a pre-competitive space for knowledge sharing to occur. CPAD leverages its aggregated database and core competencies of data management, advanced quantitative analytics, and regulatory science, to 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. The complexity and diversity of CPAD’s data pose a challenge for researchers in terms of data processing. To address this, a user-friendly web-based interface called the "actionable data model" (ADM) tool was developed. This tool allows users to generate analysis-ready data subsets based on participant characteristics filters in a simple, web-based user interface. The ADM tool captures relationships between data domains for fast querying and enables easy integration with statistical analysis programs.

Results: As of July 2023, CPAD’s clinical trial repository contains 73 studies with 100,812 individual anonymized patient records. A prototype ADM tool was built using the R-Shiny framework, allowing for initial data exploration and analysis subset creation. The ADM tool includes a dashboard with variable lists, summary statistics, and visualization. Users can perform data exploration and visualization using the current version of the application. A collection of users has tested the tool end-to-end, from navigating the user interface to creating relevant analysis subsets and using them to build statistical models for disease progression and clinical trial enrichment. Logistic regression models were initially used to predict the risk of developing AD dementia in patients with mild cognitive impairment (MCI) and positive amyloid status. The analysis utilized data downloaded from the ADM tool based on user-defined characteristics, such as MCI diagnosis, positive amyloid status, baseline cognition, MRI and plasma biomarkers, and longitudinal clinical data.

Conclusions: CPAD provides the necessary legal and regulatory infrastructure that is imperative to stakeholders sharing information and data, as well as for transforming these into actionable tools and solutions to advance the drug development process. We will expand the capabilities of the tool to include tabs for data exploration and analysis subsets. The long-term goal for the ADM tool is to create a user-friendly environment for researchers to efficiently explore datasets and identify interpretable baseline characteristics of subjects across the AD continuum, aiding in disease progression prediction.
THE HUMAN BRAIN NUCLEUS INCERTUS: A NEW TARGET IN DEMENTIA? de Ávila C, Guquila A, Trenk A, Intorcia AJ, Suazo C, Nolz J, Plamondon J, Khatri D, Tallant L, Caron A, Błasiak A, Serrano GE, Beach TG, Gundlach AL, Mastroeni DF. Arizona State University; Jagiellonian University, Krakow, Poland; Arizona Alzheimer’s Consortium; Banner Sun Health Research Institute; Centre de recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec, Canada; Mayo Clinic, Scottsdale; Université Laval, Quebec, Canada; The University of Melbourne.

Background: The nucleus incertus (NI) was originally described by Streeter in 1903, as a midline region in the floor of the fourth ventricle of the human brain with an ‘unknown’ function. More than a century later, the neuroanatomy of the NI including its forebrain target regions has been described in lower vertebrates, but not in humans. Therefore, we examined the neurochemical anatomy of the human NI using several markers, including the neuropeptide, relaxin-3 (RLN3), and began to explore the distribution of the NI-related RLN3 innervation of the hippocampus.

Methods: Histochemical staining of serial, coronal sections of control human postmortem pons was conducted to reveal the presence of the NI by detection of immunoreactivity (IR) for the neuronal marker, microtubule-associated protein-2 (MAP2), two markers present in rat NI, glutamic acid dehydrogenase (GAD)-65/67 and corticotropin-releasing factor type-1 receptor (CRF1), and RLN3, which is highly expressed in a major population of NI neurons in diverse species. RLN3 mRNA was detected by multiplex, fluorescence in situ hybridization. Postmortem pons sections containing the NI from an Alzheimer's disease (AD) case were immunostained for phosphorylated-tau (AT8 antibody), to explore potential relevance to neurodegenerative diseases. Lastly, sections of human hippocampus were stained to detect RLN3-IR and somatostatin (SST)-IR, as SST is expressed in interneurons targeted by RLN3 projections in rodents.

Results: In the dorsal, anterior-medial region of the human pons, neurons containing RLN3- and MAP2-IR, and RLN3 mRNA-positive neurons were observed in an anatomical pattern consistent with that of the NI in other species. GAD65/67- and CRF1-immunopositive neurons were also detected within this area. Furthermore, RLN3- and AT8-IR were co-localized within NI neurons of an AD subject. Lastly, RLN3-IR was detected in neurons within the CA1, CA2, and DG areas of the hippocampus, in the absence of RLN3 mRNA. In the DG, RLN3- and SST-IR were co-localized in a small population of neurons.

Conclusions: Aspects of the anatomy of the human NI are shared across species, including a population of RLN3-expressing neurons and a RLN3 innervation of the hippocampus. Accumulation of phosphorylated-tau in the NI suggests its possible involvement in AD pathology. Further characterization of the neurochemistry of the human NI will increase our understanding of its functional role in health and disease.

Background: Age-related changes in brain morphometry and microstructure play a critical role in both normal and pathological aging, often associated with cognitive performance and there is a need to better differentiate normal from disease state alterations. Non-human primate brains provide an excellent model to determine lifespan-related brain changes and quantitative MRI offers essential tools for evaluating age-related morphometry and microstructure. Tensor-based morphometry (TBM) maps local volume changes to identify regions of age-related atrophy while diffusion tensor MRI (DTI) can probe cellular level changes.

Methods: We examined volumetric changes and structural integrity in the whole brain, hippocampus, and white matter (WM) with TBM and DTI and correlated these with behavioral scores in eight female bonnet macaque brain specimens ranging in age from 10-25 years (human equivalent of 30 to 75 years). We collected high-resolution T2 weighted MRI and DTI (200 and 600 micron isotropic voxels respectively). Adult (n=4; age ranges=10-11 years) and aged (n=4; age ranges= 20-25 years) templates were generated using conventional and diffusion tensor-based registration, and comparison of the adult and the aged templates was enabled by warping aged to adult. For TBM, LogJ maps were calculated from deformation field between aged and adult templates and showed atrophy in the cortex but not the hippocampus, which was confirmed by ROI analysis.

Results: Whole brain volume was significantly different between the age groups (p=0.044, Cohen’s D= -1.436) while hippocampal volume was not (p=0.1). Fractional anisotropy (FA), derived from DTI, was not different between groups for global WM. Correlation analysis of volume and DTI metrics with previously collected cognitive assessments - Delayed Response (DR), Delayed Non-Match to Sample (DNMS) and Object Discrimination (OD), did not reveal strong relationship between whole brain volume or WM FA, but there was a correlation between hippocampal volume and OD.

Conclusions: The results support the idea that the hippocampus is preserved during healthy aging while the cortex undergoes age-related atrophy which is relevant for studies of degenerative disease that preferentially affect these structures.
DEVELOPMENT AND CHARACTERIZATION OF SINGLE-DOMAIN ANTIBODIES TARGETING AMYLOID-B. Ding Z, Haug KA, Corzine SW, Dresler SR, Fryer JD. Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

Background: Alzheimer’s disease (AD), the most common form of dementia, is a neurodegenerative disorder with progressive impairment of behavioral and cognitive functions. AD is pathologically characterized by extracellular amyloid-β (Aβ) plaques and intraneuronal neurofibrillary tangles in the brain. The Food and Drug Administration has recently approved two anti-amyloid antibodies (aducanumab and lecanemab) for treatment of AD. Therefore, therapeutic strategies targeting Aβ are of particular interest for treating AD.

Single-domain antibodies (sdAbs, aka nanobodies) are the smallest recombinant functional antigen-binding fragments derived from heavy-chain-only immunoglobulins. Their small size (M.W. ~15 kDa) allows targeting difficult-to-reach antigens, better tissue penetration, and the single polypeptide nature allows for easy cloning and molecular display screening (e.g., phage display). Furthermore, sdAb clones can be engineered with additional features (e.g., bivalent, target to lysosomes, etc.). Therefore, sdAbs offer broad application potential. Here, we sought to develop and characterize anti-Aβ sdAbs with the potential for treating AD.

Methods: We generated an immune sdAb library cloned from peripheral blood lymphocytes derived from a llama immunized with aggregates of Aβ(1-42). We screened our sdAb phage library and used ELISA to screen positive clones for Aβ(1-42) after two rounds of biopanning. These sdAbs candidates were validated by immunostaining with brain sections of an AD mouse model and an AD patient.

Results: We have identified 20 unique anti-Aβ sdAbs at the time of this abstract submission. Sanger sequencing identified these unique clones with overall nanobody structure intact. We have tested our initial sdAbs clones for their ability to work for immunostaining. These sdAbs are successfully able to recognize fibrillar Aβ in the brain sections of an AD mouse model as well as an AD patient.

Conclusions: We have successfully identified several sdAbs for Aβ. Characterization of their therapeutic function in vivo will be our immediate future study.

Neurovascular alterations have recently emerged as a common feature of many neurodegenerative diseases including ALS. These vascular alterations occur prior to motor neuron degeneration in a mouse model of ALS. Human postmortem studies of the blood-brain barrier (BBB) solidify these findings, with structural impairments of the neurovascular unit (NVU) affecting endothelial cells as well as supporting perivascular fibroblasts and pericytes. We have recently performed an extensive analysis of the human postmortem blood-CSF barrier (BCSFB) in ALS and non-neurodegenerative disease controls (NNDC) and discovered transcriptional and ultrastructural alterations in the NVU suggesting a leaky barrier into the central nervous system (CNS). In order to identify cell-specific changes in brain barriers as well as intrinsic differences in the BCSFB between slow progressing ALS, fast progressing ALS and ALS with frontotemporal dementia (ALS-FTD), we have performed single nuclear RNA-sequencing on postmortem choroid plexus tissues. We identified differential enrichment of various ALS related genes including Fus, C9orf72, hnRNAA1, and Ataxin2 in choroid plexus epithelial cells of ALS and ALS-FTD compared to non-neurodegenerative disease controls (NNDC). In addition, macrophages from fast-ALS but not slow- ALS BCSFB exhibit an enrichment in Th17 differentiation pathways highlighting the unique immune signature of various ALS subtypes. This study highlights for the first time unique and intrinsic alterations in BCSFB cell types in ALS.
LOW CLINICAL SENSITIVITY AND UNEXPECTEDLY HIGH INCIDENCE FOR NEUROPATHOLOGICALLY DIAGNOSED PROGRESSIVE SUPRANUCLEAR PALSY. Driver-Dunckley ED, Zhang N, Serrano GE, Dunckley NA, Sue LI, Shill HA, Mehta SH, Belden C, Tremblay C, Atri A, Adler CH, Beach TG. Mayo Clinic Arizona; Banner Sun Health Research Institute; Barrow Neurological Institute; Brigham and Women’s Hospital & Harvard Medical School; Arizona Alzheimer’s Consortium.

Background: The clinical diagnosis of PSP remains difficult due to the variability and inconsistency in the presenting phenotypes. Often the diagnosis of PSP is not made until autopsy. Multiple prior autopsy-validated studies have shown suboptimal sensitivity while specificity is high. A recent update of consensus neuropathological criteria for PSP allows an improved assessment of clinical diagnostic accuracy. Determine the prevalence, incidence, and clinical diagnostic accuracy for neuropathologically-diagnosed progressive supranuclear palsy (PSP) with data from a longitudinal clinicopathological study, using Rainwater criteria to define neuropathological PSP.

Methods: All subjects were enrolled in the in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP) and had annual standardized research clinical assessments by neuropsychologists, subspecialty behavioral and movement disorders neurologists, as well as comprehensive neuropathological examinations after death. A subset of subjects who lacked dementia or parkinsonism at enrollment were used to calculate the PSP incidence rate. The Rainwater neuropathological criteria were used to define PSP while clinical findings were used to separate subjects into incidental PSP (iPSP) and clinically manifest PSP based on the presence or absence of parkinsonism or dementia. The density of neuronal tangles and tufted astrocytes were semi-quantitatively graded in a set of brain regions typically affected by PSP. Prevalence and incidence rates were calculated.

Results: Of 954 autopsy cases, 101 met Rainwater criteria for the neuropathologic diagnosis of PSP. Of these, 87 of these were termed clinicopathological PSP as they also had either dementia or parkinsonism or both while 14 lacked either syndrome and were thus designated as iPSP. Density scores for all microscopic lesion types were greater in clinicopathological PSP than in iPSP, in all considered brain regions. The prevalence of clinicopathologically-defined PSP subjects in the entire autopsy dataset was 9.1% while the incidence rate was estimated at 780 per 100,000 persons per year, roughly 50-fold or more than most previous clinically-determined PSP incidence estimates. A clinical diagnosis of PSP was 99.6% specific but only 9.2% sensitive based on first examination, and 99.3% specific and 20.7% sensitive based on the final clinical exam. Of the clinicopathologically-defined PSP cases, 35/87 (~40%) had no form of parkinsonism at first assessment while this decreased to 18/83 (21.7%) at final assessment. The most specific clinical signs were downgaze palsy and square-wave jerks, both with ~ 98% specificity but low sensitivities, between ~15-18%. In comparison with PD subjects, falls occurred earlier in PSP, at medians of 3 and 9 years before other symptoms. Comorbid high Braak Alzheimer’s disease stage was associated with a lower probability of PSP clinical diagnosis.

Conclusions: Our study and others with autopsy validation confirm a high specificity but low sensitivity for the clinical diagnosis of PSP. We found specificity to be over 99% while sensitivity was very low, ranging from 9.2% at first assessment to 20.7% at final assessment. The low clinical sensitivity for PSP is likely primarily responsible for previous underestimates of the PSP population incidence rate.

Background: Previous work has shown that data-driven methods for classifying MCI based on comprehensive neuropsychological test data can reliably identify MCI subtypes that show stronger associations between cognition and dementia risk factors than do classifications based on conventional diagnostic methods such as the “consensus diagnosis” approach. We aimed to extend this work to the National Alzheimer’s Coordinating Center (NACC) sample.

Methods: Cluster analysis was performed with baseline neuropsychological data from participants aged 50 years or older (mean=71.6 years) without dementia in the NACC Uniform Data Set (n=26,255), and repeated with only data from the “normal cognition” subsample (n=16,005). The UDS tests examined included measures of memory, attention/working memory, processing speed/executive functioning, and language. Raw scores were converted into demographically-adjusted (age, education, sex) z-scores based on the performance of a robust cognitively normal group. Survival analyses examined progression to MCI or dementia.

Results: Five clusters were identified: “Optimal” cognitively normal (oCN; 13.2%), “Typical” CN (tCN; 28.0%), Amnestic MCI (aMCI; 25.3%), Mixed MCI-Mild (mMCI-Mild; 20.4%), and Mixed MCI-Severe (mMCI-Severe; 13.0%). Rate of progression to dementia differed across the cluster-derived groups (oCN < tCN < aMCI < mMCI-Mild < mMCI-Severe). Comparison of the classification methods showed that cluster analysis identified more MCI cases than consensus diagnosis. Within the NACC “normal cognition” subsample, five clusters emerged: High-All Domains (16.7%), Low-Attention/Working Memory (Low-WM; 22.1%), Low-Memory (36.3%), Amnestic MCI (aMCI; 16.7%), and Non-amnestic MCI (naMCI; 8.3%), with differing rates of progression to MCI/dementia (High-All < Low-WM = Low-Memory < aMCI < naMCI).

Conclusions: Our data-driven method of classifying participants into MCI subtypes outperformed the consensus diagnostic approach by providing more precise information about risk for future progression, and revealing heterogeneity in cognitive performance and progression risk within the NACC “normal cognition” group. Results have implications for future research by demonstrating a method to identify empirically-derived subtypes of subtle cognitive decline and MCI that optimize prediction of risk for future MCI/dementia.

Background: We previously examined the impact of using a cerebellar, pons, or cerebral white matter (WM) reference region (RR) on the ability of each to distinguish cortical measures of fibrillar amyloid-(Aβ) deposition with baseline data in unimpaired presenilin (PSEN1) E280A mutation carriers and non-carriers (NC) from the Alzheimer’s Prevention Initiative Autosomal Dominant Alzheimer’s Disease (API ADAD) Colombia Trial (NCT01998841). In this study, we extend our findings by comparing these RRs on their ability to distinguish longitudinal changes in cortical measures of serial Aβ-PET scans from the completed clinical trial.

Methods: We estimated template-based (SPM12) cortical mean change using baseline, 2, and 5-year florbetapir PET standard-uptake value ratios (SUVRs) with three different RRs (whole cerebellum, pons, and WM) and compared carriers on placebo (placebo-carriers, n=82) with NC all on placebo (NC, n=83). We calculated Cohen’s D with [95% CI] and standard deviation of NC as effect-sizes for 2 and 5-year cortical changes. Additionally, we characterized cerebellar Aβ burden in carriers on crenezumab (treatment-carriers, n=81), placebo-carriers, and NC, using our previously reported method targeting the whole cerebellum region-of-interest (ROI) with pons as RR to estimate cerebellar-to-pons-SUVRs and compare using a mixed-model repeated-measures ANOVA adjusted for age but not multiple comparisons.

Results: As expected, placebo-carriers had significantly greater SUVR change compared with NC for all three RRs. However, the pons RR was best at detecting 2-year changes (d=1.75[1.39-2.11]), and WM and pons were best at detecting 5-year changes in cortical-Aβ levels between placebo-carriers and NC (pons d=2.01[1.64-2.39], WM d=2.51[2.10-2.92]). Additionally, treatment-carriers had higher cerebellar-to-pons-SUVRs compared with placebo-carriers at baseline and 2-years, but not 5-years (p=.034, p=.027,& p=.06,respectively), both carrier groups had higher cerebellar-to-pons-SUVRs compared to NC at each interval(p<.001). Cerebellar-to-pons-SUVRs continued to increase within carrier groups at each interval (5-year>2-year>baseline, p<.05) and remained constant within the NC-group(p>.05).

Conclusions: Use of pons for 2-year and WM or pons RRs for 5-year changes may improve the power to track longitudinal increases and evaluate Aβ-modifying treatments in 2 and 5-year studies, in this ADAD population. A cerebellar RR may be confounded by early Aβ deposition in the cerebellum which can artificially reduce average cortical Aβ-PET SUVRs even in preclinical stages of ADAD.

Background: The Internet of Health Things is crucial in helping promote health and wellbeing in the community. For family caregivers of people with Alzheimer's disease and other related dementias (ADRD), using emerging technology translates into a golden opportunity to join programs to help manage their caregiving stress and distress from the comfort of their homes. Bringing skill-building caregiving interventions to the caregiver’s location helps resolve various barriers to participation, such as lack of transportation, being homebound due to chronic illness or functional impairments, and conflicts with work schedules. However, little is known about the economic savings and environmental impact of using emerging technologies to deliver caregiving interventions. This work examines the Techno-Economic Analysis (TEA) and a Life Cycle Assessment (LCA) of the intervention “Through Alzheimer’s Eye” compared to the hypothetical in-person delivery of the same intervention.

Methods: "Through Alzheimer's Eyes" is a pilot study consisting of 4 group sessions of 90 minutes each delivered virtually. The intervention covered topics such as communication skills, managing challenging behavior and unhelpful thoughts, self-care, and mindfulness. It also included a different weekly virtual reality experience about Beatriz, an older Latina with Alzheimer's disease. The TEA evaluates and interprets the financial costs and benefits of the intervention and the materials used. The TEA examined the total economic cost of delivering the training to twenty participants for the virtual intervention compared to a hypothetical in-person scenario on (i) the lower-end of the costs and (ii) the higher-end of the costs. LCA is a rigorous tool that quantified the environmental impact of delivering the intervention to the twenty participants, including transportation, shipping, materials used, and snacks.

Results: Results indicated that the virtual intervention was associated with lower participant costs than the hypothetical in-person intervention; caregivers' costs decreased by almost 100%. The virtual delivery of the intervention also has the potential to reduce costs by up to 40% from the organizational perspective; however, it could be slightly higher price if the organization lacks the resources available to deliver the intervention in-person that are free of charge. Environmentally, the virtually-delivered intervention had up to 97% less carbon emissions than the hypothetical in-person delivery of the intervention. Furthermore, video-communication delivery of the intervention has the potential to reduce some of the hassles of looking for respite to attend caregiving interventions and allow caregivers to join from their preferred location across the country eliminating the need to travel.

Conclusions: Caregiving interventions and training can be adapted and translated to virtual settings to enhance equitable access and reach a more diverse population while caring for the environment. Virtual interventions can potentially reduce expenses for the organization delivering the intervention. For caregivers, connecting online can save time and additional stress by connecting from their preferred location, avoiding traveling, and finding respite. Potential travel savings in time and money not only have an impact in economic terms but also protect the environment by drastically reducing carbon emissions. This remarkable cut in carbon emissions translates into a sustainable practice that promotes environmentally friendly solutions, ultimately impacting the population's overall health.
EXPANDING ARIZONA’S DEMENTIA CAPABLE SYSTEM: INSIGHTS FROM OVER 3,000 WORKSHOP ATTENDEES. Gonzalez-Pyles S, Carbajal B, Carbajal L, Cordova L, Glinka A, Coon DW. Arizona State University; Arizona Alzheimer’s Consortium.

**Background:** Arizona is projected to be the state have the largest percentage increase of people living with Alzheimer’s disease between 2020 and 2025 (Alzheimer’s Association, 2023). This project funded by the US Administration for Community Living (US ACL) was designed to help expand Arizona’s dementia capable system efforts and brought together key partners including the state unit on aging in Arizona (Department of Economic Security’s Division of Aging and Adult Services), the Desert Southwest Chapter of the Alzheimer’s Association, Area Agency on Aging, Region One, Pima Council on Aging, the Arizona Caregiver Coalition, and the Promotores HOPE Network—all under the leadership of the Center for Innovation in Healthy and Resilient Aging within Arizona State University’s Edson College of Nursing and Health Innovation. Notably, the project focused on helping to address three gap areas in need of programs and services including those people a) Living Alone with Alzheimer’s disease and related disorders (ADRD) and their caregivers; b) Living with IDD and ADRD and their caregivers; and, c) Living with ADRD and their caregivers in the Latino Community. It included ACL trainings and workshops delivered both in person prior to COVID-19 and virtually afterwards as well as through options counseling activities and its evidence-based programs (CarePRO-IDD, CarePRO for the Latino Community, and EPIC-Living Alone).

**Methods:** This presentation focuses solely on the ACL project’s trainings and workshops delivered in English and Spanish and offered to professionals and the lay public (i.e. older adults and family caregivers). Workshops were developed based on the scientific and clinical literatures with feedback from providers and community members. Key facts and figures were updated in the workshops across the multi-year project, and the workshops were modified for Zoom in response to COVID-19 and stay-at-home orders. In person workshops only took place in Arizona; however, Zoom delivery expanded the project’s reach across the nation.

**Results:** Workshops were delivered in English and Spanish to 3,674 participants across the three gap areas. Post-only evaluations were collected with response rates varying across topic: Living Alone with ADRD (46.8%); Living with IDD and ADRD (45.3%); and Living with ADRD in the Latino Community (39.9%). Response rates were lower when workshops were delivered via Zoom. Respondents who self-identified as Latino/Hispanic or as a Spanish speaker varied across workshops as well: Living Alone with ADRD (59.1% Latino/Hispanic; 37.1% Spanish speaker); Living with IDD and ADRD (47.1%; 23.6%); and Living with ADRD in the Latino Community (79.5%; 56.6%). Over 80% of attendees overall were women and almost 40% described their race as other than White. Post-workshop outcomes included high levels of satisfaction with the program and the presenters (all > 85%) as well as evidence that participants learned something new (>84%), learned something they could use (>80%), and felt confident they could help this population based on their workshop experience (>96%).

**Conclusions:** Our US ACL project workshops offered in English and Spanish were well-received and successfully reached diverse groups of providers, people living with ADRD, and family caregivers even when held during the COVID-19 pandemic. Positive outcomes (e.g., increased knowledge, skills, and/or tools) were achieved after participating in the trainings and workshops offered by the project. These outcomes were related to all three gap areas and across professionals, community members living with ADRD, and family caregivers.
MINISCOPE IMAGING OF CEREBROVASCULATURE BEFORE AND AFTER EXPERIMENTAL HEAD INJURY. Griffiths DR, McQueen KA, Vail T, Lifshitz J. University of Arizona-College of Medicine; Phoenix VA Health Care System; Arizona Alzheimer’s Consortium.

Background: Miniscope imaging is an investigative technique to record dynamic processes in the brain of freely behaving rodents. However, miniscope hardware and imaging are technically challenging to combine with most TBI models.

Methods: In this study, we developed a novel approach for repeated miniscope imaging of cerebral vasculature pre- and post-injury. We hypothesized that head injury will increase blood brain barrier permeability leading to extravasation of fluorescent dyes into the parenchyma. Adult male BALB/c mice underwent surgery to implant a GRIN lens and secure miniscope hardware to the skull. Two weeks post-surgery, a miniscope was attached to acquire baseline images of cerebrovasculature visualized with intravenous fluorescent-labeled dyes. After baseline imaging, the miniscope was detached and replaced with a protective cap. Anesthetized mice received weight drop head injury (Height: 94cm, Weight: 100g) that allowed free head rotation. After injury, the protective cap was detached and replaced by the miniscope. After imaging, mice were aldehyde perfused and brains processed to quantify fluorescent dye levels and associated neuropathology (immunohistochemistry) in the imaged parenchyma.

Results: No extravasation of dye was observed 3 hours after a single head injury or immediately after repeated head injuries spaced three hours apart. Miniscope imaging results were confirmed with immunohistochemistry.

Conclusions: Our study demonstrates that miniscope imaging, combined with weight drop head injury, can visualize dynamic cerebrovascular changes in the mouse brain post-TBI. Our method allows for single or repetitive injury with imaging pre- and post-injury and may translate to other in vivo imaging techniques (2-photon). Further studies will investigate the relationship between head injury parameters and cerebrovascular pathology.

Background: Object recognition tasks are commonly used to assess learning and memory processes in rodents. Such tasks are extremely useful as they can be used to investigate the function of targeted brain regions without the need for extensive training protocols. 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 (Ennaceur & Delacour, Behav. Brain. Res., 1988, 31:47).

Methods: In this task, animals are allowed to freely explore two different pairs of identical objects across two sample phases, and then, during a test phase one copy of each familiar object is simultaneously presented. Greater exploration of the temporally more remote familiar object over the temporally more recent familiar object has been observed in several rodent species/strains, and it has been shown that lesions to the medial prefrontal cortex significantly disrupt performance on this task in young rats (Mitchell & Laiacona, Behav. Brain Res., 1998, 97:107; Belblidia et al., Behav. Brain Res., 2023, 437:114151; Barker et al., J. Neurosci., 2007, 27:2948; Barker & Warburton, J. Neurosci., 2011, 31:10721). In humans, prefrontal cortex-dependent memory exhibits some of the most dramatic and early changes relative to other brain functions with normative aging (Park et al., Psychology and Aging, 2002, 17:299). Although the TOR task has been utilized in a number of studies of early development, there has been little research on the impact on performance in animals of older ages. The purpose of this study was to investigate whether this task could be used to detect age-related performance changes in a rodent model of healthy aging. We tested male Fischer 344 (F344) rats of three separate age groups, young (4-6mo), adult (8-9mo), and old (23-27mo), using both published protocols, and modified protocols to increase exploratory behaviors.

Results: In spite of improvement of overall engagement and exploration with the modified procedures, we were unable to replicate results consistent with what has been reported by others employing the TOR task. A number of reasons for this might be offered, such as strain differences (Ennaceur et al., Behav. Brain Res., 2005, 159:247; van Goethem et al., Behav. Brain Res., 2012, 232:323), and the ages of the animals tested, as ours were clearly mature or old, and most other studies utilized animals of younger or much younger ages.

Conclusions: We report this here to contribute to a growing literature concerning rodent strain related differences in behavioral performance.
ALTED BASAL GANGLIA GENE NETWORKS FOR VOCAL FUNCTION IN NORMATIVE AGING AND PARKINSON’S DISEASE. Higgins CM, Miller JE. University of Arizona; Arizona Alzheimer’s Consortium.

Background: Aging processes in middle life are thought to render the brain more vulnerable to Alzheimer’s (AD) and Parkinson’s diseases (PD), but the “how” remains elusive. Therefore, identifying the molecular pathways in the aging brain that may be potential new loci for disease development is crucial. We propose that vocal behavior is a reliable biomarker for these studies due to its sensitivity to normal aging and early appearance in neurodegenerative diseases. Our objective is to pinpoint the genetic changes that occur in vocal control brain regions during normal aging and discern how these genetic pathways become disrupted in a clinically-manifest disease state. To carry out our objective, we use the adult male zebra finch songbird, which is an advantageous animal model to study brain mechanisms involved in human vocal motor control.

Methods: RNA was extracted and sequenced (seq) from Area X, a song-dedicated finch basal ganglia nucleus, following two hours of solo singing (or quiet) to correlate song measurements with mRNA expression patterns. In the normative aging dataset, we compared genetic results across young adult, middle age, and old age finches (n=12/group). To evaluate the impact of a PD vocal phenotype on the Area X network, young adult males received a bilateral injection of an adeno-associated virus (AAV) which contained the human (h) PD-associated gene, SNCA (alpha-synuclein, n=7) or control (n=9). Our prior publication (Medina et al., PLOS ONE, 2022) established that AAV-driven overexpression of hSNCA results in reduced vocalizations, and softer, shorter, and poorer quality syllables similar to the human vocal deficits. RNA seq data was mapped to the zebra finch genome, followed by Weighted Gene Co-Expression Network Analysis (WGCNA), in which genes are grouped into clusters of modules based on their mRNA co-expression patterns, correlated to traits, and then highly connected genes (“hubs”) that are potential biological drivers of network activity are identified.

Results: Combining RNA seq data across the three finch age categories, we detect prominent song-associated modules in Area X which become more fragmented in middle age and old adults. Module size is reduced, indicating fewer genes and/or changes in connections among genes. In the AAV-hSNCA group compared to controls, we also detect altered mRNA expression patterns with weakening of correlations to song metrics. We identified at least 19 differentially expressed genes, also found in human PD datasets, that include potential hubs associated with mechanisms for oxidative stress, vesicular trafficking, and calcium channel activity among others. At least 22 AD-related genes were identified whose functions span cholesterol metabolism, inflammatory regulation, calcium channels, and transcription.

Conclusions: Our findings reveal changes in molecular networks that contribute to early neuropathological changes in vocalizations with normative aging and PD. Future directions involve protein validation of critical pathways to identify druggable targets.
Dissociating Memory Precision from Retrieval Success in Healthy Older Adults and Mild Cognitive Impairment. Hill PF, Sanchez D, Ekstrom AD. University of Arizona; Arizona Alzheimer’s Consortium.

Background: Episodic memory, or memory for unique experiences and details from the past, declines during healthy aging. Impaired episodic memory is also reported as an early symptom of Alzheimer’s disease (AD). However, standardized assessments of memory performance are limited in their accuracy to predict progression of early-stage AD pathology. At the same time, the types of episodic memory tests often used in clinical and research settings typically measure performance in terms of categorical response options (e.g., ‘old’ or ‘new’). This ‘all-or-none’ approach commonly used in neuropsychological assessment for quantifying memory performance might miss out on subtle variation in the fidelity or quality mnemonic representations retrieved from memory.

Methods: Twenty-eight cognitively healthy older adults and seven older adults with MCI completed five study-test cycles of a continuous report item-location memory task. A subsample of 18 healthy older adults performed the task while undergoing high-resolution fMRI. During the study phase, participants viewed trial-unique objects located around the perimeter of an invisible circle. During the test phase, old and new objects were presented in the center of the screen and participants were instructed to recall the original location of each object using a continuous analogue response dial to indicate their response. Distance error (in degrees) between the remembered and true location of each object served as a continuous measure of spatial memory retrieval. Trial-wise distance errors were fit with a probabilistic mixture model to estimate two distinct memory processes that are often conflated by categorical response memory paradigms: the ability to accurately retrieve prior details from memory (i.e., retrieval success), and the fidelity of details successfully retrieved from memory (i.e., memory precision).

Results: Behavioral measures of item recognition, retrieval accuracy, and memory precision were numerically reduced in the MCI cohort relative to healthy older adults, though these differences were not statistically significant. Critically, we observed substantial individual differences in memory precision that were independent of retrieval success and performance on standardized assessments of verbal and visuospatial memory. Turning to the fMRI data, memory precision effects were identified by contrasting successful memory trials that were remembered with high and low precision. Encoding-related activity predictive of subsequent memory precision was evident in the left hippocampus along with robust bilateral effects in dorsomedial frontal and occipitotemporal cortices. Precision effects at retrieval were modest by comparison, yielding a single cluster in the left intraparietal sulcus.

Conclusions: Precision-based measures of episodic memory appear to capture subtle changes in cognitive function during early stages of AD progression that cannot be readily accounted for by standardized assessments of verbal and visuospatial memory. Future analyses will be aimed at determining whether subtle changes in memory precision are sensitive to the preclinical course of AD pathogenesis.
REGIONAL DIFFERENCES IN BACTERIAL 16S rRNA GENE SEQUENCES AND LPS/LTA EXTRACTED FROM POST-MORTEM BRAIN TISSUE OF AD PATIENTS AND CONTROLS.


Background: In previous experiments we identified low levels of DNA in post-mortem brain tissue taken from Alzheimer’s disease (AD) patients and control individuals. Here, we specifically assessed the differences between two brain regions from those subjects, the superior frontal gyrus (SFG) and the inferior temporal gyrus (ITG). Using data derived from bacterial 16S rRNA gene sequencing, we characterized the five predominant phyla and their relative abundance in each tissue and each subject group. Further, we used principal components analysis, PERMANOVA, and dissimilarity rankings to assess the differences between the tissues and to evaluate which phyla drove the differences observed. We further validated the data by evaluating the balance between components associated with gram-negative and gram-positive bacteria in each tissue and subject group in comparison with the relative abundance of gram-negative and gram-positive bacterial sequences in those tissues.

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 analyses of relative abundance with comparisons between brain regions and subject groups. Additional statistical analysis was conducted in R 4.1.2 using methods from Gloor (Gloor, 2017) for analysis of compositional microbiome data. Commercial ELISA kits were used for analysis of lipopolysaccharide (LPS) and lipoteichoic acid (LTA) in tissue from the same subjects. ELISA data was analyzed using Prism software.

Results: Brain tissue samples from both the SFG and ITG were found to be dominated by the presence of 5 phyla of bacteria: Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, and Proteobacteria. Of these phyla, Proteobacteria was the most dominant, composing ~50% of bacterial sequences in the SFG and ~75% of sequences in the ITG, regardless of subject group. Principal components analysis found that the Proteobacteria and Firmicutes phyla most strongly distinguish ITG from SFG. At the class level, ITG and SFG were primarily distinguished by Gammaproteobacteria and Bacilli. As 16S rRNA sequencing data is reliant on an amplification technique and can be affected by low level contamination, we used ELISA testing for LPS and LTA to demonstrate the presence of bacterial components in tissue from the same subjects and to support sequencing findings. In addition, we evaluated the relative abundance of gram-negative versus gram-positive phyla bacterial sequences, which ultimately correlated well with the ELISA data.

Conclusions: The various analyses performed demonstrated that both bacterial rRNA gene sequences and bacterial components (LPS and LTA) are commonly present in brain tissue from both AD patients and controls. While earlier research on this small group of subjects wasn’t able to identify clear differences in bacterial composition between individual subject groups, perhaps due to the large within-group variability, we were able to identify significant differences in bacterial composition between two brain regions, the ITG and the SFG. These regional differences were consistent in all subject groups. Statistical analysis supported simple comparisons of relative abundance, and the relative abundance of gram-negative versus gram-bacterial sequences mirrored that of the LPS and LTA analyses in those tissues.
FALL PREVENTION QUALITY IMPROVEMENT PROJECT. Johnson K, Chaung M. Arizona State University; Longevity Institute; HonorHealth Family Practice; Arizona Alzheimer’s Consortium.

**Background:** Recurrent falls are linked to functional decline and mortality. One in three older adults will fall with 50% being recurrent fallers. Risk factors for recurrent falls include balance and mobility (33% increased risk), medication (51% increased risk), dementia (45.5% increased risk), psychological (39% increased risk), and sensory and neuromuscular (51% increased risk).

**Purpose:** Determine whether individual based regular activity defined as 30 minutes, five days a week improved Timed Up and Go (TUG) scores in seconds and reduced fall risk. Fall risk was defined as fear of falling and two or more falls in one year. Regular activity included choice of an exercise prescription, Epic dot phrase for patient education on chair yoga poses, images of guided poses and link to video, and Silver Sneakers Fitness Program. physical therapy, aerobic exercise, walking, Tai Chi, stepper, and stair climbing.

**Methods:** Method: Quality Improvement study; Sample: Twenty male and female participants 70 to 93 years of age; Setting: HonorHealth Family Practice.

**Results:** 20 participants completed baseline TUG through post TUGT1. 5/20 (25%) were low risk (TUG time ≤ 12 seconds) and 15/20 (75%) were high risk, (≥ 12 seconds). The low risk group had an increase in baseline TUG to post TUGT1, which was not favorable for functional improvement. The high risk group had a decrease in baseline TUG to post TUG T1, p = .053, which was favorable for functional improvement.

6/20 (30%) completed baseline TUG, post TUGT1, and post TUGT2 with a statistically significant positive functional improvement (p = .032). A reduction in TUG time in seconds demonstrated a positive functional improvement overtime.

**Conclusions:** Findings demonstrate regular activity can improve TUG scores which could transition to fewer falls and reduce falls risk. Having participants choose their exercise activity can promote exercise adherence overtime. Further research is needed with studies using larger sample sizes, standardized measurement outcomes, and longer follow-up periods, to inform evidence-based recommendations overtime.
WHAT MATTERS TO YOU ABOUT YOUR HEALTH AND HEALTH CARE? Johnson K, Chaung M, Berdeja J, Shaw A. Arizona State University; HonorHealth Family Practice; Arizona Alzheimer’s Consortium.

Background: The number of older adults, individuals ages 65 years and older, is growing rapidly. As we age, care often becomes more complex. Health systems are frequently unprepared for this complexity, and older adults suffer a disproportionate amount of harm while in the care of the health system. The Age-Friendly Health System initiative through the Institute for Healthcare Improvement focuses on evidence-based care for older adults by incorporating the 4Ms framework; what matters, medications, mentation, and mobility to guide care of older adults. The participating HH Family clinic addresses three of the 4M’s framework, the “what matters” was not addressed. There was an opportunity to improve practice outcomes, aligning with HonorHealth ICARE value of empathy; being vulnerable and seeking first to understand others to best meet their needs. Purpose: Introduce and incorporate the 4Ms into HonorHealth Family Practice to know and align care with each older adult’s specific health outcome goals and care preferences.

Methods: Design: Quality Improvement; Setting: HonorHealth Family Practice.

Sample: Patients discharged from hospital, observation, and or Emergency Room, and who are 65 years and older. Measurable outcomes: Reduction in repeat hospitalizations within the first three months; Total patients who were assessed using 4Ms; Increase in Patient Satisfaction; Increase in patient compliance with medical plan/goals.


2. Medication: Age-Friendly medication used that does not interfere with what matters to the older adult. Medication Reconciliation verified at hospital follow up visit. Assess current medication: (considered high risk include Benzodiazepines, Opioids, Highly-anticholinergic medications, sedatives and sleep medications, Muscle relaxants, Tricyclic antidepressants, Antipsychotics).

Age-Friendly medication used that does not interfere with what matters to the older adult.

3. Mentation: The care team assesses mood and cognition to maximize autonomy of cognitively impaired older adults and not diminish their self-image.

Mood/Mentation addressed:
“Are you, close friend or relative concerned about your mood ?
“Are you, close friend or relative concerned about your cognition ?
Patient Health Questionnaire-9 (PHQ-9). Screening tool for depression.
Mini Cog: Screening for cognitive impairment in older adults
GAD-7: Screening tool for generalized anxiety disorder.

4. Mobility: Identify and set daily mobility goal with older adult that supports what matters, and review and support progress toward patient’s goal.

Functional level/mobility addressed:
Independent activities of daily living:
Independent in cooking: (yes__ no__)
Independent in cleaning: (yes__ no__)
Independent in shopping: (yes__ no__)
Independent in mediation management: (yes__ no__)
Independent in transportation: (yes__ no__)
Independent in managing finances: (yes__ no__)
Activities of Daily Living: (ADL)s
Independent in feeding: (yes ___ no___)
Independent in bathing: (yes ___ no___)
Independent in dressing: (yes ___ no___)
Independent in toileting: (yes ___ no___)
Independent in grooming: (yes ___ no___)
Independent in transfers: (yes ___ no___)
Independent in walking: (yes __ no___)
Timed Up and Go (TUG)
Fall risk.
Identify and set daily mobility goal with older adult that supports what matters, review and support progress toward patient’s goal.

Intervention: Met with the Geriatric team of healthcare providers to develop a 4M template and strategy to implement the 4M's. The team identified the Medicare Annual Wellness Visit would not be a visit to include the 4M's as their patients were not interested in participating in the Wellness visit. The team identified the "Hospital Follow Up visit was well received and attended. This clinic has hospital follow up reserved slots for patients who need a follow up appointment. Hospital Care Coordinator generates a list of patients who require a follow up visit post discharge. Healthcare providers generate a report on visit type and hospital follow up. A "follow up visit" template was developed to include the 4 M's. The 4M's are introduced to the patient and completed.

Results: From 12/13/23 – 7/21/23, 67 patients who met inclusion criteria participated in 4M's. 28/67 (42%) of participants; too soon to assess for repeat hospitalization; 1st 3 months post hospital follow up visit. 33/39 (85%): participants had no repeat hospitalizations within 1st 3 months. 70/72 (97%) participants had all 4M's addressed. 70/72 (97%) participants were asked What Matters to You? 72/72 (100%) participants were assessed for mentation. 72/72 (100%) participants were assessed for mobility. 72/72 (100%) participants were assessed for medication.

Conclusions: The Age-Friendly Health System 4M's can improve care for older adults. The healthcare provider team that adopted the 4M's provide geriatric care to older adults and have incorporated the 4M's into their practice environment. Care teams’ goal: Create long lasting qualitative change, acknowledging that older adults’ goals and preferences may change over time as health status changes.

Background: Postmortem brain tissues have been used to characterize some of the molecular networks and drivers associated with Alzheimer’s disease (AD). In this study, we extend our previous work of a deep learning approach to characterize the molecular changes associated with the severity of AD-related neuropathology and cognitive impairment, by applying the framework to different brain regions with larger sample sizes.

Methods: We trained multi-layer perceptron (MLP) models for classification of neuropathologically confirmed AD vs. healthy controls (HC) using the transcriptomic data of three brain regions (dorsolateral prefrontal cortex (DLPFC, Total N = 1092), posterior cingulate cortex (PCC, Total N = 647), and head of caudate nucleus (HCN, Total N = 717)) respectively from the ROSMAP study. We performed z-score normalization for each gene expression and randomly split data in ratio 80:20 with matching class (AD and HC) distributions for training and testing. We embedded the expression profiles of all the subjects to the same Uniform Manifold Approximation and Projection (UMAP) space using the final layer of the trained models and obtained progressive trajectories that mirrored AD pathological severity and cognitive impairment of the whole cohort. Interpretable technique SHapley Additive exPlanations (SHAP) was explored to explain model predictions and obtain significant genes contributing to AD. Network analysis was then carried out to identify key gene modules presented in the models underlying AD progression of different brain regions.

Results: The MLP models differed for each dataset with the number of layers ranging between 3-5 and achieved the best AUC of 0.911, 0.925 and 0.829 on DLPFC, PCC and HCN datasets respectively. The AD severity indexes (SI) calculated from the trajectory were highly correlated with neuropathology biomarkers (R ~ 0.6, p < 1e-11) and global cognitive function (R ~ 0.7, p < 2.2e-16). Significant genes identified by the SHAP explainer revealed common and specific transcriptomic signatures from different brain regions implicated in AD.

Conclusions: This study illustrates the potentials of deep learning methods to multi-omic data to characterize the molecular networks associated with increasingly severe clinical and neuropathological stages of neurodegenerative diseases like AD. This offers the opportunity to discover drug targets and/or biomarkers.

Background: Addressing modifiable risk is an important part of a comprehensive strategy to reduce the risk of incident mild cognitive impairment (MCI) and dementia. Alcohol use is one modifiable risk factor with good potential for early identification and intervention. Substantial evidence demonstrates that chronic and heavy alcohol use increases the risk of dementia, but the effect of infrequent alcohol use versus moderate to heavy use on the risk for progression from cognitively unimpaired (CU) to MCI or from MCI to dementia is not known.

Methods: We used data from Alzheimer’s Disease Research Center participants at least 65 years of age in the National Alzheimer’s Coordinating Center (NACC) database to examine the relationship between two levels of self-reported alcohol use on rates of clinical progression from CU to MCI and from MCI to dementia. Cox proportional hazard models were used to characterize and compare rates of clinical progression over 84 months in a) 418 CU and 137 participants who reported no/infrequent use and b) 49 CU and 203 MCI participants who reported moderate/heavy use, after controlling for age, sex, educational level, presence or absence of APOE4 and Hispanic ethnicity.

Results: There was no significant difference in alcohol use in CU and MCI impaired groups at baseline and no significant differences in risk of progression from either CU to MCI (p=0.14) or from MCI to dementia (p=0.32).

Conclusions: This study was unable to detect a significant difference between self-reported low/infrequent and moderate/heavy alcohol use on rates of progression to MCI and dementia. Larger studies could address potential differences with greater statistical power; and emerging blood-based biomarkers could be used in legacy plasma samples to clarify the extent to which different levels of alcohol use have any preferential impact on Alzheimer’s disease and related disorders.
MANGANESE PORPHYRIN ANTIOXIDANT HAS SEXUALLY DIMORPHIC EFFECTS ON MITOCHONDRIAL HYDROGEN PEROXIDE LEVELS IN VULNERABLE PARKIN-NULL DROSOPHILA DOPAMINERGIC NEURONS. Juba AN, Hamel R, Tovmasyan A, Buhlman LM. Midwestern University; Barrow Neurological Institute; Arizona Alzheimer’s Consortium.

Background: Parkinson’s disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to decreased ability to control coordinated movements. The dopaminergic protocerebral posterior lateral one (PPL1) region of the Drosophila melanogaster brain is functionally homologous to the SNpc, and loss of the parkin protein causes degeneration of SNpc and PPL1 neurons. Our lab has previously shown that parkin-null Drosophila exhibits swollen, fragmented PPL1 mitochondria that have elevated hydrogen peroxide levels and decreased glutathione redox equilibrium. To elucidate triggers of oxidative stress, we raised flies on food supplemented with manganese porphyrin antioxidants MnTnBuOE-2-PyP5+ and MnTE-2-PyP5+, which interact with nuclear factor E2-related factor 2 (Nrf2) and promote S-glutathionylation of protein cysteine. We use flies expressing highly sensitive fluorescent redox probes to determine the effects of supplementation on PPL1 mitochondrial hydrogen peroxide levels and glutathione redox equilibrium.

Methods: Control (park +/+) and parkin-null flies (park -/-) expressing redox-sensitive probes (mito-roGFp2-Orp1 for hydrogen peroxide levels and mito-roGFp2-Grx1 for glutathione redox equilibrium) in tyrosine hydroxylase-producing neurons were raised on standard food or food supplemented with 10 µM MnTnBuOE-2-PyP5+, MnTE-2-PyP5+. Flies were separated by sex, and brains were dissected on days 4-6, fixed, and incubated with an anti-tyrosine hydroxylase antibody followed by an Alexa 594 secondary antibody to identify dopaminergic neurons. Z-stacks of PPL1 mito-roGFp2s in oxidized and non-oxidized confirmations were captured, and the total volume of oxidized and non-oxidized reporter emissions were calculated for one PPL1 region. Two-way ANOVA were performed to determine the effects of sex and treatment on the ratio of oxidized to non-oxidized roGFp2.

Results: Female park -/- PPL1 mitochondrial hydrogen peroxide levels were higher than those for males. MnTnBuOE-2-PyP5+ supplementation decreased female park -/- mitochondrial hydrogen peroxide levels but increased those of males. No changes were detected in park +/+ flies.

Conclusions: Our observation of sexual dimorphism in parkin-null PPL1 mitochondrial hydrogen peroxide levels contributes to a limited pool of evidence for sexual dimorphism in parkin loss-of-function models. Many neurodegenerative diseases like Alzheimer’s affect females and male in a sexually dimorphic manner. Fundamental differences in brain mitochondrial redox environments in neurodegenerative disease patients could have important implications in development of therapeutic strategies, including further exploration of use of Mn porphyrin redox-active molecules. MnTnBuOE-2-PyP5+ appears to promote differential redox states that depend on the redox environment to which they are exposed.
RETINOBLASTOMA BINDING PROTEIN 7 (RBBP7), A KEY COMPONENT OF CHROMATIN-REMODELING COMPLEXES, PROTECTS AGAINST PATHOLOGICAL TAU ACETYULATION AND PHOSPHORYLATION AND IS REDUCED IN ALZHEIMER’S DISEASE. Judd JM, Winslow W, Serrano GE, Beach TG, Piras IS, Huentelman MJ, Velazquez R. Arizona State University; Arizona Alzheimer’s Consortium; Banner Sun Health Research Institute; Translational Genomics Research Institute.

Background: Aberrant chromatin remodeling and epigenetic dysfunction contribute to pathogenic gene expression in Alzheimer’s disease (AD). Past work has shown that epigenetic dysregulation may contribute to pathological tau, a key pathology in AD. Recently, we identified the Retinoblastoma Binding Protein 7 (Rbbp7) as a potential target for AD interventions. Rbbp7 is the chaperone component of chromatin-remodeling complexes to their nuclear targets, thereby mediating epigenetic modification. Our previously published data show that Rbbp7 mRNA is down regulated in AD patient brains compared to age-matched controls (CON). Additionally, Rbbp7 mRNA is negatively correlated with Braak stage (a tau pathology measure), and positively correlates with brain weight. Further supporting a role in neurodegeneration and tau pathology, Rbbp7 is downregulated in the PS19 mouse model of tauopathies, and its genetic overexpression in hippocampal (Hp) CA1 reduced tau acetylation, phosphorylation, and neuronal death.

Methods: The goal of the present study is to better understand the relationship between protein level of Rbbp7 and AD pathology and to determine whether utilizing the AAV/PHP.eB serotype to overexpress Rbbp7 throughout the brain reduces tau pathology more broadly in PS19 mouse. First, we obtained frontal cortical brain samples from severe AD (AD-Sev, n = 10), moderate AD (AD-Mod, n = 12), and CON (n = 9) human cases (balanced for sex) from Banner Sun Health’s Brain and Body Donation Program, that included cognitive scores (Mini-Mental State Examination (MMSE)), brain weight, CERAD neuritic plaque density, and Braak stage. Next, in mice, we retro-orbitally injected an AAV/PHP.eB to upregulate Rbbp7 globally in PS19 and NonTg mice at 3.5 months, prior to tau pathogenesis. Tissue was collected at 8.5 months.

Results: Rbbp7 protein levels are significantly reduced in AD-Mod and AD-Sev compared to CON. A significant positive correlation shows that higher Rbbp7 protein levels are associated with better MMSE and higher post-mortem brain weight. There were significant negative correlations between Rbbp7 levels and both CERAD neuritic plaque density and Braak stage, consistent with our previous report. In mice, we found significantly elevated levels of Rbbp7 protein in the cortex and Hp that was associated with a significant reduction in phosphorylated Tau at Threonine 181 and Serine 396. Multi-omics analysis using ATAC- and RNA-seq to assess epigenetic and transcriptomic changes of Hp tissue are ongoing.

Conclusions: Collectively, these results expand on our previous work showing that reduced Rbbp7 contributes to AD pathogenesis and that rescuing its levels reduces tau pathologies.
REHABILITATING LANGUAGE IN PRIMARY PROGRESSIVE APHASIA WITH TARGETED PHONOLOGICAL TREATMENT AND TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS). Kielar A, Nickels KV, Rising KL, Beeson PM. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer’s disease can result in a progressive and debilitating loss of language function manifesting as the logopenic variant of Primary Progressive Aphasia (lvPPA). In such cases, the neuropathological changes associated with AD accumulate in the left posterior temporo-parietal regions that support language processing, disrupting the dorsal language network that critically supports phonological skills for spoken and written language. The resulting language profile is characterized by reduced and slowed speech production, word retrieval difficulties, and impaired reading and writing. Although treatment research is in its early stages, there is limited, but encouraging, evidence that behavioral treatment directed toward strengthening weakened phonological skills can improve language function. Given the deliberating and progressive nature of the impairment, there is a pressing need to develop targeted interventions that would maximize the function of residual components of critical language networks and potentially slow the language decline. The aim of the present study was to improve language function in PPA by combining speech language therapy with fMRI-targeted transcranial direct current stimulation (tDCS) applied over preserved brain regions in the language processing network.

Methods: In a double-blinded, cross-over design 12 individuals with confirmed diagnosis of lvPPA (3 males; Age: M=70 years, SD =4.6; Edu=18 years, SD=4.6; Post onset=3.3 years, SD=1.9) were randomized to receive 10 sessions of phonological intervention with active tDCS or sham first. Following 2-months rest period, they were crossed over to the other treatment Phase. Response to treatment, generalization and maintenance were evaluated before and after each treatment phase as well as two months after the intervention. Active tDCS was delivered for 20 minutes at 1.5mA using 5x7 cm2 saline-soaked sponge electrodes. The active electrode was positioned over the preserved tissue in either the inferior frontal or posterior brain regions and determined individually for each participant based on the results of structural and functional neuroimaging and computational modeling of tDCS current flow.

Results: For both tDCS and sham groups treatment resulted in significant improvement of phonological skills. However, those receiving active tDCS first showed stronger generalization and maintenance of treatment gains. Functional value of our treatment protocol was evident in the tDCS first group on written narratives which contained more meaningful content with better spelling, and performance at follow-up significantly surpassed pre-treatment levels. These gains occurred in the context of relatively stable performance on other measures of cognition. These findings support the feasibility of our treatment protocol, and strongly support our hypotheses that individuals with lvPPA can improve phonological skills and that this will support language ability.

Conclusions: Our work to date suggests a particularly robust outcome after active tDCS with further consolidation of learning over rest phase, and maintenance at follow-up. Our study is the first to document that improved phonological skills resulted in better functional communication ability (text-level writing) relevant to the everyday lives of individuals living with PPA. Our study contributes to a growing body of evidence demonstrating that tDCS is a safe intervention that has potential to enhance benefits of speech-language treatment.

Background: Physical and cognitive activities are associated with decreased risk of mild cognitive impairment and dementia. However, the longitudinal associations between physical and cognitive activities with trajectories of Alzheimer’s disease (AD) neuroimaging biomarkers among older adults free of dementia remain unclear.

Methods: We conducted a longitudinal study derived from the population-based Mayo Clinic Study of Aging, including individuals aged ≥ 50 years who were free of dementia. Participants had information on physical and cognitive activity engagement in midlife (ages 30-45 for participants aged 50-69; ages 50-65 for participants aged ≥ 70) and late-life (12 months prior to baseline assessment), and AD biomarker assessments. We calculated linear mixed-effect models to examine the association between baseline physical and cognitive activity composite scores for mid- and late-life, and trajectories for individual yearly change in amyloid deposition (measured by PiB-PET), tau burden (measured by Tau-PET), regional glucose hypometabolism (measured by FDG-PET), cortical thickness (measured by MRI), and white matter hyper intensities (WMH, measured by FLAIR-MRI). The models were adjusted for age, sex, and APOE ε4 carrier status.

Results: The sample included 2794 persons (52% males; 2500 cognitively unimpaired, 294 with MCI). The mean [SD] age was 72.6 [9.9] years; 786 participants were APOE ε4 carriers. Although, overall, participants showed an increase in amyloid deposition, tau burden, WMH, and a decrease in glucose metabolism and cortical thickness over time, those with higher late-life physical activity experienced less pronounced increase in Tau-PET SUVR over time [estimate for late-life physical activity with time interaction: -0.002; 95% CI -0.004, -0.001; p = 0.005]. In addition, participants with higher cognitive activities in midlife [est. for midlife cognitive activity with time interaction: 0.001; 95% CI 0.0001, 0.003; p = 0.031] and late-life [est. for late-life cognitive activity with time interaction 0.002; 95% CI 0.0003, 0.003; p = 0.012] had less pronounced decrease in FDG-PET SUVR over time, and those with higher cognitive activities in midlife also had less pronounced increase in Tau-PET SUVR over time [est. for midlife cognitive activity with time interaction: -0.002; 95% CI -0.003, -0.0002; p = 0.031]. There were no further significant interactions.

Conclusions: Preliminary findings suggest significant associations between 1) late-life physical activity and less tauopathy, and 2) cognitive activities in mid- and late-life with less synaptic dysfunction over time. Further research is needed to validate study findings.

Background: The density and neuroanatomic localization of neurofibrillary tangles (NFT) are important to its contribution to cognitive impairment; they are associated to subclinical stages when restricted to subcortical locations while they are almost always associated with dementia when they are widespread in the neocortex. However, this is less clear for stages in between and cases with Braak NFT stage IV are sometimes associated with dementia and sometime not. Additionally, clinicopathological studies have demonstrated the importance of mixed pathologies as an important factor in the development of Alzheimer’s disease (AD) and other dementias. The presence of mixed brain pathologies may account for these cases with clinical dementia. We, therefore, aimed to compare the presence of additional neuropathologies in cases with Braak NFT stage IV with and without clinical dementia.

Methods: Subjects from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP) at Banner Sun Health Research Institute (BSHRI) that had a neuropathological Braak NFT stage IV and were selected and had received a cognitive evaluation within 2 years of death were selected. Logistic regression modelling, controlling for age, sex and education was performed using different neuropathologic characteristics to predict the presence of dementia or no dementia. Neuropathological characteristics included plaque density, Lewy body pathology, cerebral amyloid angiopathy (CAA), cerebral white matter rarefaction (CWMR) and total infarct volume. There was no case with progressive supranuclear palsy (PSP)-related pathology and cases with frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) were excluded.

Results: A total of 342 subjects were included. Of these, 188 were demented and 154 were not demented. Demented subjects had a higher plaque density, a higher Lewy body stage and density, a higher total tangle score, a higher cerebral amyloid angiopathy (CAA) score and a lower proportion of female (38% vs 54%) was observed. Logistic regression modelling identified neuritic plaque density and Lewy body pathology to be 2 independent predictors of dementia. When matched for low or high plaque density, Lewy body pathology is the only independent predictor of dementia. When excluding Lewy body pathology, CWMR is an independent predictor of dementia.

Conclusions: Our preliminary result suggests that the postmortem presence of co-pathologies may contribute to the presence of dementia in cases with Braak NFT stage IV. Our future direction includes looking into other pathology such as number of microinfarcts, TDP43 pathology and studying synaptic density in demented and non-demented cases matched for these pathologies. Artificial intelligence modeling will also be used to predict dementia drivers in Braak stage IV.
MEMORY, AFFECTIVE, AND MOTOR DYSFUNCTION IN PERSONS WITH NEURODEGENERATIVE MEMORY DISORDERS. McElvogue MM, Steffes L, Burke A, Stokes AM, Prigatano GP. Barrow Neurological Institute; Arizona Alzheimer’s Consortium.

Background: A previous study has shown that patients with mild cognitive impairment of the amnestic type (MCI-A) demonstrate significant dysfunction not only on measures of memory, but also on measures of affect expression and perception on the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) compared with healthy controls. Previous research has also shown that patients with MCI-A have a greater frequency of invalid finger tapping movements than healthy controls. The two goals of this study were (1) to replicate and expand comparisons of patients with MCI-A to those with subjective memory complaints (SMC) and Alzheimer’s dementia (AD) on the BNIS; (2) to explore the relationship between the frequency of invalid tapping movements and their association with impairments in memory and affect sub-scores on the BNIS. It is hypothesized that the number of invalid tapping movements will be greater in individuals who show impairment in memory and affective expression and perception.

Methods: Four groups of participants, including normally functioning older adults (n = 10; 4 males; 72 ± 7 years), SMC (n = 19; 8 males; 70 ± 6 years), MCI (n = 21; 13 males; 75 ± 5 years) and probable early AD (n = 11; 6 males; 75 ± 6 years) were included in this analysis. The BNIS and the modified version of the Halstead Finger Tapping Test (HFTT) were administered. A single factor ANOVA was conducted to compare the effect of cognitive status (group) on BNIS total score as well as on performance levels for memory and affect sub-test scores with Tukey HSD post hoc comparisons. Independent samples t-tests were conducted to compare the relationship of memory test performance on the BNIS as a function of the invalid finger tapping responses on the HFTT. For purposes of this exploratory study, a “normal” level of memory function was defined as ≥ 5 out of 7 possible memory subscale points and ≥3 out of 4 possible on the affect subscale.

Results: There was a significant group effect on BNIS score, with significantly lower total BNIS scores in AD than in SMC and HC, and in MCI than in SMC and HC (with p<0.001). There was a significant effect of group on BNIS memory subscale score [F(3, 54) = 32.3, p < 0.001] with post hoc comparisons indicating significantly lower scores in AD than in SMC (p < 0.001) and HC (p<0.001), as well as in MCI than in SMC (p <0.001) and HC (p<0.001). There was also a significant effect of group on BNIS affect subscale score [F(3, 54) = 4.2, p = 0.01], with SMC scoring significantly higher than MCI (p=0.01), though no significant differences were found between the AD group and all other groups. The number of invalid taps was significantly higher in the “abnormal” than the “normal” memory scoring group in the right hand, left hand, and bilaterally (t(56) =-3.7, p<0.001; t(56) =-3.6, p<0.001; t(56) =-3.9, p<0.001, respectively). However, the number of invalid taps was significantly greater in the “abnormal” than the “normal” affect cohort in only the left hand, (t(56) =-1.7, p=0.04).

Conclusions: This study replicated and expanded on a previous finding that patients with MCI-A have impairments not only in memory but in affect expression/perception compared to normal healthy controls and persons with subjective memory complaints. The total number of invalid tapping movements was greater in persons that showed memory and affective disturbances, but only the number of invalid tapping movements in the left hand correlated with affective disturbances when collapsing across groups.

Background: Astrocytes provide key neuronal support, and their phenotypic transformation is strongly implicated in neurodegenerative disorders including Alzheimer's disease (AD). Metabolically, astrocytes possess modest mitochondrial oxidative phosphorylation (OxPhos) activity, yet the pathological role of astrocytic OxPhos in neurodegeneration remains to be defined.

Methods: We generated the TfamAKO mice, in which transcription factor A mitochondrial (Tfam) is deleted selectively in astrocytes. Behavioral, electrophysiological, immunostaining, transcriptomics, metabolomics, and magnetic resonance imaging analyses were employed to characterize AD-relevant phenotypes of TfamAKO mice, which were further compared to an AD mouse model (5xFAD). Primary cell cultures and co-cultures were used to determine the cell autonomous and non-autonomous mechanisms by which disrupted astrocytic OxPhos induces astrocyte reactivity, neuroinflammation and neurodegeneration.

Results: Here we show that the brain critically depends on astrocytic OxPhos to degrade fatty acids (FAs) and maintain lipid homeostasis. Aberrant astrocytic OxPhos induces lipid droplet (LD) accumulation followed by neurodegeneration that recapitulates key features of AD including reactive astrogliosis, synaptic loss, microgliosis, demyelination, and cognitive impairment. Mechanistically, when FA load overwhelms astrocytic OxPhos capacity, elevated acetyl-CoA levels induce astrocyte reactivity by enhancing STAT3 acetylation and activation. Intercellularly, lipid-laden reactive astrocytes stimulate neuronal FA oxidation and oxidative stress, activate microglia via IL-3 signaling, and inhibit the biosynthesis of FAs and phospholipids required for myelin replenishment. Moreover, the metabolic and transcriptional signatures of the hippocampus of TfamAKO mice highly overlap with that of 5xFAD mice.

Conclusions: We reveal a lipid-centric, AD-resembling mechanism by which astrocytic mitochondrial dysfunction progressively induces neuroinflammation and neurodegeneration.

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Background: Alzheimer’s disease (AD) is an irreversible neurodegenerative disorder, which underlying pathogenesis remains largely a mystery. In the last several years, it has been suggested that neurolipids, which originate from membrane lipid precursors that include endocannabinoids (eCB) and sphingosine 1 phosphate (S1P) and possess agonistic or neuromodulatory properties within the gray (GM) and white matter (WM) are dysregulated in the frontal cortex (FC) in AD. Although the development of mass spectrometry, which provided a faster and more accurate detection of lipids in brain, alterations that occur in the AD cortex compared to healthy controls remain an active area of research.

Methods: We investigated eCB and S1P neurolipid-based signaling in relation to the lipidome in FC samples obtained from people who died with an antemortem clinical diagnosis of no cognitive impairment (NCI, n = 5; 86.27 ± 4.8 years), mild cognitive impairment (MCI, n = 5; 83.32 ± 7.4 years) and mild/moderate AD (mAD, n = 5; 92.04 ± 5.4 years) from the Rush Religious Orders Study cohort using autoradiography and matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) to localize the distribution of these lipids within the FC GM and WM. In addition, we performed a comparative MALDI-MSI analysis using tissue from younger healthy controls (mean age 68 ± 7, n = 5). Specifically, [35S] GTPgS autoradiography activity-mediated by CB1, S1P1 and M2/M4 muscarinic acetylcholine Gi/o coupled receptors (CB1R, S1P1R and M2/M4 mAChRs) and MALDI-MSI were used to determine receptor activity and positive/negative ionization lipid levels, respectively, in FC WM and GM.

Results: Quantitative analysis revealed an upregulation of M2/M4 mAChRs in FC layers V-VI in MCI compared to NCI. Cortical layer V-VI CB1R activity was also increased in mAD compared to NCI. Conversely, WM S1P1R activity was significantly downregulated in mAD compared to NCI. MALDI-MSI analysis showed upregulation of WM docosahexaenoic acid enriched phosphatidic acid (PA-DHA) and diacylglycerol 36:1 in MCI and AD compared to NCI, while WM arachidonic acid enriched phosphatidylinositol (PI-AA) were downregulated in mAD compared to NCI. In addition, WM PA-DHA and PI-AA showed an upregulation in the older compared to younger NCI cases. Correlation analysis revealed that alteration in WM PI-AA correlated with S1P1R activity and with perceptual speed performance in the clinical groups.

Conclusions: Together these data suggest that WM lipid, eCB and S1P neurolipid systems alterations are related to myelin dysfunction in the early stages of AD, resulting in connectome disruption.
GENOTYPIC EFFECT ON MICROBIOME COMPOSITION AND COLONIZATION IN A DROSOPHILA MELANOGASTER MODEL OF PARKINSON’S DISEASE. Olson SC, Chagolla SM, Call GB, Midwestern University; Arizona Alzheimer’s Consortium.

Background: Parkinson’s disease (PD) is often associated with predominantly motor and neurological symptoms. Recently, non-motor symptoms have begun to be associated with PD, the most common being gastrointestinal (GI) disturbances. Due to the high prevalence of these GI symptoms, it is thought that there is a mechanism of communication between the gut and brain. Our laboratory has found that the microbiome has developmental effects in PD model flies. Another study by our laboratory found Acetobacter tropicalis present in 72% of various PD model flies, compared to 47% in control flies, indicating that there may be something important about A. tropicalis in PD model flies.

Methods: To further pursue the microbiome differences seen between PD model and control flies, we inoculated both with a combination of equal amounts of four different bacterial strains, including L. brevis, L. plantarum, A. pomorum, and A. tropicalis. The adult flies were homogenized, plated, and the colonies were counted. To assess whether leaky gut syndrome (LGS) contributes to the changes in bacterial growth, we performed a Smurf assay. Additionally, to determine the location of any bacterial overgrowth, the gut of control and PD model flies were dissected, separated into distinct sections, and plated. The experiment was replicated using a trans-heterozygous PD model (park25/Df(3L)BSC553) to confirm our results.

Results: Overall, there was a much higher level of total colonization in the homozygous park25 flies compared to controls, and all flies that received the combination inoculation had an increased relative amount of A. tropicalis in their microbiome. The Smurf assay results did not indicate the presence of LGS. It was determined that the majority of the increased growth was occurring specifically in the crop, with all other sections showing no significant difference between park25 and control flies. The trans-heterozygous model, which exhibited a decrease in climbing and flight ability, also demonstrated a similar colonization phenotype like the park25 homozygous flies.

Conclusions: Both of the PD models have a notable increase in the amount of bacterial colonization when compared to control flies, with A. tropicalis being the predominant colonizer. The increased colonization occurs in the crop but is not due to LGS. This is evidence for genotype affecting microbiome composition. This could be a potential mechanism behind the gut dysbiosis observed in PD patients.
AMYLOID BETA ROLE IN TBI AND IMPLICATIONS FOR INCREASED RISK OF ALZHEIMER’S DISEASE. 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 including Alzheimer’s disease. Short term pathological changes after TBI result in parenchymal and axonal deposition of key protein variants associated with neurodegenerative diseases. In particular, increased levels of amyloid beta are generated immediately after TBI, at least partially as a protective measure to control hemorrhage at the blood brain barrier. We hypothesized that experimental TBI would result in the short term generation and longer term accumulation of key toxic protein variants, including amyloid-beta, 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 as well as IgG, monomeric amyloid beta and phosphorylated tau. 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: Acute effects of TBI (7 DPI) included substantial presence of IgG in brain tissue, predominantly localized near the site of injury, indicative of damage to the blood brain barrier. Strong staining of amyloid-beta was also observed at 7 DPI, where staining largely overlapped with the presence of IgG, suggesting a potential beneficial role of amyloid beta in repairing blood brain barrier damage following brain injury as previously observed. Consistent with these results, all the correlations between protein variant levels and behavioral deficits at the 7 DPI acute timepoint were between the A4 extracellularly generated oligomeric amyloid-beta variant and in brain regions near the site of injury. These results indicate a rapid generation of amyloid beta following injury as a protective mechanism to minimize brain damage. Long term sub-acute behavioral deficits were all between either an intracellularly generated oligomeric amyloid-beta variant (C6T) or an oligomeric tau variant (F9T). Both of these protein variants associate very strongly with and are excellent biomarkers for AD.

Conclusions: Levels of different ADRD related proteins were elevated shortly after TBI, and in general levels declined and behavior deficits resolved within 14 DPI. However, levels of amyloid beta are sharply upregulated after injury as a potential response to control bleeding into the brain. We show that total amyloid-beta levels particularly near the site of injury are quite dramatically increased shortly after TBI, and levels of small oligomeric amyloid-beta aggregates correlate with acute behavioral deficits. While these changes essentially resolved by 14 DPI, individual mice showed long term sub-acute behavioral deficits that correlate with generation of specific amyloid-beta and tau variants strongly associated with early stages of AD. These results indicate that effective therapeutics targeting amyloid-beta should selectively target amyloid-beta variants.
implicated in chronic behavioral deficits such as the C6T variant, rather than variants that play a role in maintaining the integrity of the blood brain barrier. Targeting the extracellularly generated amyloid aggregates run the risk of increasing the risk of cerebral hemorrhage in treated patients as observed in several clinical trials targeting extracellular amyloid-beta aggregates.

Background: Transactive Response (TAR) DNA Binding Protein (TDP-43) is a highly conserved RNA & DNA binding protein composed of 414 amino acids that primarily resides in the cell nucleus. The translocation and aggregation of TDP-43 from the nucleus to cell cytoplasm is a common pathological feature of many neurodegenerative diseases like amyotrophic lateral sclerosis (ALS), Frontotemporal lobar dementia (FTLD), and Alzheimer’s Disease (AD). While there is substantial evidence to support phosphorylated TDP-43 (p-TDP-43) aggregation in the CNS, recent studies have reported the presence of pTDP-43 aggregation in Schwann Cells cytoplasm in peripheral nerves of ALS subjects. Despite efforts in clinical diagnosis of ALS using medical history, clinical examination and electrophysiological testing, there are no specific biomarkers available. Here, we determine if p-TDP43 aggregates are present in peripheral tissue of cases with known TDP43 pathology in the spinal cord to explore the use of peripheral tissue biopsies as a potential biomarker to improve clinical diagnosis.

Methods: In this study we performed immunohistochemistry (IHC) against pTDP-43 using an antibody that detects p-TDP-43 at residues 409 and 410. We selected five cases from the Brain and Body Donation Program at Banner Sun Health Research Institute’s with motor neuron disease or FTLD known to have positive p-TDP-43 inclusions in the spinal cord. We screened sciatic nerve paraffin sections (6um) from those five cases. In addition, paraffin sections from other peripheral organs such as the submandibular gland, lower esophagus, stomach, colon, rectum, bicep muscle, quadricep muscle, psoas muscle, sciatic nerve, scalp, and spinal cord were screened for one of the five cases, a severe ALS case. Free-floating 40um sections of muscle and submandibular gland were used as follow up confirmation.

Results: Only one of five cases, a middle-aged man with a c9orf72 repeat expansion mutation, had potentially specific pTDP43 positive staining in the sciatic nerve, submandibular gland and muscle.

Conclusions: Our preliminary findings suggest that pTDP-43 aggregation might not be limited to the CNS. Additional cases will be screened to determine the prevalence of pTDP43 expression in the periphery in ALS and FLTD cases. The development of reliable and non-invasive techniques to detect and monitor peripheral pTDP-43 pathology in living individuals would be a great advance towards better clinical diagnoses.
DEFAULT MODE NETWORK SPLICING PROTEIN ALTERATIONS IN DOWN SYNDROME WITH ALZHEIMER’S DISEASE-RELATED DEMENTIA. Perez SE, Nadeem M, He B, Malek-Ahmadi M, Mufson EJ. Barrow Neurological Institute; Banner Alzheimer’s Institute; Arizona Alzheimer’s Consortium.

Background: Down syndrome (DS) forms the largest population with a genetic predisposition to develop Alzheimer’s disease (AD) and by the fourth decade of life exhibit tau containing neurofibrillary tangles (NFTs) and Aβ plaques, which increase with age. However, only about 70% develop dementia. We recently reported that DS with AD-related dementia (DSD+) display a greater number of NFTs consisting of a more advanced tau pathology compared to DS people without dementia (DSD-) in the frontal cortex (FC), a component of the default mode memory network (DMN), suggesting that differences in tau pathobiology are linked to DS dementia. Another hub of the DMN episodic memory connectome is the precuneus (PreC), which appears resilient to extensive tau pathology suggesting differential neuronal vulnerability within the DMN. Although the cellular mechanisms that underlie the differences in tau pathobiology between DSD+ and DSD- and DMN regional vulnerability remain unknown. Recent observations suggest that RNA splicing proteins play a role in tau pathogenesis in AD and DS.

Methods: Here, we quantified the level of several tau-related splicing proteins (i.e., phospho-RNA polymerase II (pS5,2 and pS5-RNA pol II), serine/arginine splicing factor 2 (SRSF2), small nuclear ribonucleoproteins U1-70K and U1A, heterogenous ribonucleoproteins A2/B1 (hnRNPA2/B1), and kinase CLK1 involved in phosphorylation of SR splicing factors) as well as tau isoforms (3Rtau and 4Rtau) by immunoblotting of frozen FC and PreC tissue samples obtained from DSD+ and DSD-.

Results: In the FC we found a significant upregulation of hnRNPA2B1, pS5,2-RNA pol II and 4Rtau in DSD+ compared to DSD-, while FC U1-70K protein levels were downregulated in DSD+ compared to DSD-. Conversely, only the 3Rtau protein levels were significantly upregulated in the PreC in DSD+. Correlational analysis revealed that FC U1A protein values were positively correlated with CLK1 and 4Rtau correlated with Braak staging across clinical groups. PreC U1-70K were associated with hnRNPA2/B1 and 3Rtau correlated with Braak staging. Comparison between the two DMN hubs revealed an upregulation of the CLK1 protein levels in FC compared to PreC in DSD-, while in DSD+ FC SRSF2 and 4Rtau protein levels were upregulated. FC pS5,2-RNA pol II and U1-70K were downregulated compared to PreC.

Conclusions: These findings suggest that tau-related splicing protein alterations are greater in the FC in DSD+ and contribute differentially to DMN regional pathobiology in DS.

**Background:** In this study we utilized data from All of Us (AoU) research program to assess risk factors associated with the onset of Alzheimer’s Disease (AD). The AoU research program has gathered data from a diverse group of over a million participants from various regions across the U.S. This includes initial physical assessment, self-reported surveys, and high-throughput genetic data.

**Methods:** We used the most recent Controlled Tier Dataset v7 (CDRv7), which includes the clinical and demographic data for 410,235 individuals and short-read Whole Genome Sequencing (srWGS) for a subset of 146,804 participants. We primarily focused on the medical conditions and measurements data tables. Firstly, we included participants with medical conditions not related to AD or to AD risk, along with medications. For the medical conditions, we selected individuals of both sexes, aged at least 60 years, with associated srWGS data, obtaining a final cohort of 72,044 participants (average age 69.0 ± 6.2; sex ratio F:M 1.27). For the measurements, the number of participants varied depending on the specific variable, with a range from 2 to 78,265. The measurement maximum sample size did not align with the conditions because age estimation for those measurements was based on the date of testing, rather than on a fixed cutoff date. The AD polygenic risk score (AD-PRS) was calculated as described by Maree et al. (PMID: 29484742) with the SNPs (adj-p < 0.05) from Lambert et al. (PMID: 24162737) and included in AoU srWGS (N=3,739). Finally, we assessed the relationship between PRS score, medical conditions, and measurements using a linear model, adjusting for sex and age. In both cases, PRS was the dependent variable, while the conditions (presence/absence) and measurement value were the predictors.

**Results:** We included variables with a condition frequency or measurement performed in at least 1% of the cohort (N=720 for conditions, and N=783 for measurements), obtaining 1,076 and 362 variables, respectively. After adjusting for Bonferroni correction, we found 9 and 18 variables to be statistically significant, respectively. The condition most strongly associated was hypothyroidism (frequency: 14.0%; β =-4.345; adj-p=6.7E-11), showing a lower average AD-PRS in affected versus non-affected (43.2 and 47.9, respectively). The top measurement was height, showing a positive correlation with AD-PRS (β = 0.005; adj-p = 7.8E-20). We further analyzed the hypothyroidism finding, including the administration of hypothyroidism medications in the model (as a dichotomous variable), and still found a significant result (adj-p = 2.9E-06). Finally, we replicated these findings using the UK Biobank data (N=390,543), confirming the results after the adjustment for age and sex (Bbeta=-2.970; p=1.3E-23).

**Conclusions:** Our study revealed that participants with hypothyroidism have a lower genetic risk for AD, as estimated by PRS. This suggests that hypothyroidism could potentially be considered as a modifier for AD risk, interacting with the genetic component. Mechanisms proposed are related to the association of low thyroid hormones with increased amyloid precursor protein gene expression (PMID: 17199430), as well as a decrease of thyroid-releasing hormone, associated with tau phosphorylation (PMID:12214133) and reduction in acetylcholine (PMID:24171118). Although previous studies have highlighted the association of hypothyroidism with AD and cognitive impairment (PMID: 35321339, 18663163, 28343318), our study expands on these findings by considering the genetic component of AD.

In women, decreases in circulating ovarian hormones and the onset of menopause have been associated with cognitive decline and increases in dementia risk. In preclinical rodent models, it has been well-documented that ovarian hormones, and surgical removal thereof via ovariectomy (Ovx), impact cognitive processes. In addition, we have recently shown that hysterectomy alone impairs cognition in a rodent model. However, the molecular underpinnings of the impacts of surgical reproductive tract manipulations are poorly understood. In this study, we use transcriptomics to identify hormone-uterus-brain-behavior relationships at the molecular level. To examine the uterus gene expression profile with and without its primary hormonal stimulator, the ovaries, uterine tissues were collected from an animal model with and without Ovx. RNA sequencing of the uterine tissues revealed broad scale changes in gene expression after Ovx, and correlations with specific aspects of learning and memory are ongoing. RNA sequencing of brain regions involved in learning and memory in the same animals whose uteri were profiled is currently being performed in order to identify genes differentially expressed in the brain following removal of ovarian hormones. Collectively, this work will show how the uterus is impacted by removal of its primary hormonal stimulator, as well as how removal of the ovaries affects the central nervous system, together yielding insight into the molecular factors underlying changes in cognitive function with reproductive tract manipulation. The knowledge gained from this study will have profound impacts on deciphering hormone-uterus-brain-behavior relationships, and will directly address the gap in the field regarding molecular contributions to cognitive outcomes associated with varied experiences of menopause.
POTENTIAL GREATER RELATIVE REDUCTION OF WHITE MATTER HYPERINTENSITY ACCUMULATION WITH INTENSIVE SYSTOLIC BLOOD PRESSURE CONTROL AT YOUNGER AGES. Pruizin JJ, Reboussin DM, Nassrallah I, Cushman W, Gupta A, Williamson J, Tariot PN, Pajewski NM. Banner Alzheimer’s Institute; Wake Forest University School of Medicine; University of Pennsylvania; University of Tennessee; University of Kansas Medical Center; Arizona Alzheimer’s Consortium.

Background: White matter hyperintensities (WMH) visualized on magnetic resonance imaging (MRI) likely indicate the presence of small vessel vasculopathy and reduced perfusion. Systolic blood pressure (SBP) is the modifiable risk factor most strongly associated and predictive of future WMH volume (WMHV) accumulation, although advanced age is the strongest overall predictor of greater WMHV. Lowering SBP reduces WMHV accumulation, however it is unknown if age at which SBP begins influences the degree of WMHV reduction. We examined potential distinctive effects of intensive SBP control on WMHV accumulation at different ages.

Methods: We examined the difference in change in log transformed longitudinal WMHV accumulation, adjusted for intracranial volume, in participants from the Systolic Blood Pressure Intervention Trial (SPRINT) MRI sub study at different ages, comparing 251 participants randomized to an SBP goal <120 mm Hg to 201 participants randomized to an SBP goal of <140 mm Hg stratified into three age groups (<65, 65-75, and >75 years old). We then calculated the ratio of WMHV at follow up to that at baseline according to age at randomization by SBP group.

Results: The average SBP during treatment for participants in the goal <120 mm Hg group (intensive treatment) were 120 mm Hg (<65), 121 mm Hg (65-75), and 123 mm Hg (>75). Mean SBP in the goal <140 mm Hg group (standard treatment) were 135 mm Hg (<65), 135 mm Hg (65-75), and 136 mm Hg (>75). The average interval between baseline and follow up MRI was 3.9 years for both groups. The intensive BP group <65 years old had the least WMH accumulation compared to the standard BP control group, followed by those 65-75 years old, with participants >75 years demonstrating the smallest difference in accumulation (Figure 1). Plotting the ratio of WMHV at follow up MRI to that at baseline according to age at randomization in both groups suggests SBP lowering at younger ages results in a larger proportional effect in reducing WMHV accumulation (Figure 2). These results did not reach statistical significance.

Conclusions: Lower SBP might have a greater effect on WMHV accumulation at younger ages. Large prospective studies that include younger individuals closer to the age at which WMH start to accumulate are needed to determine potential differential effects of SBP lowering across the lifespan.

**Background:** Matrin 3 is a highly conserved nuclear matrix DNA and RNA binding protein. Mutations in Matrin 3 have been associated with distal myopathy, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia, while its haploinsufficiency has been shown to cause early neurodegeneration. In addition, aggregates of wild type Matrin 3 have been recently detected in AD brains with granulovacuolar degeneration, and preliminary data from our group shows alterations in subcellular localization of the protein in frontal cortex of AD and FTD. To date there is no in depth analysis of the role of Matrin in human dementias. Here we investigate the role of Matrin 3 in neurodegeneration using two complementary approaches. We assessed Matrin 3 subcellular localization and biochemical alteration in human postmortem tissues from non-neurodegenerative disease controls, AD and FTD patients, and correlate changes to neurodegenerative pathological hallmarks. Taken together, data generated from this work will shed light on the extent of matrin 3's involvement in the neurodegenerative disease spectrum.

**Methods:** We examined the subcellular localization of Matrin 3 within subregions of patient brain tissues using immunohistochemistry.

**Results:** Our results demonstrate that Matrin 3 pathology is found within the brains of patients with dementias. Cytoplasmic mislocalization, nuclear aggregates, and nuclear loss were observed in a variety of different dementias/neurodegenerative states including Frontotemporal lobar degeneration, Alzheimer's Disease, and Down Syndrome.

**Conclusions:** These findings demonstrate the matrin 3 pathology is not isolated to amyotrophic lateral sclerosis and found in different dementias. These data suggest that matrin 3 may have a broader role in neurodegeneration, and can be altered in a variety of disease states. Future work will be focused on understanding how matrin 3 is altered in disease, and how those alterations could influence function. Completion of those studies could possibly illuminate novel disease mechanisms.

Background: Women develop Alzheimer’s disease (AD) at a 2:1 rate compared to men. Changes associated with menopause exacerbate a midlife bioenergetic crisis that, when unsuccessfully resolved, leads to white matter degradation and ultimately brain atrophy. Understanding how white matter structural properties differ between sexes and evolve over midlife transitions may provide insight into the exacerbated AD risk for women. Here, we report differences in white matter bundle properties comparing pre- (n=40, 44.1±3.34y), peri- (n=60, 49.6±3.90y), and post-menopausal women (n=70, 56.0±4.12y) to age-matched males.

Methods: Diffusion weighted MRI was acquired for each participant. Data were preprocessed with QSIPrep and analyzed using a fixel-based approach implemented in MRtrix (v. 3.0.3). Fiber density (FD), cross-section (FC), and a combined density/cross-section metric (FDC) were compared between sexes after controlling for age, education, APOE e4 carrier status, and total brain volume (FC and FDC only). Continuous covariates were standardized to 2 standard deviations. Analyses were conducted using connectivity-enhanced fixel-based permutation analyses and thresholded at family-wise error corrected p<0.05.

Results: Pre-, peri-, and post- menopausal women exhibited greater FD and FDC in the corpus callosum, inferior occipito-frontal fasciculus, cortico-spinal, and cingulum bundles. By contrast, males had greater fiber cross section in the splenium of the corpus callosum (compared to pre-), (compared to peri-), and in fibers near the left uncinate fasciculus and inferior longitudinal fasciculus (compared to both peri- and post-menopausal women). After controlling for age, education, total brain volume, and APOE e4 carrier status, a smaller cluster of fibers in the left splenium survived multiple comparisons correction demonstrating greater fiber cross-section in post-menopausal women compared to peri-menopausal women.

Conclusions: Women across menopausal transition states exhibited greater fiber density than their age-matched male counterparts in commissural and association tracts, which agrees with previous work demonstrating stronger inter-hemispheric connections in women. However, peri- and post-menopausal females exhibited 4-8% decrease in fiber cross section in uncinate fasciculus fibers, which have been implicated in Alzheimer’s related cognitive decline. These findings suggest that reductions in white matter cross-section, particularly in regions associated with Alzheimer’s disease, may begin for women in menopause and be an early indicator of neurodegenerative risk.

Background: Age, female sex and the APOEε4 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. We previously identified LOAD-associated transcriptomic signatures as a function of both sex and APOE genotype. Here we extend these analyses to examine the association between these signatures and imaging-derived phenotypes (IDPs).

Methods: Brain RNA-Seq datasets from the ROSMAP (syn8456637) were obtained from the RNA-Seq Harmonization Study 1on AMP-AD, including 369 frontal cortex samples from APOEε3/ε3 and APOEε3/ε4 individuals. For each sex (Male, Female)-genotype (APOEε3/ε3, APOEε2ε3/ε4) condition, differentially expressed genes (DEGs, p-value < 0.05) between individuals with LOAD and cognitively normal controls were identified. IDPs were generated from a sample of individuals (n = 1155) obtained from ROSMAP, including n=62 also present in the RNA-Seq Harmonization Study. T1-weighted MRIs were processed using Fastsurfer (v.2.0.4) and cortical thickness (CT) and subcortical volumes (SV) were computed from the Desikan-Killiany Atlas and Freesurfer’s subcortical atlas. After multi-site harmonization and covariate adjustment for age, education, and total brain volume (SV only), effect sizes (Cohen’s d) were computed for controls vs. AD for each sex (male/female)-genotype (APOEε3/ε3 or APOEε4 carriers) pairing. We then filtered the DEG lists to include those genes present in the Allen Human Brain Atlas and the correlations between these effect sizes and the mean regional expression of the top 10 up and downregulated DEGs. Correlations were fit using spin (cortical thickness) or sign shuffling (subcortical volume) permutation tests.

Results: Compared to cognitively unimpaired individuals, those with AD exhibited lower CT and SV in generally anticipated patterns, with the largest differences noted for cortical thickness in temporal and posterior cingulate regions as well as the hippocampus. However, male APOEε4 carriers had greater CT in a more extensive range of regions. Greater regional mean expression of the up (female APOEε3/ε3, male APOEε4) and down (female APOEε3/ε3, male APOEε3/ε3, male APOEε4) regulated DEGs was associated with less CT in AD patients (r = 0.21-0.41, p < 0.046). In APOEε4 carriers, greater mean up (male, female) and down (female APOEε3/ε3, male APOEε3/ε3, male APOEε4) DEG expression was associated with greater SV in the AD patients (r = -0.48 -0.57, p < 0.043), while greater mean downregulated DEG expression in APOEε3/ε3s showed smaller SV (r = 0.56, p = 0.021). Notably, greater median APOE expression was correlated with less CT in AD patients across sex-genotype pairings (r = 0.38-0.86, p < 0.002), lower SV (females, all genotypes) and greater SV (male APOEε3/ε3). Interestingly, no associations between median DEG expression and CT were observed in female APOEε4 carriers.

Conclusions: Our analyses provide novel associations of sex and APOE genotype specific transcriptomic signatures and imaging derived brain features in LOAD brains. Our findings suggest the following: 1) median APOE expression is strongly associated with loss of cortical thickness in AD patients regardless of sex or genotype; 2) risk-factor specific, transcriptome-level dysregulation exhibits risk-factor specific CT and SV association profiles; 3) precision medicine, risk-factor specific prevention and therapeutics targeting transcriptome level dysregulation would be expected to alter the magnitude of association between gene expression and CT/SV profiles. The present analyses support the identification and use of risk-factor specific biomarkers of target engagement for preventative and therapeutic interventions.
A FLEXIBLE SCHEME FOR TEACHING NEURODEGENERATIVE DISEASE TO GRADUATE STUDENTS: USING THE SPECTRUM OF GENETIC CAUSATION AS AN ORGANIZING PRINCIPLE. Restifo LR. University of Arizona; BIO5 Research Institute; Arizona Alzheimer’s Consortium.

Background: The development of safe and effective treatments for neurodegenerative disorders has lagged behind that of most other types of medical conditions. There is a compelling argument for teaching the next generation of neuroscientists more about these challenging diseases from both basic-science and clinical perspectives. The starting premise is the importance of teaching clinical diagnostic logic, including differential diagnosis and disease classification, along with the research that revealed pathophysiology, underlying mechanisms, and avenues for drug discovery. Together, these teaching goals represent a major challenge.

Methods: Over a period of 30 years, a graduate-level 'disease course' at University of Arizona has been developed by repeated trials with varying course formats and content, as well as an evolving approach to prerequisites and student evaluation. I present a classroom-based strategy that avoids hyper-focus on individual molecules, signaling pathways, cellular subtypes, neuroanatomical regions, or any specific research methodology.

Results: To choose which neurodegenerative diseases to cover, a two-fold approach was used. First, focus on several exemplar diseases in depth rather than cover many superficially. Second, use the spectrum of genetic causation to create a 4-part disease menu to select from. At one end of the spectrum, the Simple Monogenic Group includes Huntington's disease, spinal muscular atrophy, and Duchenne muscular dystrophy. The Heterogeneous Monogenic Group includes diseases that are caused by mutations in any of a large number of genes, e.g., peripheral neuropathies, spinocerebellar ataxias, and the degenerative subset of sensori-neural deafness. Next, the Familial-or-Sporadic Group, contains the 'big three' – Alzheimer’s, Parkinson's, and amyotrophic lateral sclerosis – as well as Lewy body disease, frontotemporal dementia and prion diseases. In this group, single genes, gene-X-environment (GXE) interactions, and polygenic inheritance can all play a role. Finally, the Complex Disease due to GXE Group includes multiple sclerosis, neuromyelitis optica, and autoimmune encephalitis.

In addition to the difficulty of the material, other challenges emerged. Future neuroscientists are inclined to believe what they read in the literature. At the outset, most are unaware of the need to assess the validity of cellular and animal models used for research or to question prevailing hypotheses about disease mechanisms. Many assume that diagnostic criteria are stable and valid. Not all are familiar with basic genetics concepts. Variation in students' academic backgrounds is a double-edged sword. At times, it can promote outstanding classroom discussion. However, a substantial fraction of students is reluctant to participate; the pandemic did not help.

Conclusions: Students from a wide range of life science disciplines respond well to comprehensive exploration of exemplar neurodegenerative diseases, including differential diagnosis and systems-level pathophysiology. Alongside the breadth and depth of knowledge gained, they develop essential analytical reasoning skills that can enhance their current and future research. Incorporating clinical concepts and controversies into a research-emphasis course may help bridge the cultural divide between scientists and physicians.

**Background:** Arizona is the home to an NIA-Designated ADRC Center but, there is a historically disproportionately low enrollment of Hispanic/Latino research participants compared to Arizona's diverse population.

**Methods:** We used data from the National Alzheimer's Coordinating Center (NACC) to investigate the recruitment of Hispanic/Latino participants in Arizona beginning in the year of 2003 to 2023. We examined the retention of 261 AZ ADRC participants from their initial diagnosis to the last visit diagnosis. We evaluated three distinct categories of recruitment in order to find the methods that are most effective. Relevant categories included are magazine/paper ads, internal site campaigns, and face-to-face interactions.

**Results:** New Hispanic/Latino ADRC participants were at its highest recruitment rate in the year of 2022 with 50 participants. During recruitment screening 44.7% of participants indicated they were interested in the study in response to magazine/paper ads, 26.9% due to internal site campaigns, and 28.4% due to face-to-face interactions.

**Conclusions:** Results suggest most effective methods to increase enrollment are through magazine/paper ads. Targeted media advertising should be regularly employed and combined with face-to-face interactions and internal site campaigns.
SEX-SPECIFIC MULTIPARAMETER BLOOD TEST FOR THE EARLY DIAGNOSIS OF ALZHEIMER’S DISEASE AND POTENTIAL IMPLICATIONS FOR THERAPEUTIC TRIALS.

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 Aβ and tau, however small soluble oligomeric forms of Aβ, tau and TDP-43 are widely considered to be the relevant toxic protein variants and represent promising early stage biomarkers for AD. We developed a pool of reagents that very selectively bind toxic oligomeric variants of these proteins and show that a panel of these reagents can very effectively diagnose early stage presymptomatic AD cases using a multiparameter blood test.

Methods: We utilized a panel of nine different scFvs developed in our lab in a sensitive sandwich ELISA to detect biomarker variants present in human blood plasma. The nine different scFvs were used as capture antibodies and a phage display version of a pan specific anti-Aβ, tau or TDP-43 scFv was used as a detection antibody. Bound detection phage were identified using an avidin-HRP antibody 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: To identify early stage AD biomarkers, we divided the plasma samples collected from patients that converted to AD into groups: 1) samples collected prior to clinical diagnosis of MCI (pre-MCI), 2) samples collected before diagnosis of AD. We analyzed results obtained comparing only the preMCI plasma samples from the AD cases to the cognitively normal cases and six of the nine scFvs showed statistically significant differences including an Aβ variant (C6T), four tau variants (D11C, ADTau2, ADTau4 and ADTau6) and the TDP-43 variant (AD-TDP3). When presymptomatic AD cases were separated by sex, different biomarker patterns between males and females were observed. Using specific biomarker panels, ROC analysis identified 11 out of 11 female AD cases and 13 of 14 male AD cases, specificity of 96% for presymptomatic identification of AD cases. The sex specific biomarker panel also identified 5 of the 25 control cases as also being presymptomatic AD cases, well within the expected number of undiagnosed presymptomatic AD cases for the control group. Significantly, 4 of these 5 flagged presymptomatic control cases showed a decline in MMSE score at the last time point tested and also an increase in biomarkers levels in blood samples taken from the last time point, suggesting that at least 4 of the 5 flagged controls were correctly identified as presymptomatic AD cases. Interestingly, there were significant differences in the Aβ and tau biomarker variant profiles between male and female AD cases, where males had a stronger dependence on Aβ variant levels and females had a stronger dependence on tau variant levels.

Conclusions: A simple multiparameter blood based assay using sex-based panels of reagents targeting protein variants selectively present in human AD samples can diagnose early presymptomatic AD cases with very high sensitivity and specificity. The differences in Aβ and tau variant biomarker profiles detected in male and female AD cases may also explain the differences observed in clinical trials targeting Aβ where significant therapeutic benefit has been observed in male AD cases but not in female AD cases.
AGE-DEPENDENT CEREBRAL MICROVASCULAR DYSFUNCTION IN APOE4 KNOCK-IN MICE. Silva JF, Pires PW. University of Arizona; Arizona Alzheimer’s Consortium.

Background: Apolipoprotein E (ApoE) is involved in the transport of cholesterol through its interaction with ApoE receptors. ApoE is found in three isoforms: ε2, ε3, and ε4, of which the ApoE4 isoform is strongly linked to an increased risk of Alzheimer’s disease, a condition associated with significant vascular dysfunction. Although there has been significant progress in understanding how ApoE4 drives amyloid pathology in the brain, its effect on cerebrovascular function remain poorly defined. We hypothesized that presence of ApoE4 allele will lead to age-dependent cerebral microvascular dysfunction in mice.

Methods: Parenchymal arterioles from 6-months-old and over 18-months-old male and female ApoE4 and ApoE3 (controls) knock-in mice were isolated for ex vivo using pressure myography. Basal cortical perfusion and neurovascular coupling were evaluated by laser speckle contrast imaging. Data are means ± SEM, analyzed by two-tailed Student’s t-test.

Results: Arterioles from 6-months-old ApoE4 mice have significantly lower myogenic tone compared with aged-matched ApoE3 mice, a difference that was not present in arterioles from mice >18 months-old. Further, although 6-months-old ApoE4 mice did not show significant structural and biomechanical arteriolar changes, our preliminary data showed that arterioles from 18-months-old ApoE4 mice have increased vessel and lumen diameters with no changes in wall thickness when compared to arterioles from ApoE3 mice, suggesting the occurrence of outward eutrophic remodelling. As a consequence of the increase in lumen diameter without adaptations in wall thickness, arterioles from ApoE4 mice showed high levels of radial wall stress when compared with ApoE3. Basal cerebral perfusion shows a trend to be higher in 6-months-old ApoE4 mice when compared with ApoE3. There was no change in neurovascular reactivity in mice with 6-month-old or over 18-months-old.

Conclusions: Our preliminary data suggest that presence of the ApoE4 allele leads to an age-dependent increase in spontaneous myogenic tone and structural outward arteriole remodeling in parenchymal arterioles of mice.

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**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 observed in aging and Alzheimer’s disease. We previously reported our results from a study that examined 30 micrometer coronal brainstem sections along the rostral-caudal axis of the LC from a colony of 30 cognitively assessed rhesus macaques ranging in age from 7 to 32 years (human equivalent ~21-96 years). We used AMIRA software to reconstruct the LC from tyrosine hydroxylase (TH)-immunofluorescence and Nissl-stained serial sections aligned with previously collected MRI data. Using this method, we established the 3D structure of the LC nucleus and its subnuclei: LC lateral, LC medial, and LC compact (Sinakevitch et al. Program No. 574.08. 2022 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2022.)

**Methods:** Here we present further analysis and description of one of the LC subnuclei: LC compact. The LC compact is the area of the LC with the highest neuronal density. It is located within the LC medial nucleus, which is comprised of both a densely packed region and a more scattered region of TH-positive cell bodies within periaqueductal gray (PAG), which surrounds the 4th ventricle. Analysis from a subset of the macaques (n=8) reveals that the rostro-caudal extent of the whole LC is between 2.10-2.55 mm. LC compact extends rostro-caudally from 1.44-1.95 mm within LC medial and it has TH-positive neurons with similar structure and cell diameters ranging from 29-43 micrometers. In rhesus macaques the LC compact has three subregions: rostral, middle, and caudal. The rostral LC compact begins with a small area of cells with high density near the enlarged mesencephalic nerve (me5) in the PAG. The middle LC compact extends through almost all the LC medial along the dorso-ventral axis, and the caudal LC compact is a small area with the highest density of cells.

**Results:** The volume of the LC compact varied from 0.62-0.92 mm3 (on each side) and comprises up to 69% of the total TH-positive cells in the LC. The fact that the LC compact closely follows the me5 tract raises the question of whether this structure may interact with the me5 tract.

**Conclusions:** These detailed characterizations of LC compact might be used to further examine the specificity of the impact of age on this LC subnucleus.
DISSOCIATIVE EFFECTS OF AGE ON NEURAL DIFFERENTIATION AT THE LEVEL OF STIMULUS CATEGORIES AND INDIVIDUAL STIMULUS ITEMS. Srokova S, Aktas ANZ, Koen JD, Rugg MD. University of Arizona; University of Texas, Dallas; University of Notre Dame; Arizona Alzheimer’s Consortium.

Background: Increasing age is associated with age-related neural dedifferentiation, a reduction in the selectivity and specificity of neural representations, a phenomenon which has been proposed to contribute to cognitive decline in older age. Recent findings indicate that, when operationalized in terms of neural selectivity for perceptual stimulus categories, age-related neural dedifferentiation, and the age-invariant association with memory performance, are largely restricted to the cortical regions typically recruited during scene processing. The factors which contribute to age-related neural dedifferentiation are currently unknown.

Methods: We examined neural selectivity at the levels of stimulus categories and individual stimulus exemplars using multivoxel pattern similarity analysis (PSA) of fMRI data. Cognitively healthy young and older adults viewed images of objects and scenes. Some items were presented singly, while other items were followed either by an exact repetition of the image or a visually similar exemplar. Category-level selectivity was computed as the difference between within-category similarity (e.g., average correlation between all scene trials with all other scene trials) and between-category similarity (e.g., average correlation between all scenes with all objects). Item-level selectivity was computed as the similarity between a given trial and its repeat (or similar lure) minus the average similarity with all other repeats (or lures) belonging to the same image category.

Results: Consistent with recent findings, category-level PSA revealed robustly lower differentiation in older than younger adults in the scene-selective, but not object-selective, cortical regions. By contrast, at the item-level, robust age-related declines in neural differentiation were evident for both stimulus categories. Moreover, we identified an age-invariant association between category-level scene-selectivity in the parahippocampal place area and subsequent memory performance, but no such association was evident for item-level metrics.

Conclusions: Prior research indicates that while scene-related selectivity is reduced in older age and is correlated with cognitive performance independently of age, category-level selectivity for object stimuli is typically not moderated by age or memory performance. Here, we demonstrate that neural dedifferentiation is evident for both scene and object exemplars when it is defined in terms of the specificity of neural representations at the level of individual exemplars. These findings suggest that neural selectivity metrics for stimulus categories and for individual stimulus items depend on different neural mechanisms which are differentially impacted by increasing age.
APOE E4 ASSOCIATED WITH INCREASED ABSTRACT AND NEGATIVE WORD USE DURING NATURALISTIC SPEECH IN COGNITIVELY UNIMPAIRED OLDER ADULTS. Stoica T, Deffner A, Andrews E, Thayer SC, Griffith C, Andrews-Hanna J, Grilli MD. University of Arizona; George Mason University; University of Colorado; Arizona Alzheimer’s Consortium.

Background: Unprompted thought – often arising during resting state contexts – is linked to activity in the brain’s default network, a neurobiological target of pathology in Alzheimer’s disease. Characterizing resting state cognition in older adults can therefore provide new insights into Alzheimer’s disease risk, while also informing changes associated with healthy aging. One way resting state cognition might differ in older adults is emotional tone. It is well established that most typically aging older adults exhibit a “positivity bias” relative to young adults in attention and memory. Yet, whether this age-associated difference in emotional processing persists during periods of verbalized unconstrained thought is relatively unexplored. Older adults may also differ in the balance of concrete and abstract word use during resting state cognition. Verbalized concrete knowledge may arise in the form of mental associations and images, while verbalized abstract knowledge may emerge as verbal-based inferences and reflections. Prior work suggests that concrete and abstract concepts may vary in their relationships to the two subsystems of the default network, which may be differentially affected by typical aging and Alzheimer’s disease. However, the impact of older age on the use of concrete and abstract concepts during resting state cognition is unclear. To address these gaps in knowledge, we used a resting state “Think Aloud” paradigm to capture young and cognitively unimpaired older adults orally narrating their unconstrained thoughts. We then analyzed their word use for emotional tone and concrete/abstract make-up. To understand the potential role of higher risk for Alzheimer’s disease on resting state cognition, we also examined the impact of the ε4 allele of the apolipoprotein E (APOE) gene among the older adults.

Methods: Across three studies, we asked a total of 221 participants (77 young adults and 144 cognitively unimpaired older adults, including 67 APOE ε4 carriers and 77 non-carriers) to speak their thoughts freely out loud (Think Aloud Paradigm) and assessed whether any age differences existed in their emotional properties or concrete/abstract word use. Additionally, we investigated whether APOE ε4 carrier status had any effect on these novel metrics of resting state cognition.

Results: Compared to young adults, cognitively unimpaired older adults used a more diverse repertoire of negative and positive emotional words (emotional diversity), as well as concrete words (concrete diversity), in the oral narratives of their resting state cognition. Among the older adults, APOE ε4 carriers spoke more negative words and more abstract words overall, compared to non-carriers, but emotional and concrete diversity did not significantly differ by APOE ε4 status.

Conclusions: These novel findings suggest that typical cognitive aging may be associated with an increase in the use of unique positive words during unconstrained thought. The age-associated positivity effect, therefore, may manifest in resting state cognition, similar to other, previously documented, aspects of cognition. These findings also suggest that higher risk for Alzheimer’s disease, as indicated by APOE ε4 status, may be associated with an increase of negative and abstract thought during resting state cognition. Our future work will examine how these behavioral outcomes map onto the default network. This research adds important insights into Alzheimer’s disease risk, may have implications for other clinical disorders whose natural thought content may differ, and informs future neuroimaging studies probing the role of the default mode network in aging.

Background: Idiopathic REM sleep behavior disorder (RBD) is a strong known predictor of a final clinicopathological diagnosis of a Lewy type alpha-synucleinopathy (LTS). Reduced olfactory function is an early symptom of synucleinopathies and also has been repeatedly associated with the presence of postmortem LTS. We aimed to assess the combined value of a clinician diagnosis of probable RBD (PRBD) and olfactory function in predicting the post-mortem presence of LTS in a broader, less-selected, volunteer elderly population.

Methods: Using data from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), 636 autopsied subjects were evaluated for PRBD (based on clinician taken history and/or Mayo Sleep Questionnaire (MSQ)), completed movement and cognitive assessments, performed an UPSIT olfactory test, and had neuropathological assessment. Of these 155 subjects had PRBD.

Results: Histological evidence of LTS was significantly more frequent in those who had PRBD (110/155: 71%) than those without (173/481: 36%) (p<0.001). A low UPSIT score (≤20) was found in 70% of subjects with PRBD and the presence of LTS was significantly more frequent in cases with PRBD and a low UPSIT (98/109: 90%) than in cases with PRBD only (71% see above) or cases with a low UPSIT score (210/306: 67%) (Both p<0.001). Overall sensitivity of PRBD diagnosis for predicting LTS was 38.9%, and specificity 87.3% while sensitivity of a low UPSIT score was 74.2% and specificity 72.8%. When combining both PRBD diagnosis and a low UPSIT score, sensitivity for predicting LTS was 34.6% and specificity 97%.

Conclusions: PRBD, diagnosed without sleep study confirmation, combined with a low UPSIT is highly specific for predicting postmortem presence of LTS. Reduced olfactory function may be a useful biomarker to screen for subjects for a sleep study. The use of both PRBD assessment and olfactory function may provide a cost-effective means of predicting LTS in a broader community.

Background: The olfactory bulb is known to be involved early in the pathophysiology of Parkinson’s disease (PD). Lewy-type α-synucleinopathy, the principal neuropathological hallmark of PD, has been found to start in the olfactory bulb. Accordingly, olfactory dysfunction is an early manifestation of PD. Identifying the mechanisms through which PD affects the olfactory bulb could lead to a better understanding of the etiology of olfactory dysfunction in PD and the pathophysiology of PD. In addition, we could uncover key molecules, gene-based biomarkers and potential therapeutic targets to early diagnose and treat PD. We specifically aimed to assess gene expression changes and affected pathways by whole transcriptomic profiling of the OB of subjects with clinicopathologically defined PD in comparison to controls.

Methods: A total of 20 subjects with a clinicopathological diagnosis of PD and 20 control subjects, were selected from the Arizona Study of Aging and Neurodegenerative disorders (AZSAND) and the Brain and Body Donation Program (BBDP). Control cases did not have dementia, movement disorder or any major neuropathological diagnosis. Bulk RNA sequencing from frozen human olfactory bulbs was performed. Biostatistical analysis compared PD cases with controls and included differential gene expression, cell and pathway enrichment analysis and co-expression network analysis. Olfactory UPSIT score, performed prior to death, was correlated with expression of olfactory related gene expression.

Results: Differential expression analysis revealed a total of 2164 significantly differentially expressed genes (DEGs) in the olfactory bulb of PD cases when compared to controls, of these 1090 were upregulated and 1074 were downregulated. Significantly downregulated pathways included neurodegeneration, Parkinson’s disease, oxidative phosphorylation, and olfactory transduction. Uregulated pathways were involved in the immune and inflammatory responses, protein transport and catabolism as well as glutathione metabolism. An overrepresentation of microglial and astrocytes related genes was observed amongst upregulated genes, and excitatory neurons related genes amongst downregulated genes. UPSIT olfactory score correlated with gene expression of genes coding for G-coupled protein, calcium binding protein including proteins expressed in glial olfactory ensheathing cells, neuropeptides expressed in GABAergic granule neurons such as neurogranin and somatostatin, synaptic marker protein, and dopaminergic and cholinergic receptors.

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Background: Sex differences in Alzheimer's disease (AD) may contribute to disease heterogeneity and affect prevalence, risk factors, disease trajectories and outcomes. Depression impacts a large number of patients with AD and has been reported to be more prevalent in women. We aimed to better understand the interaction between sex, depression and AD neuropathology, which could have implications for detection of symptoms, earlier diagnosis, therapeutic management, and enhanced quality of life.

Methods: We compared 338 cases with clinicopathologically confirmed AD (46% women) to 258 control cases (50% women), without dementia, parkinsonism or a significant pathological diagnosis. Depression was assessed both, using the Hamilton Depression Scale (HAM-D), and as being reported in their medical history combined with treatment with antidepressant medication.

Results: In the control group, women showed a higher depression severity, and a higher proportion of women were found to meet the cut-off score for depression on the HAM-D (32% vs 16%) and having an history of depression (33% vs 21%), while these sex differences were not observed in AD. Further, in both groups, female sex independently predicted the presence of depression, with covariates for age and cognitive status. AD subjects had higher mean HAM-D scores, were more likely to meet cutoff scores for depression (41% vs 24%) and have a history of depression than controls (47% vs 27%). When comparing the increase in frequency of depression in controls versus AD, the difference was significantly greater in men (AD men - control men: 24%) than in women (AD women - control women: 9 %). Although subjects with depression were more likely to have higher levels of AD neuropathology, these differences were not observed when investigating the control or AD group separately.

Conclusions: Control women had a higher likelihood and severity of depression than control men, but this sex difference was not noted when considering only those with pathologically defined AD, emphasizing the importance of considering sex in aging studies. AD was associated with higher rates of depression and men may be more likely to report or be diagnosed with depression once they develop AD indicating the importance of more frequent depression screenings in men.

Background: Essential tremor (ET) is a common movement disorder in which cerebellar microscopic and volume alterations have been repeatedly reported although with disagreement between studies. However, pronounced heterogeneity was found with regard to cerebellar volume alterations. This study aimed to assess post-mortem cerebellar volume in subjects with or without ET, as compared with subjects with multiple system atrophy (MSA), a well-established cerebellar neurodegeneration.

Methods: Cases with ET (n = 29), MSA (n = 7) and non-demented control cases without any movement disorder (n = 22) were selected from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), a longitudinal clinicopathological study with annual research-dedicated clinical assessments by neuropsychologists, subspecialist movement disorders and cognitive/behavioral neurologists, with comprehensive neuropathological examinations after death. Group comparisons were controlled for common age-related neurodegenerative and cerebrovascular pathologies. Cerebellar volumes were calculated using digital images of slices taken at the time of autopsy, immediately after brain removal and before fixation.

Results: Cerebellar volume was not reduced in ET subjects compared to controls. The two groups did not differ in terms of incidental cerebrovascular and Alzheimer’s disease neuropathology. In contrast, cerebellar volume was significantly reduced in subjects with MSA when compared to ET and control subjects.

Conclusions: In a well-characterized cohort, postmortem cerebellar volume measurements suggest that there are no volume alterations in ET when compared to controls, in contrast to significant cerebellar atrophy in subjects with MSA.
PREPAREDNESS OF ARIZONA OCCUPATIONAL, PHYSICAL, AND SPEECH THERAPY PRACTITIONERS FOR WORKING WITH CLIENTS WITH ALZHEIMER’S DISEASE AND RELATED DEMENTIAS. Turner T, Ayala P, Christensen S, Venkatesh M. Midwestern University; AT Still University; Arizona Alzheimer’s Consortium.

Background: Dementia is a general term used to describe a progressive neurodegenerative disease that impairs one's ability to remember, think, or make decisions that interfere with everyday activities (CDC, 2019). 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. Individuals lose their mobility, ability to communicate, and independence to complete daily living activities or meaningful tasks by themselves (Alzheimer's Society of Canada, 2019).

Training for dementia care is essential for those working with persons living with dementia (Takizawa et al., 2017). Professionals need to be able to work with the persons living with dementia (PwD) and their care partners. They need a broad set of skills to most effectively do so (De Vriendt et al., 2018). One study found that assessment for cognition and delirium were inadequate in acute care despite access to physical, occupational, and speech therapy services (Timmons et al., 2016). Another study found an increase in rehabilitation clients with dementia diagnoses and a lack of knowledge regarding dementia care and an accurate understanding of capabilities of a PwD (O'Brien et al., 2019). It is important to understand the preparation and readiness.

Methods: A purposive sample was used to recruit practitioners from each discipline (Physical, Occupational, and Speech Therapy) and from the following adult practice settings: Acute Care, Acute Rehab, Skilled Nursing, Home Health, and Outpatient Rehab. Researchers were able to recruit 75 participants. Each participant completed a demographic/background survey. Eighteen focus groups were held with mixed disciplines and settings. The Focus Groups were moderated by one of the investigators. The discussion focused on practitioner knowledge of ADRD and comfort level in working with clients with an ADRD diagnosis. Focus sessions were recorded and transcribed. Transcripts, notes, documents, and any other related materials are in the process of being reviewed, coded, and then combined into themes. Coding and Thematic analysis will be completed by the PI/Co-PI of the same discipline and 2 work study students of the same discipline.

Results: Preliminary findings show a lack of knowledge of how to and where to find quality intermediate and advanced level continuing education. Also noted was the barrier of time and a desire for therapy managers to provide guidance on furthering education.

Conclusions: Therapy managers can support their teams by identifying high quality educational resources, hosting educational in-services, and supporting practitioner continuing education. Academic faculty can support therapist knowledge through provision of advanced training. Additionally, they can guide managers toward high quality resources available.

Background: Growing evidence supports that vascular comorbidities (hypertension, diabetes and hyperlipidemia) and vascular diseases (cerebral small vessel disease and carotid artery disease) play a role in Alzheimer’s disease (AD) pathophysiology. However, female versus male risk for these diseases is the opposite; females have an increased risk for AD, and males generally have an increased risk for most cardiovascular diseases. We hypothesized that one or more vascular comorbidities would have a differential effect on men vs. women concerning their AD risk.

Methods: Mariner insurance includes claims data from 2010 through October 2021 that were retrospectively analyzed for this exploratory study. Subjects 45 years of age or older were included. The initial cohort (N=1,783,037) was divided into males or females in the first analysis. Only males and females with asymptomatic extracranial carotid artery disease (aECAD) (N=215,636 subjects) were included in the second analysis. A logistic regression model in each group was performed with the results expressed in Odds Ratio.

Results: We found that DMII and hypertension are associated with higher odds of AD; however the association is stronger in females as compared to males (OR = 1.12, 95% CI:1.09-1.15 vs. OR= 1.05, 95% CI:1.02-1.08 for DMII and OR=1.49, 95% CI:1.42-1.56 vs OR=1.28, 95% CI:1.23-1.34 for hypertension). A similar trend was observed within the aECAD population for females vs males (OR = 1.2, 95% CI:1.13-1.27 vs. OR= 1.02, 95% CI:0.96-1.08 for DMII and OR=1.52, 95% CI:1.33-1.75 vs OR=1.27, 95% CI:1.10-1.47 for hypertension). Age and other cardiovascular comorbidities did not show differential effects on AD with regards to gender.

Conclusions: Although several cardiovascular comorbidities are associated with a similar risk for AD in males and females, DMII and HTN are associated with significantly increased risk for AD in females compared to males. These data suggest that DMII and HTN may have differential physiological effects on AD development in females vs. males. These findings are useful but limited by retrospective study design, and prompt future prospective evaluations.

Background: Chronic consumption of a western diet (high fat and high sugar, HFHS) increases the risk of metabolic syndrome, obesity, insulin resistance, type 2 diabetes mellitus, cardiovascular disease, inflammation, and neurodegenerative diseases such as Alzheimer’s disease (AD). Genistein, a naturally occurring isoflavonic phytoestrogen found in soy products, is known to improve insulin sensitivity and provide anti-inflammatory and neuroprotective value. Similar benefits have also been associated with moderate exercise. The aim of this study was to determine whether dietary genistein (600 mg genistein/kg diet, Gen) or moderate intensity exercise (Ex), or both (Gen+Ex) would mitigate the progression of AD pathology in a HFHS-fed murine model.

Methods: C57BL/6J male mice (~6 weeks old) were randomly assigned to one of the following groups (n=10/group): lean control, HFHS, HFHS+Gen, HFHS+Ex, and HFHS+Gen+Ex. The HFHS diet consisted of 60% saturated fat, 20% carbohydrate and 20% protein, with drinking water containing sucrose and fructose. Moderate exercise consisted of treadmill running (5 days/week), 150 minutes/week for the 12-week study duration. Open Field testing was performed at week 11 of the study. At the end of the study brain and serum were immediately frozen and maintained at -80°C until use.

Results: HFHS-induced weight gain was significantly reduced with Ex, Gen, or Gen+Ex. Weight changes were associated with concomitant alterations in the following serum markers: insulin, glucose, MCP-1, TNF-α. Open field testing indicated that HFHS feeding significantly reduced time and entries into the center space and increased time in lateral space. Using western blot analysis, total protein expression of the following proteins was assessed in brain homogenates. We show that: (1) pGSK (involved in formation of PHF-Tau) was significantly increased by HFHS diet and this was mitigated by Gen+Ex, (2) CT20 (pathological cleavage) was significantly increased by HFHS diet, (3) 22c11 (non-cleaved APP integral membrane protein) was significantly decreased by Ex, and (4) CP13 (phosphorylated Tau) was significantly decreased by Gen+Ex. We are currently evaluating additional key proteins involved in the progression of AD and quantifying caspase-3 staining via immunofluorescence in hippocampus.

Conclusions: Genistein and exercise in combination mitigate some of the effects of metabolic syndrome on the brain of HFHS-fed male mice. These benefits are associated with concomitant improvements in the obese-diabetic phenotype.


Background: Covid-19 is a highly infectious disease caused by the coronavirus SARS-CoV-2 that was first identified in patients in 2019 and quickly spread worldwide. SARS-CoV-2 has four main structural proteins, the spike (S), nucleocapsid (N1, N2), matrix membrane (M) and envelope (E). Similar to other coronaviruses, Covid-19 primarily affects the respiratory system with common symptoms including fever, cough, runny nose, chest pain, shortness of breath, and difficulty breathing. However, people with Covid-19 illness have also reported non-respiratory symptoms including nausea, vomiting, diarrhea, loss of smell and/or taste, rashes, and confusion/delirium which may implicate other body systems. Several studies have highlighted ACE2 and TMPRSS2 as important for viral entry; these proteins are abundant in the lungs and may also be important for viral access in other organs. In this study, our aim was to survey the localization of SARS-CoV-2 in all the major organs by targeting the Envelope (E) gene using RT-qPCR. A better mapping of the distribution and relative abundance of SARS-CoV-2 throughout the entire body will help to understand its clinical effects and improve its treatment.

Methods: Tissue samples of peripheral organs were collected at autopsy from research subjects enrolled in the Brain and Body Donation Program (BBDP). Separate tools were used for each organ to avoid contamination. A post-mortem nasopharyngeal swab was performed on all subjects and sent to CLIA certified labs for SARS-CoV-2 PCR diagnostic testing. 25 subjects that tested positive were utilized in this project. Frozen tissue was collected from 22 different body sites and RNA was isolated using Qiagen RNeasy Plus Mini Kit following the manufacturer’s instructions. Presence of SARS-CoV-2 was determined with Reverse Transcription quantitative PCR (RT-qPCR) using primers and hydrolysis probes targeting the envelope (E) gene, unique to the SCV2 virus. Primers and probes for Actin were also used as a reference gene/extraction control. RT-qPCR was performed in duplicate, and positive and negative controls were included on each plate. Positive results were determined if the Cycle threshold (Ct) value was less than 40 (out of 45 cycles) in both replicates. ΔCt values were calculated and used to determine the relative abundance of SARS-CoV-2. An average ΔCt for each area was calculated as well as percent of cases positive for each area.

Results: All of the areas tested had SARS-CoV-2 presence in at least 1 subject. The respiratory system (lungs, trachea, bronchus, peribronchial lymph nodes) had the highest prevalence of SARS-CoV-2 out of all body systems. This result is consistent with COVID-19 being a primarily respiratory illness. Some areas of the digestive system (feces, colon) had relatively high percent positive and low ΔCt values. Interestingly, the quadricep muscle and the femoral nerve had relatively high presence and abundance of SARS-CoV-2 despite being unrelated and distant to the respiratory system.

Conclusions: Further research into quantifying ACE2 and TMPRSS2 receptors to see if their density correlates with the most affected organs could help understand the mechanism of infection and disease. Additional methods such as immuno-staining or in-situ hybridization may provide additional anatomical detail.
MEASURING UP: A COMPARISON OF TAPESTATION 4200 AND BIOANALYZER 2100 AS MEASUREMENT TOOLS FOR RNA QUALITY IN POSTMORTEM HUMAN BRAIN SAMPLES.


Background: Determining RNA integrity is a critical quality assessment tool for gene expression studies where the experiment's success is highly dependent on sample quality. Since its introduction in 1999, the gold standard in the scientific community has been the Agilent 2100 Bioanalyzer's RNA Integrity Number (RIN) which uses a 1-10 value system with 1 being most degraded to 10 being the most intact. In 2015, Agilent launched the 4200 Tapestation's RIN equivalent and reported a strong correlation of r² of 0.936 and median error < 0.4 RIN units. To evaluate this claim, we compared the Agilent 4200 Tapestation's RIN equivalent (RINe) and DV200 to the Agilent 2100 Bioanalyzer's RIN for 183 parallel RNA samples.

Methods: Frozen human tissue samples used in this study were collected as part of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and the Brain and Body Donation program (BBDP), a program dedicated to the longitudinal clinicopathological study of neurodegenerative diseases and normal aging. A total of 183 frozen cerebellum tissue samples from different donors were collected. Qiagen RNeasy Plus mini kits were used to extract RNA from 25mg of frozen cerebellum. A volume of 1ul of undiluted RNA from each sample was run in parallel on the Agilent 4200 Tapestation and 2100 Bioanalyzer. RIN was recorded from the Bioanalyzer and RINe and DV200 were recorded from the Tapestation 4200. A cut-off value of RIN 6.5 and DV200 of 70% was used to determine how many samples would be suitable for most downstream applications.

Results: For all 183 samples, the RIN range was between 3 to 10 with an average of 8.8 (1.06) and a median of 9.1 whereas the RINe range was 2.6 to 7.5 with an average of 5.6 (1.07) and a median of 5.8. DV200 ranges from 80.72% to 95.06% with an average of 91.08% (2.60%) and a median of 91.76%. A two-tailed paired t-test showed that the RIN and RINe were significantly different (p<0.0001) with an average difference of 3.2 RIN units. Linear regression showed that although the RIN and RINe did significantly correlate (p<0.0001), the correlation was weaker than previously reported by Agilent (r² =0.393 vs 0.936). Linear regression comparing RIN to Dv200 and RINe was also statistically significant (p<0.0001) but with weak correlations of r²=0.187 and r²=0.346 respectively. Applying a commonly used quality threshold of RIN 6.5, 175/183 (95.6%) samples would be considered fit for downstream applications, whereas only 43/183 (23.5%) would be fit using the RINe and these proportions are statistically significantly different (p<0.0001). Applying a quality cut-off value of 70% DV200, established by Illumina for sequencing, 183/183 (100%) samples would meet this standard.

Conclusions: Our results suggest that there may be larger discrepancies between RIN and RINe than previously reported, emphasizing that these measurements should not be used interchangeably. Instead, separate quality thresholds should be established for each metric. This is an important observation because currently the broader scientific community may be working under the assumption that these methods are virtually equivalent. A general premise in the field is that RIN values lower than 6.5 are not considered adequate for downstream applications. If the same standards were applied to RINe, many RINe samples will fail quality control (QC) that would pass with RIN. This was seen in our study were only 23.5% of samples would pass QC using RINe but 95.6% of samples would pass QC using RIN.
hAPOE INCREASES WEIGHT AND SURVIVAL PROBABILITY IN hAPP TRANSGENIC MOUSE MODELS. Wiegand J, Stanley T, Dalton A, Campbell L, Brinton RD. University of Arizona; Arizona Alzheimer’s Consortium.

Background: The 4th isoform of apolipoprotein E is the most prevalent genetic risk factor for Alzheimer’s Disease (AD) and transgenic hAPOE animal models are widely used. However, many studies investigate humanized APOE in isolation from key interactors, such as humanized amyloid precursor protein (hAPP).

Methods: To address knowledge gaps regarding APOE and how it interacts with hAPP, transgenic mice carrying hAPOE alleles (JAX#27894, APOE3/3 KI, https://www.jax.org/strain/027894 and JAX#29018, APOE4/4 KI, https://www.jax.org/strain/029018) were obtained and bred. APOE KI mice were subsequently bred to homozygous hAPP animals (JAX#030898, hAbeta-loxP-KI), resulting in hAPP*hAPOE mice. Mice were longitudinally tracked for identification, and the determination of susceptible and resilient subpopulations was conducted through population-level analyses including monthly weights, phenotypic observations, and survival rates.

Results: Colony-wide analyses indicated multiple key differences: 1) hAPP*hAPOE mice exhibited greater body weight compared to hAPOE mice. hAPP*hAPOE mice displayed typical weight gain throughout their lifespan, while hAPOE mice generally exhibit a failure-to-thrive phenotype. Male and female hAPOE mice did not exhibit genotypic weight differences but do display typical sex differences. No difference was observed in longitudinal barbering. 2) hAPP*hAPOE genotypes had the greatest survival probability with a median survival time of 20.15 months, followed by hAPOE genotypes with a median survival time of 14.89 months, and then hAPP mice with a median survival time of 10.36 months. 3) hAPOE mice exhibited increased incidence of dermatitis (5.921% ), this is modulated in hAPP*hAPOE (4.403% ) and hAPP strains (1.616%).

Conclusions: The addition of the hAPP gene to the well-characterized hAPOE gene substantially impacts multiple indicators including weight, survivability, and incidence of dermatitis. It is clear from these results that the addition of a singular humanized gene will result in drastic phenotype differences. Studying these genes in combination allows for identification of individual versus synergistic effects. Further work should explore how necessary other downstream neurological mechanisms are to create more translatable models.

Background: The association of aging and sporadic Alzheimer’s disease (AD) suggests that manipulation of the rate of aging may delay the incidence and/or progression of AD. Caloric restriction by intermittent fasting has been suggested to have numerous anti-aging effects. We previously found that intermittent fasting improves the memory function of aged Senescence Accelerated Mouse-Prone 8 (SAMP8) mice, a spontaneous, age-related mouse model of AD.

Methods: In this study, we analyzed the selected markers for senescence and aging in the tissues of SAMP8 mice maintained on intermittent fasting (alternate day fasting) or ad libitum access to food for 6 months.

Results: 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. In addition, Intermittent fasting suppressed the levels of senescence markers in visceral adipose tissue.

Conclusions: Our study suggests that the suppression of senescence may contribute to the beneficial effects of intermittent and that slowing the rate of aging may improve the development and progression of AD. Further characterization of other tissues is in progress.
ASSOCIATIONS BETWEEN REPORTED SLEEP AND MEMORY PERFORMANCE IN COGNITIVELY UNIMPAIRED MIDDLE-AGED AND OLDER ADULTS. Youngstedt SD, Chen K, Caselli RJ, Lee-Iannotti J, Reiman EM. Arizona State University; Arizona Alzheimer’s Consortium; Banner Alzheimer’s Institute; Mayo Clinic Arizona; Banner University Medical Center.

Background: Disturbed sleep has been associated with cognitive impairment in individuals with dementia as well as adults with normal cognitive function. Questions remain whether these associations are independent of other factors like depression. The aim of this study was to examine associations of cognitive function with sleep in individuals assessed in the Arizona Alzheimer’s Consortium.

Methods: After cleaning and addressing the missing measures, there were data from 771 adults aged 40-80 years who were cognitively unimpaired at baseline. Baseline cross-sectional associations of cognitive function (Rey Auditory Learning Test, Complex Figure Test, Wechsler Digit Span, Controlled Oral Word Association) with sleep (sleep duration, obstructive sleep apnea, insomnia, napping, sleepiness) we assessed in two ways. First, ANCOVAs were used to compare cognitive performance in participants who reported sleeping < 7 hours daily vs. those sleeping 7-8 h, and in those who reported sleeping > 8 hours daily vs those sleeping 7-8 hy, those with vs. without insomnia, those with apnea vs. those without sleep apnea, those who reported napping vs. those who did not report napping, and those with vs. without daytime sleepiness., controlling for the presence of the APOE-4 gene, age, race, education, family history, hypertension, diabetes, high cholesterol, smoking, depression, and cerebrovascular disease. Second, multinomial regression analyses compared cognitive function across levels of sleep, controlling for the same covariates.

Survival analysis was used to explore longitudinal associations of sleep with the incidence of low cognitive function in follow-up measurements ranging from 12-255 months (143±79 months). Low cognitive performance was defined as a low level based on age-, education, and sex-adjusted values on the Rey Auditory Learning-Total Learning test. Incidence of low cognitive performance was compared between the < 7 h (short sleepers) vs. 7-8 h sleepers (average duration sleepers), the > 8 h (long sleepers) vs 7-8 h sleepers, those with apnea vs. those without sleep apnea, those with insomnia vs. those without insomnia, and those with sleepiness vs. those without sleepiness, controlling for the variables listed above.

Results: In the cross-sectional analysis, individuals who reported less than 7 hours of sleep had significantly lower Rey Auditory Learning-Total Learning scores than those sleeping 7-8 hours. No other cross-sectional comparisons were statistically significant. Survival analysis showed that participants reporting daytime sleepiness had a significantly earlier onset of low values on the Rey Auditory Learning-Total Learning scores than those who did not report sleepiness.

Conclusions: We confirmed the impact of sleeping measures on cognitions independent of depression and several other factors. Daytime sleepiness was predictive of the incidence of low cognitive score on Rey Auditory Learning-Total Leaning. Limitations included an unrepresentative sample in terms of race (97% white) and education (15.7±2.5 years). This should be studied more carefully with a representative and sufficiently large sample.
THE MATHEMATICAL TOPOLOGY OF TAUOPATHIES. Sugiyama M, Panagiotou E. University of Tennessee; Arizona State University; Arizona Alzheimer’s Consortium.

We employ novel mathematical concepts from topology and geometry to analyze tau protein structures related to neurodegenerative disease. By analyzing tau filament structures from tauopathies deposited in the Protein Data Bank, we obtain a quantitative description of their topological and geometrical complexity that leads to a novel, refined classification of tauopathies. These topological metrics not only classify, but they also have the potential of explaining protein misfolding and aggregation. Our results point to specific sites of significance in tau filaments and predict mutation sites that lead to protein aggregation, which are validated by experimental data.
Arizona Alzheimer’s Consortium
24th Annual Scientific Conference

Additional Abstracts

Midlife in women typically includes the menopausal transition, a time of hormonal transformation, adaptation, and reorganization. Coincident with this dynamic period of physiological change, there are putatively modifiable factors that influence disease, short-term and long-term health outcomes, symptom emergence, and longevity. The menopause transition could be considered a window of vulnerability; however, it is also a window of opportunity for intervention. Thus, the menopause transition is a critical sensitive window whereby there is opportunity for turning points for healthy aging trajectories. Preclinical research can aid in this pursuit of scientific discovery for modifiable factors and treatments, and their particular parameters. Rodent menopause models include surgical and transitional variations, allowing detection of precise determinants impacting menopause-related outcomes. These models permit systematic manipulation of endogenous and exogenous hormone exposures across the lifespan, with infinite outcome measurements ranging from molecular to behavioral. This research is uniquely poised to address complex, interactive hypotheses with extensive control in a relatively short timeframe, including dissociation of age and menopause effects. To understand the many dynamic changes with menopause, iterative and reciprocal communication between clinical and preclinical domains of science is key.

Background: Progestogens, which include both progesterone and synthetic progestins, are a key component of hormone therapies used during menopause. Some progestogens have been shown to be cognitively detrimental; however, there is preclinical evidence that those with a strong progesterone-receptor affinity can benefit some molecular mechanisms thought to underlie cognitive function. Thus, a progestin that maximizes progesterone-receptor affinity and minimizes affinities to other receptors may be cognitively beneficial.

Methods: We evaluated segesterone-acetate (SGA), a 19-norprogesterone derivative with a strong progesterone-receptor affinity and no androgenic or estrogenic-receptor activity. Middle-aged rats underwent Sham or Ovariectomy (Ovx) surgery followed by administration of medroxyprogesterone-acetate (MPA; used as a positive control as we have previously shown MPA-induced cognitive deficits), SGA (low or high dose), or vehicle (one Sham and one Ovx group). Spatial working and reference memory, delayed retention, and anxiety-like behavior were assessed. Moreover, memory- and hormone-related protein assays within select cognitive brain areas were assessed (frontal cortex, dorsal hippocampus, and entorhinal cortex).

Results: Results showed that low-dose SGA impaired spatial working memory, while high-dose SGA had a more extensive detrimental impact, negatively affecting spatial reference memory and delayed retention. MPA administration impaired spatial reference memory and delayed retention, which is a replication of prior findings from our and other laboratories. Ovx-induced anxiety-like behaviors were alleviated by SGA; however, this effect was not shown with MPA. On two working memory measures, IGF-1R expression correlated with better working memory only in rats without hormone manipulation. Of note, any hormone manipulation, or combination of hormone manipulations, used herein altered this relationship.

Conclusions: These findings demonstrate that SGA is detrimental to spatial cognition after surgical menopause, and that surgical menopause with or without progestin administration disrupts relationships with a growth factor critical to neuroplasticity.
SEX-DEPENDENT ACCELERATED CEREBROVASCULAR AGING AND VULNERABILITY TO TRAUMATIC BRAIN INJURY IN A FIBRILLIN-1 MUTATED MOUSE MODEL. Curry T, Barrameda M, Curtin L, Hair C, Krishna G, Sabetta Z, Esfandiarei M*, Thomas T*. University of Arizona College of Medicine, Phoenix; Barrow Neurological Institute; Midwestern University; Arizona State University; Arizona Alzheimer’s Consortium.

Background: Transforming growth factor-β (TGF-β) signaling is implicated in age-dependent vascular dysfunction. Traumatic brain injury (TBI) chronically increases TGF-β, and this may drive TBI-associated accelerated aging phenotypes and vulnerability to repeated TBI. Fibrillin-1 (Fbn1) mutation chronically increases TGF-β systemic bioavailability, generating vascular dysfunction by 6-months (6M) in mice and males have elevated mortality from aneurysm, similar to Fbn1-mutated patients. We hypothesized that Fbn1-mutation promotes a sex-dependent accelerated aging phenotype, leaving the brain more susceptible to TBI.

Methods: Male and female 6M-Fbn1+/−, C57BL/6 (WT), and 12M-WT mice were utilized in IACUC-approved protocols (N=3-10/group, p<0.05).

Results: Our data demonstrate that 6M-Fbn1+/− mice are more similar to 12M-WT compared to 6M-WT, with significantly decreased in vivo posterior cerebral artery blood flow velocity assessed with ultrasound imaging, increased hippocampal blood brain barrier (BBB) permeability (Immunoglobulin G) and hippocampal microglial activation (iba-1). In vivo hippocampal electrochemical recordings showed slowed glutamate clearance (T100), elevated baseline glutamate levels, and increased neurobehavioral severity scale (NSS) scores compared to 6M-WT controls, supporting an accelerated aging phenotype. Midline fluid percussion injury was utilized to evaluate vulnerability to mild TBI (mTBI). Fifteen percent lower force of injury was required to provoke mTBI righting reflex times (5-10 minutes) in 6M-Fbn1+/− male and female mice compared to 6M-WT male mice. One-day post-injury, measures demonstrated significantly increased hippocampal BBB permeability, exacerbated microglial activation, slower in vivo glutamate clearance, and increased NSS scores compared to injured 6M-WT.

Conclusions: These findings reveal an accelerated aging phenotype in Fbn1+/− male mice with vulnerability to injury, where TGF-β is a target regulator of pathology. Funding: NIH-R36AG083385, Valley Research Partnership-P1A-5012, NIH-R15HL145646, NIH-R01NS100793, Midwestern Graduate Funds.
Background: Cortical thickness has proven to be a consistent biomarker in patients with Alzheimer’s Diseases (AD). Taking advantage of the whole volumetric cortical area with a volumetric mesh representation facilitate the use of frameworks based on graph neural network. This study introduces a novel interpretable graph Convolutional Neural Network (TetCNN) framework specifically tailored for the tetrahedral mesh structure. Also, using the adapted Gradient-weighted Class Activation Mapping algorithm (Grad-CAM), this framework can highlight the discovered regions-of-interest for patients with AD.

Methods: In our TetCNN framework, we begin by computing the volumetric Laplace-Beltrami Operator (LBO) for each tetrahedral mesh. Next, we input a set of vertex-related features, such as the 3D coordinates of each vertex, alongside the LBO, into the network. To facilitate hierarchical feature representation for large-sized input data, we implement a novel graph convolution layer based on the LBO. To further enhance efficiency, we incorporate a down-sampling and pooling layer to downsize the mesh. Finally, we use Grad-CAM for better visualization of regions that differentiate the classes of normal controls and patients.

Results: In this study we used the ADNI dataset, with 116 AD and 137 NC subjects in total. Surface construction and preprocessing steps were done in FreeSurfer and tetrahedralization was done with TetGen. Using the LBO over graph Laplacian has proven to be superior performance with average boost of ~3% on accuracy and ~5% in specificity for classification task. The outperformance is also consistent for age prediction task (regression). Despite studying a smaller number of subjects, the results of our research demonstrate comparable performance when compared to other benchmarks that utilize voxel-based representation. As for Grad-CAM, the ROIs (regions of interest) identified using the LBO are notably concentrated in the medial temporal lobe, frontal lobe, and posterior cingulate, which are regions known to be affected by Alzheimer’s disease (AD). In contrast, the ROIs obtained from the graph Laplacian are more dispersed and lack a clear and concise focus on specific areas.

Conclusions: In this paper, we proposed the first tetrahedral mesh-based CNN for the utilization in cortical volume among patients with Alzheimer’s Disease. Thickness variation being inherently embedded in volume representation, it helps Tet CNN to better find the deformation for classification and possible segmentation tasks. Moreover, as proposed, using the rich LBO over graph Laplacian in convolution operation helps with boost in performance.
DO YOU KNOW WHO I AM? A PERSON CENTERED CARE INTERVENTION. **Johnson K.**
HonorHealth Thompson Peak Medical Center; Arizona Alzheimer’s Consortium.

**Background:** The 2018 Alzheimer's Association Dementia Care Practice Recommendations included Person centered care (PCC) as a philosophy of care developed around the needs of the individual and knowing the person. When a patient is admitted to an acute care setting, there is minimal information about who that person is and what matters most to them. Person-centered care (PCC) is an approach where an individual’s values and preferences are known to guide health care, support realistic patient outcomes, and provide empathic care.

Studies support a relationship between a PCC approach and key indicators of quality care. Hospitals fall short on anticipating and responding to patients as individuals with particular needs, values, and preferences.

There is an opportunity to improve person and family engagement, promote effective communication, and coordination of care.

**Purpose:** Evaluate whether a PCC intervention using a "Get to Know Me" communication tool can change workplace climate perception and increase patient satisfaction among registered nurses (RN)s and patient care technicians (PCT)s during patient interactions.

**Methods:** Design: A pre post survey design; Setting: Medical Surgical Unit; Sample: 26 RNs and 5 PCTs. Instrument/Tools: The "Get to Know Me" communication tool was used to display information about what patients like to be called, what made them feel calm, their favorite music, past occupation, hobbies, and names of family members and pets. A Person Centered Climate Questionnaire Staff: Self-report instrument to evaluate climate of health care settings perceived as being person centered by staff. Includes 14 statements about the climate of the unit with 4 subscales: Climate of safety, climate of everydayness, climate of community, and climate of comprehensibility.

**Outcome Measures:** Three months pre/post implementation:
1. Hospital Consumer Assessment of Healthcare Providers and system (HCAHPS): Patient perspective on care; 1) "During this hospital stay how often did nurses listen carefully to you", 2) "During this hospital stay, how often did doctors listen carefully to you". 2. Person Centered Climate Questionnaire (PCQ-S). Intervention: The "Get to Know Me" communication tool was placed in patient room, visible to pt. The RN explained purpose of communication tool to patient & family. Patient, family asked to complete, staff to assist. RN to present 1 item from "Get to Know Me" tool during shift report. At discharge patient offered the "Get to Know Me" tool. When entering pt.'s room: 1) Introduce yourself, use a pleasant voice, and smile! 2) Get to patient's eye level, go slow, talk in short simple sentences, smile! 3) Let the person know you will keep him or her safe.

**Results:** PCQ-S: Cronbach's alpha coefficient of the 14 subscales English PCQ items was 0.74, indicating satisfactory level of internal consistency. The 4 subscales showed satisfactory levels of internal consistency: 0.72 climate of safety, 0.79 climate of everydayness, 0.69 climate of community, and 0.73 climate of comprehensibility. Overall compliance rate of using the "Get to Know Me Board" was 100%. A statistically significant increase from pre/post scores, “I experience my workplace as a place where it is neat and clean” (M = .5600, SD = 1.1576) (t(25) = 2.419, p < .024), “I experience my workplace as a place where it is easy for patients to keep in contact with loved ones” (M= .5600, SD = 1.0440) (t(25) = 2.682, p < .013), and “I experience my workplace as a place where patients have someone to talk to if they wish” (M = .1600, SD = 1.2207) (t(25) = 2.622, p < .015). For HCAHPS; three months, pre implementation (84% - 86%) for “nurses listening to you” and post (80% - 95%) for “always”, and “physicians listening to you” pre, (78% to 87%) and post implementation, (89% - 95%) for “always.”
Conclusions: Significant improvement in the perception of the unit as a welcoming PCC environment. Knowing your patient involves a person centered strategy where health care providers can individualize patient care for optimal engagement.

Background: Prediction of Alzheimer's disease (AD) risk for individuals with mild cognitive impairment (MCI) provides an opportunity for early intervention. Neuroimaging of different types/modalities has shown promise, but not every patient has all the modalities due to cost and accessibility constraints. To integrate incomplete multi-modality datasets, we previously published a machine learning (ML) model called incomplete-modality transfer learning (IMTL). Here we extended the capacity of IMTL to handle high-dimensional feature sets, namely, HD-IMTL.

Methods: Our dataset included 1319 T1-MRI scans from MCI patients in ADNI; among them, 1002 had FDG-PET and 612 had amyloid-PET. 156 regional volumetric and thickness features were computed from MRI and 83 and 83 regional SUVR features from FDG-PET and amyloid-PET, respectively. The goal of HD-IMTL was to jointly train 4 ML models to predict MCI conversion to AD in 36 months, with each model based on a certain combination of available modalities, namely, MRI, MRI+FDG, MRI+amyloid, and MRI+FDG+amyloid. These correspond to patient sub-cohorts that differ in their access to the imaging modalities. To handle high-dimensional features, we employed feature screening to remove noise features, performed modality-wise partial least squares (PLS) to condense remaining features into principal components (PCs), and used correlation test to select PCs. To jointly train the 4 ML prediction models, IMTL was used, which is a generative model that uses expectation-maximization (EM) in joint parameter estimation to facilitate transfer learning. To account for sample imbalance in training, the Synthetic Minority Over-sampling Technique (SMOTE) was used. An 80% vs 20% random split was used to divide the dataset into a training set and a test set. 20 splits were repeated and AUCs on the test set were averaged. For comparison, three existing ML models for incomplete-modality fusion were applied to the same dataset.

Results: The AUCs by HD-IMTL were 0.802, 0.840, 0.868, and 0.880 for sub-cohorts with MRI, MRI+FDG, MRI+amyloid, and MRI+FDG+amyloid, respectively. The AUCs by existing methods were lower, with ranges of 0.749-0.793, 0.769-0.826, 0.816-0.863, and 0.832-0.868.

Conclusions: HD-IMTL demonstrated high accuracy in predicting MCI conversion to AD for patients with varying access/availability of imaging modalities.
PLASMA BIOMARKERS REVEAL AMYLOID PLAQUES IN BRAIN BIOPSY: A PILOT STUDY.
Yang CSY, Lue LF, Beach T. MagQu Co., Ltd. (New Taipei City, Taiwan); Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: With the development of ultra-sensitive assay technology, so-called immunomagnetic reduction (IMR), tremendous evidence correlating plasma biomarkers to either cerebrospinal-fluid biomarkers, amyloid positron emission tomography, magnetic resonance imaging and clinical diagnosis has been shown. All the reported data demonstrate the roles of plasma amyloid beta (Abeta) and total Tau (T-Tau) in assessing Alzheimer's disease.

Methods: In this work, the correlations between plasma biomarkers and neuropathological features, i.e., amyloid plaques in brain, are explored. Sixteen brain biopsy and plasma samples were provided by Banner Sun Health Research Institute (BSHRI) in the US. Amyloid steins of brain biopsy were performed at BSHRI. Plasma samples were collected within 1.5 years before death. Plasma biomarkers, including Abeta1-40, Abeta1-42, T-Tau, pTau181, TDP-43, NfL, alpha-synuclein and p-alpha-synuclein129, were assayed using IMR.

Results: Three subjects show zero count of amyloid plaque in brain biopsy (neuropathological negatives), others have sparse or frequency density of amyloid plaques (neurological positives). Plasma Abeta1-40/Abeta1-42xT-Tau, Abeta1-42xT-Tau and T-Tau show significantly different levels between neuropathological positives and negatives (Abeta1-40/Abeta1-42xT-Tau: positives = 65.1 +- 11.3 pg/ml, negatives = 52.4 +- 5.7 pg/ml, p < 0.05; Abeta1-42xT-Tau: positives = 385.8 +- 41.5 pg^2/ml^2, negatives = 340.4 +- 14.9 pg^2/ml^2, p < 0.05; T-Tau: positives = 20.1 +- 0.6 pg/ml, negatives = 23.2 +- 2.7 pg/ml, p < 0.05).

Conclusions: The results imply that T-Tau plays a role in the formation of amyloid plaques in brain.
Institutional Information

Research Summaries and Key Personnel
From Each Participating Institution
ARIZONA STATE UNIVERSITY

Over a decade ago, 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, honing in on academic excellence, the highest quality education and training, inclusiveness to a broad demographic, and maximum societal impact. Underscoring this exemplary new path, ASU has been ranked number one for innovation by U.S. News and World Report for the last eight years (2015-2022). With Alzheimer’s disease affecting roughly one in nine people 65 years old and over, and one in three people 85 years old and over, research on Alzheimer’s disease (AD) 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 helps provide 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 Research Center. The ASU team includes leaders in the development of novel models to: advance our understanding of aberrant processes upstream from amyloid- and tau-related pathology for the development of therapeutic interventions (Brafman laboratory); identify specific toxic variants of key neuronal proteins that contribute to disruption of neuronal proteostasis in early stage of AD (Sierks laboratory); detect and target injury-induced Alzheimer’s disease pathology (Stabenfeldt laboratory); increase our understanding of late onset AD through holistic analysis of complex network of interconnected processes using a systems approach (Karr laboratory); investigate the spatial and cellular context of viruses within post-mortem brain tissue from people with AD who are also infected with an AD-associated virus (Readhead laboratory); examine the effects of apoE4 dose on advanced diffusion tensor imaging measures (Ofori laboratory); study the utility of peripheral extracellular vesicles in predicting CNS microglial activation state to provide insight into early neurodegeneration (Mastroeni laboratory); determine the memory, anxiety-like, and inflammatory impacts of estrogen therapy after surgical menopause (Bimonte-Nelson laboratory); examine sex-dependent changes in learning and flexible cognition during aging (Verpeut laboratory); reduce recruitment costs in AD clinical trials with geometric machine learning (Wang laboratory); test the feasibility and dose-response of an online visuospatial training game for older adults (Schaefer laboratory); study the effects of dynamic lighting on sleep parameters and mood in older adults with dementia (Sharp laboratory); evaluate a tattoo-like wearable device to monitor the health and safety of patients living with AD (Klein-Seetharaman laboratory) and, assess the impact of Zoom-based delivery of a skills training and care planning intervention for people living alone with early stage cognitive decline (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, to optimize the trajectory of brain aging using both preclinical and clinical approaches, and to advance care and caregiving models and interventions that enhance the quality of life of people living with Alzheimer’s disease and their informal caregivers. Moreover, it is noteworthy that the assets in the research programs at ASU within the Arizona Alzheimer’s Consortium represent a range of colleges, institutes, and centers across ASU.
ASU and Phoenix-based Banner Health, one of the nation’s largest nonprofit health systems, have launched a research alliance to advance the scientific study, treatment and prevention of Alzheimer’s, Parkinson’s and other neurodegenerative diseases. The partnership includes the establishment of the Neurodegenerative Disease Research Center1. The center is an extension of the partners’ work with the Arizona Alzheimer’s Consortium and is envisioned to become one of the world’s largest basic science centers for the study of Alzheimer’s and other neurodegenerative diseases. The Center expected to grow to include about 20 new laboratories and additional affiliated laboratories. It will foster push-pull relationships between big data and other analyses of post-mortem and other human data sets and experimental models and leverage 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.

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), Dr. Heather Bimonte-Nelson (ASU), and Dr. Yonas Geda (Barrow Neurological Institute) 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

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<tr>
<th>Name (last, first)</th>
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Banner Alzheimers Institute (BAI) overarching goals are to find and support the approval and widespread availability of Alzheimer’s disease (AD) prevention therapies as early as 2025; set a new standard of medical and non-medical care and support for cognitively impaired persons, at-risk persons, and their families; and forge models of multi-disciplinary, multi-institutional collaboration and resource sharing in biomedical research.

BAI has made pioneering contributions to the unusually early detection, tracking, study and diagnosis of AD, the discovery of genetic and non-genetic risk and protective factors, disease-mechanisms, promising modifying and prevention therapies, the validation of brain imaging methods and blood tests for the diagnosis of AD, and the accelerated evaluation of disease-modifying and prevention therapies. It launched a new era in AD prevention research, introduced many research paradigms, methods and trials needed to accelerate the evaluation and approval of effective prevention therapies, and established several collaborative paradigms and resource sharing programs to have the greatest impact.

BAI’s ongoing efforts have given the field a chance to find effective secondary prevention therapy in cognitively unimpaired persons with biomarker evidence of amyloid plaques as early as 2025, extend therapies to be administered at home as early as 2026 and identify primary prevention therapies in cognitively unimpaired persons at genetic risk who do not yet show biomarker evidence of amyloid plaques as early as 2027. Its medical clinical, family and community services program, and wide range of education, outreach and support programs have established a best-in-class approach to the care of patients and their families, and it has implemented approaches to extend its impact to the primary care setting and underserved communities. It has found impactful ways to complement, enhance and benefit from close working relationships with organizational partners inside and outside of the Arizona Alzheimer’s Consortium (AAC).

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 diagnosis and course of disease. 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’s) Clinical Core and oversees an annual conference on AD and Dementia in Native Americans. Its Banner Dementia Care Initiative seeks to optimize the identification and evaluation of cognitive problems, address a broad range of the affected person’s and family’s needs, reduce unnecessary hospitalization and maintain affordability to health care payers.

BAI conducts numerous clinical trials of investigational treatments, observational clinical studies and research registries, including many led by researchers within the Alzheimer’s Prevention Initiative (API). Its researchers, in collaboration with partnering organizations, oversee an NIA-sponsored cohort study of cognitively unimpaired persons with two, one and no copies of the APOE4 allele, which has helped to conceptualize the preclinical stages of AD, an NINDS-sponsored study of chronic traumatic encephalopathy (CTE) in former National Football League and college football players, and one of the Precision Medicine Initiative’s (PMI’s) first healthcare provider-led cohort programs in a partnership between University of Arizona and Banner Health. It has begun to capitalize on a shared resource of blood samples, longitudinal data and post-
mortem neuropathological data at Banner Sun Health Research Institute (BSHRI) to support the head-to-head comparison of emerging blood-based biomarkers in the diagnosis and study of AD.

BAI’s state-of-the-art NOMIS Brain Imaging Center includes two PET/CT systems, a 3T MRI, cyclotron, radiochemistry laboratory, and computational image analysis laboratory. It provides imaging resources and expertise, research PET tracers, image-analysis methods, data and biological samples for researchers inside and outside of Arizona. Its researchers, facilities and resources support numerous clinical and observational trials, including a longstanding collaboration with Mayo Clinic, for longitudinal brain imaging study of cognitively unimpaired persons with two copies, one copy and no copies of the APOE4 allele, reflecting three levels of genetic risk for late-onset AD, and image-analysis techniques with improved power to characterize subtle brain changes over time. Its researchers collaborate with the University of Antioquia and Massachusetts General Hospital for studies of PSEN1 E280A mutation carriers and non-carriers from the world’s largest autosomal dominant AD kindred in Colombia. It was a founding member of the AD Neuroimaging Initiative (ADNI) PET Core, in which it was responsible for the development, testing and use of voxel-based image analysis techniques with improved power to detect and track AD. AAC funds complement research activities supported by competitive grant awards from NIA-sponsored research grants, private foundation grants and clinical trials. Imaging and other data and image-analysis techniques from BAI’s NIA-sponsored ADRC and studies of cognitively normal APOE ε4 carriers and non-carriers provide a core resource for interested investigators inside and outside of Arizona.

BAI, BSHRI, and its partners have begun to 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 to find and support the use of promising amyloid and other blood tests for AD and related disorders. These partner organizations, TGen, and ASU (e.g., at the ASU-Banner Neurodegenerative Disease Research Center [NDRC]) have also developed a shared resource of DNA and RNA sequencing data from different brain cell types and regions in high-quality brain samples from AD cases and controls and have used big data analytical techniques to characterize networks and drivers at which to target in the discovery of new treatments. 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 means 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, BAI’s API has helped make it possible to find and support the approval and availability of effective AD prevention therapies far sooner than otherwise possible. It includes a growing number of prevention trials in persons who, based on their genetic and/or biomarker findings, are at increased risk for AD, including the very first AD prevention trial in Colombian members of the world’s largest autosomal dominant AD (ADAD) kindred, who are virtually certain to develop AD and become cognitively impaired at the median age of 44. Its ongoing prevention trial of a recently established amyloid plaque-clearing antibody therapy, performed in partnership with Eli Lilly, has a realistic chance to find an effective prevention therapy as early as 2025, and other prevention trials of a next generation antibody therapy are on the way. These and other trials are intended to evaluate the investigational treatments in potentially license-enabling prevention trials, support the qualification of biomarker endpoints likely to be associated with a clinical benefit in prevention
therapies and provide a shared resource of data and biological fluids for the research community after the trials.

BAI’s web-based Alzheimer’s Prevention Registry (www.endALZnow.org) has provided updates about advances in prevention research and opportunities to enroll in prevention trials to nearly 400,000 individuals; its GeneMatch Program (www.endALZnow.org/genematch) has characterized APOE genetic test results in more than 100,000 of these participants, provided a resource of interested research participants to a growing number of AD prevention trials and related studies and developed suitable ways to inform interested individuals about their APOE-related risk and/or biomarker findings. It continues to champion new ways to identify and support enrollment in prevention trials (e.g., using an amyloid-beta blood tests), and address the logistical, ethical and scientific issues involved in this endeavor.

BAI’s organizational aims include:
1. To leverage imaging resources in the early detection, tracking, and diagnosis of AD, the clarification of genetic and non-genetic risk factors, and other collaborative research studies inside and outside of Arizona.
2. To leverage imaging resources in the early detection and tracking of related diseases (e.g., chronic traumatic encephalopathy [CTE]).
3. To implement, evaluate and use PET radiotracer techniques (e.g., for the assessment of amyloid and tau pathology) in the study of AD and related disorders.
4. To develop image-analysis techniques and composite cognitive test scores with improved power to detect and track AD and evaluate AD-modifying and prevention therapies.
5. To accelerate the evaluation of AD prevention therapies through API’s preclinical AD trials and enrollment registries.
6. To introduce a novel approach for the early phase evaluation of APOE and other AD-modifying drug and gene therapies using CSF and blood-based biomarkers in biomarker positive persons.
7. To help provide the blood samples, imaging methods and (with BSHRI) post-mortem neuropathological assessments needed to characterize and compare the accuracy of emerging blood tests for the diagnosis of AD and related disorders, and to establish the generalizability of these methods to persons from under-represented Hispanic/Latino and Native American groups.
8. To support the evaluation of non-pharmaceutical prevention therapies intended to promote cognitive health.
9. To advance the science of research participant engagement and AD study participation, including in under-represented groups.
10. To share data and biological fluid samples with the research community, establish a public resource of blood samples from thousands of well characterized persons, help the field develop and test blood tests for AD and related disorders as soon as possible, advance the roles of blood-based biomarkers in research, treatment evaluation and clinical care, and advance the complementary research goals of our partners inside and outside Arizona.
11. To provide a care model that more fully addresses the needs of patients and families and BAI, and to develop and evaluate the cost-effectiveness of a dementia care program that better addresses the needs of patients and family caregivers in the Banner Health Accountable Care Organization in the Banner Dementia Care Initiative.
12. To support the clinical research and Native American outreach, education and enrollment goals of the Arizona ADRC.
13. To promote the further development, productivity, and close working relationships of research programs involved in the fight against AD and related disorders.
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<td>Amador, Ricardo</td>
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<td>Clinical Research Program Manager</td>
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<td>Anderson, Allan</td>
<td>MD</td>
<td>Medical Director, Toole Family Memory Center, BAI Tucson</td>
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Banner Sun Health Research Institute (BSHRI) is a world-renowned Alzheimer’s disease (AD) and Related Disorders (ADRD) and cognitive aging research and clinical care institute established in 1986 in the heart of Sun City, Arizona, the nation’s first planned retirement community. As intended, BSHRI contributes significantly to diagnostic and therapeutic advances and profoundly impacts the scientific study of AD/ADRD, Parkinson’s disease (PD), other age-related brain disorders, and healthy cognitive aging.

BSHRI includes: a) 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 30 ongoing NIH, foundation, and biopharma-sponsored state-of-the-art clinical trials and observational cohort studies for AD/ADRD, PD and movement disorders and cognitive aging; d) The Center for Healthy Aging, with a Longevity Longitudinal Cohort Study of over 1,574 research participants (502 active), including 170 individuals of age 85 or older and 84 individuals of age 90 years or older, for the study of cognitive aging; as well as a free, community service, Brain Health Check-In (BHCI) Program (>837 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 >125 education programs per year (nationally, internationally, regionally and locally) and leadership in world-renowned continuing education programs; training in neuropsychology, cognitive neurology and movement disorders for students, residents and post-doctoral fellows; a highly productive neuroscience scholars summer research internship program for under-represented and other 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; and g) Where historically, the state’s largest number of productive basic scientists in the fight against AD, who were well-known for their major contributions to the study of amyloid and tau processing, brain inflammation, epigenetics, and the roles of cholesterol and cerebrovascular disease in AD, were located prior to 2017 (these basic science programs since relocation to ASU). From July 2001 to June 2016, BSHRI served as the applicant organization for the Arizona ADCC on behalf of the organizations in the Arizona Alzheimer’s Consortium, and it remains home to the ADCC’s Administrative Director, Andrea Schmitt, and multiple leaders in the AARC consortium including Drs. Alireza Atri, Geidy Serrano, and Thomas Beach.

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. All participants consent to donate their brains and/or bodies after death. The BBDP is unique for: a) its rapid autopsy program, with a median 3.5-hour post-mortem interval allowing unusually high tissue quality, optimizing post-mortem discovery research on the >2,500 expired donors, who have had comprehensive neurological assessments during life and neuropathological examinations after death; b) the unusually 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 numerous clinically and neuropathologically normal control subjects for genetic and other research studies; c) whole body donation, banked organs and tissues from >780 expired donors since 2005, and the opportunity to relate brain pathology to biological features of other body organs; and d) approximately 280 annual tissue distributions to advance research in Arizona and around the world. The BBDP includes many research participants in the Arizona ADCC’s Clinical and Ancillary BBDP Cores and the ADCC’s Neuropathology Core, in partnership with Mayo Clinic Arizona and Barrow Neurological Institute. In addition, it continues to play critical roles in the neuropathological validation of amyloid PET, tau PET, and other ante-mortem biomarker measurements in end-of-life (e.g., hospice) patients, thus contributing to FDA approval of molecular imaging/PET measurements in the clinical setting. The BBPD continues to provide a tissue resource for genome-wide genetic, transcriptomic and proteomic data from different brain regions and cell types, and to contribute to numerous research studies, collaborations, grants, and dozens of annual publications and impactful findings.

Since 2016, BSHRI has undergone significant changes, shifting focus from basic sciences to clinical and translational science and clinical services, and setting the stage for BSHRI and its organizational partners to further develop its AD/ADRD, PD and movement disorders, and aging clinical, research, education, training and outreach programs. These changes include: a) Ongoing harmonization of Banner Alzheimer’s Institute’s AD/ADRD-related clinical, family and community services, clinical research and clinical trials programs on its downtown Phoenix and BSHRI campuses including launch and housing the Dementia Care Partners community care navigation and support program; b) Further growth of comprehensive and integrated multidisciplinary services at The Cleo Roberts Memory and Movement Disorders Centers including recruitment of several clinicians/clinician-scientists; c) Successful implementation (with AAC pilot funding to PI Dr. Danielle Goldfarb (Cabral) and Co-I Dr. Alireza Atri) of an ultrasound lumbar puncture (LP) program; d) Successful launch and expansion of the Brain Health Check-In (BHCI) community service program at the Center for Health Aging; since December 2018 these walk-in or scheduled BHCI's have provided >837 individuals with free brain health concern status assessments along with feedback, information, education, resources and referrals; e) Substantially enhancing clinical and biological (biofluid/serum) characterization of the BSHRI’s Longevity Study cohort (see current AAC report of pilot funding in FY 2022-23, Dr. Alireza Atri PI), and harmonizing important elements and increasing co-enrollment in the Longevity Study and BBDP programs; f) Ongoing strategic planning for the development and further growth of clinical, aging and clinical/translations research programs, services, and training and education programs on the BSHRI campus -- in addition to BSHRI’s large clinical, family and community services, PD-related “NeuroWellness,” and clinical trials programs, its scientific, education and outreach efforts include >125 international, national, regional, and community presentations per year; BSHRI staff provided >15,000 person/hours of medical/health professional education, scientific or community lectures, presentations and programs, including co-sponsoring and co-directing (Dr. Atri) the world-renowned Harvard Medical School annual 4-day CE course (Dementia: A Comprehensive Update). In 2023 see link: https://cmecatalog.hms.harvard.edu/dementia-comprehensive-update; g) Expanding the BBDP in impactful ways, including achieving ~700 annually assessed prospective brain donors; inclusion of blood, CSF and/or imaging data and samples in many BBDP participants; and development of a public resource of sorted cells, and a resource of omics data from different cell types and regions that differ in the vulnerability and resilience to elements of AD pathology (to help us and our TGen, NDRC and other consortium colleagues, and other researchers better clarify disease networks, and new treatment targets); and h) Serving as the lead institution for the Clinical Core, Biomarker Core (Co-lead), and Neuropathology Cores for the newly NIH(NIA)-funded (in 2022) AZ Alzheimer’s Disease Research Center (ADRC; P30 expanded NIH funding mechanism that replaced the AZ Alzheimer’s Disease Center, ADC).
# INSTITUTIONAL RESEARCH SUMMARIES AND PERSONNEL

## BANNER SUN HEALTH RESEARCH INSTITUTE

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<th>Name (last, first)</th>
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<td>Atri, Alireza</td>
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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 2022 and 2023, program clinicians led 23 active clinical trials and funding generously matched by the Institute’s resources provides for support of pilot research project award including development of novel imaging and cell based biomarkers for Alzheimer’s and related dementias and various studies of new approaches to disease-modifying treatments, including monoclonal antibodies against pathological protein targets such as amyloid and p-tau, neuromodulation therapies, and therapies that improve cognitive function by stabilizing tau proteins. They continue to be a leader in pushing the boundaries of care through novel neurosurgical approaches, such as deep brain stimulation for Alzheimer’s. Additionally, they conduct neuroimaging, biomarker, and observational trials to gain a greater understanding of the disease and to better tailor future therapies.

Among the clinical investigators, Dr Sabbagh has received several grants. These include R01AG059008, A Phase II Clinical Trial for the Assessment of Safety, Tolerability, and Efficacy of Lenalidomide in Patients with Mild Cognitive Impairment Due to Alzheimer’s Disease; GC-2013717 Assessment of Lenalidomide for Alzheimer’s Disease; LBDA1811MS Research Center of Excellence (RCOE) designation; R01 AG073212 Repurposing Siponimod for Alzheimer's Disease; BNF grant # Arizona Alzheimer's Consortium (AAC) Project, Detection of alpha-synuclein in neurodegenerative diseases; ARPA OSRA Number is 23-500-197-20-49 Impact and mechanisms of COVID on neurological function and health outcomes.
Dr Yonas Geda is a Physician Scientist (formally trained by NIH/K01 and Harold Amos Foundation) with decades of experience in clinical research. He has a global recognition (as evidenced by his H-Index and award winning publications at global level) for his research on lifestyle factors, Neuropsychiatric symptoms and the risk of Mild Cognitive Impairment, Alzheimer’s disease and related disorders. His work is funded by an R01 (PI: Geda. NIH/NIA AG 057708), R01 (PI: Reiman, NIH/NIA AG069453), U01 (PI: Petersen. AG006786), R43 (PI: Tsow and Forzani), Barrow Neurological Foundation and other funding agencies.

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 new ideas about disease mechanisms and treatment opportunities. Laboratory and clinical resources devoted to this enterprise have also increased, and investment in faculty and resources is expected to continue and grow.

The Department of Translational Neuroscience at BNI is home to leading scientists and physician-scientists in neurodegenerative disease research, including Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis (ALS), as well as neuroimaging, traumatic brain injury, cerebrovascular diseases, and stroke.

Robert Bowser, PhD, is Chief Scientific Officer and Chair of Translational Neuroscience for BNI. He is an internationally recognized leader in ALS research. His research at BNI is focused on discovery and validation of biomarkers for ALS and other neurodegenerative diseases. Additionally, his research explores the mechanisms underlying neurodegeneration, new technologies for the delivery of drugs into the central nervous system and defining the spatial expression of genes relative to neuropathology within human tissue samples. He has active funding from the Department of Defense (DoD) AL2000-61 on targeting chitinases as a novel therapy for ALS, NINDS funding (NS116385) to generate and characterize novel mutant MATR3 knock-in mouse models of disease; funding from Target ALS of over $1.5M per year for a post-mortem tissue banking program in ALS and a natural history study of ALS that collects longitudinal clinical measures, biofluids and at-home measures of speech and respiration; funding from the Chan Zuckerberg Initiative to expand diversity in ALS research and participation of patients in rural communities; and recently was awarded two additional DoD grants (AL220164 and AL220103) that total over $1.5M with Drs. Medina and Bakkar to study longitudinal neuroimaging and protein biomarkers in ALS patients as well as AAV mediated modulation of the retinoid pathway as a novel treatment for ALS.

Professor Elliott Mufson, PhD, is a pioneer in the application of single cell gene array technology to study the genetic signature of neurons during the progression of AD. Dr. Mufson’s research focuses on the pathobiology of the normal and diseased human brain, including the neurobiology of mild cognitive impairment, which is a precursor to AD, Down syndrome, and traumatic brain injury. He is the head of a multicenter program project grant (P01AG14449) from the National Institute on Aging (NIA) entitled the “Neurobiology of Mild Cognitive Impairment in
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.

Assistant Professor David Medina, PhD, specializes in investigating neurodegenerative diseases including ALS, FTD, and AD, with a particular focus on identifying new molecular pathways using preclinical models. His research endeavors also involve the evaluation of innovative therapeutic strategies. Notably, he has received funding from the NIH/NINDS to develop novel mouse models of ALS and FTD. Furthermore, Dr. Medina has been honored with a multiyear Therapeutic Idea Grant from the Department of Defense, which will support the development of gene therapy approaches targeting ALS and other neurodegenerative conditions.

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 and astrocytes in ALS and FTD (R01NS120331, R21NS125861) and on mechanisms of neurodegeneration in LBD (R21NS128550).

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 was designed to advance imaging technology to improve patient diagnosis and care, serve as an imaging resource for the greater research community, and provide education in medical imaging. Ashley Stokes, PhD, 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.
# INSTITUTIONAL RESEARCH SUMMARIES AND PERSONNEL

## BARROW NEUROLOGICAL INSTITUTE

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<tr>
<th>Name (last, first)</th>
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<tr>
<td>Acothley, Skieff</td>
<td>BS</td>
<td>Research Assistant</td>
</tr>
<tr>
<td>Baez Cruz, Jessica</td>
<td>BS</td>
<td>Psychometrist</td>
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<tr>
<td>Bakkar, Nadine</td>
<td>PhD</td>
<td>Neuroscientist; Assistant Professor, Translational Neuroscience</td>
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<tr>
<td>Bergamino, Maurizio</td>
<td>PhD</td>
<td>MR Research, Neuroimaging Innovation Center</td>
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<tr>
<td>Bowser, Robert</td>
<td>PhD</td>
<td>Chief Scientific Officer; Professor and Chair, Translational Neuroscience</td>
</tr>
<tr>
<td>Burke, Anna</td>
<td>MD</td>
<td>Geriatric Psychiatrist; Director, Alzheimer’s and Memory Disorders Program</td>
</tr>
<tr>
<td>Shawna Cunningham</td>
<td>MS</td>
<td>Senior Research Tech</td>
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<tr>
<td>Garcia, Angelica</td>
<td>BS</td>
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<tr>
<td>Garcia Suarez, Jonathan</td>
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<tr>
<td>Geda, Yonas</td>
<td>MD</td>
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<td>Addison Gralen</td>
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<td>Guerrero, Emyr</td>
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<td>Keeling, Elizabeth</td>
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<tr>
<td>Jennifer Levy</td>
<td>BSc</td>
<td>Research Technician</td>
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<tr>
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<tr>
<td>Stokes, Ashley</td>
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<tr>
<td>Vanessa Ortega</td>
<td>MS</td>
<td>Lab technician, Translational Neuroscience</td>
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Critical Path Institute (C-Path) is a nonprofit, public-private partnership with the U.S. Food and Drug Administration (FDA) created under the auspices of the FDA’s Critical Path Initiative program in 2005. C-Path’s aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies. These pre-competitive standards and approaches have been termed “drug development tools” (DDTs) by the FDA, which established a process for official review and confirmation of their validity for a given context of use. C-Path orchestrates the development of DDTs through an innovative, collaborative approach to the sharing of data and expertise. We build consensus among participating scientists from industry and academia with FDA participation and iterative feedback. The process, depending on the use case, culminates in a formal application to FDA for official “qualification” of the DDT for a given use in product development. Qualified DDTs then become open standards for the scientific community which, in turn, may be assured of the scientific rigor under which they were developed and of the FDA’s understanding and acceptance of their validity.

The Critical Path for Alzheimer’s Disease (CPAD) consortium accelerates drug development for patients with chronic neurodegenerative disease leading to dementia, primarily Alzheimer disease. CPAD is collaborating with industry, regulators, and academia to leverage the wealth of drug development knowledge that the consortium members possess and enable pre-competitive widespread data sharing from clinical trials in AD. CPAD curates an aggregated database of anonymized patient-level data using CDISC consensus standards, from 73 different Phase II and III clinical trials and observational studies. The CPAD database is leveraged to develop various DDTs, such as model-informed disease progression models and clinical trial simulation tools that can be used for optimizing clinical trial design. CPAD is leading a precompetitive effort with leading academic and industry experts to 1) test and validate a tau-PET quantification method that harmonizes derived measures across different tracers and cohorts, and 2) explore and evaluate the readiness of tau-PET as a surrogate marker in AD drug development to support accelerated drug approval. Also, CPAD and the Alzheimer’s Association’s Global Alzheimer’s Association Interactive Network (GAAIN) collaborate on establishing a neuroimage analysis framework, based on the LONI pipeline workflow, that is generalizable and reproducible, for use in clinical trials.

The CPAD database includes a rich variety of biomarker modalities (e.g., imaging, cerebrospinal fluid, blood) and longitudinal clinical endpoints, offering great potential for answering key questions in AD trial design related to screening, enrichment, and tracking disease progression. However, the complexity and diversity of CPAD’s data pose a challenge for researchers more skilled in modeling than data processing. To address this, a user-friendly web-based interface called the "actionable data model" (ADM) tool has been developed to further enhance the utility of the CPAD database, facilitating data exploration, supporting model-informed drug development, and advancing research to increase the scientific understanding of Alzheimer’s disease.
The CPAD-developed DDTs will drive the potential for scientific discovery and provide solutions to optimize the design of clinical trials of AD drugs intended for regulatory review in support of marketing approval.
## CRITICAL PATH INSTITUTE

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<td>Sivakumaran, Sudhir</td>
<td>PhD</td>
<td>Executive Director, Critical Path for Alzheimer’s Disease Principal Investigator</td>
</tr>
<tr>
<td>Cullen, Nicholas</td>
<td>PhD</td>
<td>Associate Director, Critical Path for Alzheimer’s Disease Quantitative Scientist and Modeler</td>
</tr>
<tr>
<td>Lau, Corissa</td>
<td>MBA</td>
<td>Project Manager, Critical Path for Alzheimer’s Disease</td>
</tr>
<tr>
<td>Pauley, Mike</td>
<td>MS</td>
<td>Quantitative Medicine Developer</td>
</tr>
<tr>
<td>Podichetty, Jagdeep</td>
<td>PhD</td>
<td>Quantitative Medicine Director</td>
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MAYO CLINIC ARIZONA

The main goal of this research program is to determine the correlation between genetic risk for Alzheimer’s disease (apolipoprotein E [APOE] genotype) and the effect of normal aging on certain measures of cognitive function, brain volume, brain metabolism, cerebral amyloid deposition, and potential plasma biomarkers (APOE fragments and others). It supports and extends our goals and efforts in our NIA funded Alzheimer’s Disease Research Center. The principal institutions involved in this collaborative research effort are Mayo Clinic Arizona (primary site), Banner Alzheimer 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 whom we had stored DNA further fostering collaboration and extending our range of scientific inquiry. We also are in the process of analyzing a large cohort of resilient agers through a collaboration with Drs. Owen Ross and Neill Graff-Radford from Mayo Clinic Florida, as well as the impact of recent novel genetic risk factors on cognitive aging trajectories.

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 in APOE e4 carriers in their 50s, is confined to memory during the early preclinical phase but there is an increase in self-awareness of decline that is not mirrored by informant observation. In later stages of preclinical Alzheimer’s disease, as patients get within a few years of incident MCI conversion, executive measures begin to decline and informant observations begin to parallel self-reports of decline. Finally, by the time MCI emerges, memory, executive skills, and in some cases visuospatial skills begin to decline; and subtle personality changes begin characterized by increased proneness to stress and reduced openness to new ideas and experiences. Missing from the preclinical profile is any indication of depression, but the development of personality changes lays the groundwork for behavioral manifestations which begin to emerge during the MCI stage.

In addition to our cognitive studies, we have created a biobank of plasma, serum, and DNA that has served as a core resource for collaborative members.

To date we have:
1. analyzed the longitudinal trajectories of all our measures, identified those showing significantly greater acceleration of decline in APOE e4 carriers relative to noncarriers, and developed a cognitive profile of APOE e4 driven pathological aging that defines the cognitive profile of preclinical Alzheimer’s disease.
2. compared our incident cases of mild cognitive impairment (MCI) to a clinical (prevalent) group of matched patients to further define an early and late preclinical/early clinical phase in which we begin to see decline in non-memory measures, especially those sensitive to executive functions.
3. characterized the significance of subjective impairment as voiced by one’s self as well as by one’s informant and showed that both reflect an early stage of decline in a small subset, but that stress related symptoms overshadow the cognitive changes so that subjective impairment alone is an unreliable indicator of imminent decline.

4. showed that personality traits that increase one’s proneness to stress further speed up age-related memory decline, and this effect is more apparent in APOE e4 carriers reflecting their inherent predilection for Alzheimer’s disease. In contrast we found that the developmental sex-based cognitive advantages of women over men regarding verbal memory and men over women regarding visual memory do not buffer the rate of decline associated with APOE e4.

5. advanced a modification of the amyloid cascade hypothesis that shifts the role of amyloid from a gain of toxicity of the abeta peptide fragment to the loss of homeostasis and function of the APP system.

6. utilizing graph theoretical analytics of functional MRI data in cognitively normal carriers and non carriers of the APOE e4 allele, we identified that carriers showed a relationship between steepness of verbal memory decline and left hippocampal connectivity, in advance of hippocampal volume changes.

7. showed that in our cohort of older adults undergoing longitudinal assessment, we did not detect evidence for lingering adverse neuropsychological and behavioral effects following COVID 19 infection that was not severe enough to require ICU admission or prolonged hospitalization.

These types of analyses will continue well into the future permitting us to achieve our longer term goals of:

1. correlating changes in cognition and behavior with structure, metabolism, and pathology

2. determining rates of symptomatic conversion from preclinical Alzheimer’s disease to MCI, and from MCI to dementia

3. developing a personalized predictive model based on genomic and other presymptomatic parameters for the timing of symptomatic conversion

4. inform the design of primary and secondary prevention clinical trials

5. provide a core resource to all our collaborative partners

6. correlating nontraditional measures of neuropsychiatric status such as intellectual achievement, sleep patterns, and personality factors with presymptomatic cerebral amyloid levels.

7. Determine the relative time course of change for emerging blood based biomarkers that begin preclinically and may be helpful in determining not only biomarker status but time to symptomatic conversion.

8. Contribute to the development of a personalized, inexpensive, and widely accessible diagnostic based on EEG through a deep learning approach in collaboration with an industry sponsor.
### Mayo Clinic Arizona

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<tr>
<td>Woodruff, Bryan</td>
<td>MD</td>
<td>Principal Investigator, Behavioral Neurologist</td>
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<tr>
<td>Caselli, Richard</td>
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<td>Co-Investigator, Behavioral Neurologist</td>
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<tr>
<td>Locke, Dona</td>
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<td>Co-Investigator, Neuropsychologist</td>
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<tr>
<td>Wicklund, Meredith</td>
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<td>Co-Investigator, Behavioral Neurologist</td>
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<tr>
<td>Dumitrascu, Oana</td>
<td>MD</td>
<td>Co-Investigator, Cerebrovascular Neurologist</td>
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<tr>
<td>Ezenne, Adaeze</td>
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<td>McCarty, Monica</td>
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<td>Brostrom, Debra</td>
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<td>Baxter, Leslie</td>
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<tr>
<td>Fryer, John</td>
<td>PhD</td>
<td>Neuroscientist</td>
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MIDWESTERN UNIVERSITY

Midwestern University is a university of health sciences dedicated to the education of future health professionals. Midwestern has Colleges of Osteopathic Medicine, Graduate Studies, Optometry, Dental Medicine, Podiatry, Pharmacy, Veterinary Medicine, and Health Sciences. Within those Colleges are many additional programs including Nurse Anesthesia, Physician Assistant, Cardiovascular Sciences, Biomedical Sciences, various advanced nursing degrees, Occupational Therapy, Physical Therapy, Speech-Language Pathology, and Doctor of Psychology. Midwestern University also has several dual-degree programs including the Precision Medicine Program and a Master of Public Health program. We have multiple university-based clinics including the Multispecialty Clinic, the Eye Institute, the Dental Institute, and the Companion Animal Clinic. Midwestern has a rapidly growing and diverse research community focused on disease-specific research as well as basic science research. Our scientists and clinicians (for both human and veterinary patients) are involved in many different research efforts, with collaborations throughout Arizona and the U.S. Midwestern supports a broad range of research, from neurological disorders and cancer to infectious diseases and anatomical studies. The research environment at Midwestern is highly collaborative and designed to use the collective expertise of our colleagues to achieve common goals.

Multiple interdisciplinary research programs have been developed in the last few years and are thriving. The MWU Clinical Research Services (CRS) provides a comprehensive setting to conduct clinical trials, translational research and technology development regarding human and veterinary drugs, biologics, devices, nutritional products, and diagnostics. Midwestern has also developed the Nanomedicine Center of Excellence in Translational Cancer Research, with the goal of applying new technologies to the treatment of cancer. 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 link between consumption of a Western diet and Alzheimer’s pathology, specifically in regard to the brain-gut-bone axis.

4) 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.

5) Assessing the readiness of physical, occupational, and speech therapy practitioners to work with Alzheimer’s disease patients as well as patients with related dementias.

6) Identifying probiotics and bacterial genes that improve motor function in a Drosophila Parkinson’s disease model. This study involves a metagenome-wide association analysis.

7) Examining a proposed link between a protein that protects the chromosome ends against shortening (RAP1) and a protein localized to astrocytes (GFAPδ), which also interacts with presenilin-1. Telomere shortening is a molecular cause of cellular aging, and advancing age is the greatest known risk factor for AD. This project studies the possibility that GFAPδ variants will modulate the accumulation of amyloid deposits in a cell culture model. This study also evaluates the ability of RAP1 and GFAPδ to activate gamma-secretase as well as the DNA-binding properties of RAP1.

8) 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 SAMP8 mice. In addition, this study examines exercise-induced mitigation of cellular senescence as a peripheral control mechanism for Alzheimer’s disease using the same mouse model.

9) Evaluating the role of progranulin transport and processing in Alzheimer’s disease with the goal of developing new therapies.
### MIDWESTERN UNIVERSITY

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<tr>
<td>Jentarra, Garilyn</td>
<td>PhD</td>
<td>Administrative Principal Investigator</td>
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<tr>
<td>Abel, Kelsey</td>
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<tr>
<td>Al-Nakkash, Layla</td>
<td>PhD</td>
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<tr>
<td>Anderson, Sarah</td>
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<td>Bae, Nancy</td>
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<td>Brobeck, Teresa</td>
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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 of the software needed for microbiome and transcriptome analyses installed, including the popular QIIME 2 microbiome bioinformatics platform (https://qiime2.org; developed by PI Caporaso’s team of students and professional software engineers at PMI). The PMI at NAU has an in house 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

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<td>Wood, Colin</td>
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The Translational Genomics Research Institute (TGen) is a non-profit biomedical research institute whose mission is to make and translate genomic discoveries into advances in human health. TGen is dedicated to bringing the breakthroughs in genomics research to the bedside and benefit of patients. Its focus on translational research involves coupling, in novel ways, basic and clinical science with emerging molecular technologies to accelerate the development of therapeutics and diagnostics for human disease. Part of the unique nature of TGen is its collaborative relationships with academic institutions, clinical practices and corporate entities, each aimed at accelerating discovery-based research towards application.

The Neurogenomics Division of TGen is the home of Alzheimer’s disease (AD) and aging research programs within TGen. AD and aging has been a focus of the Division since its inception. The Neurogenomics Division is subdivided into several disease-oriented research clusters. Each cluster represents a unique cross-pollination between basic researchers and clinicians with the endgame being successful clinical trials that ultimately lead to improved treatments and diagnosis. These clusters include geneticists, molecular and cellular biologists, brain imaging researchers, proteomics specialists, drug development teams, and other experts.

The Division has accomplished several milestones in AD research including: (1) the first high-density genome screen to identify common heritable risk factors for AD, (2) the identification of a key genetic driver of episodic memory function in healthy individuals, (3) the first large-scale study identifying cell-specific genes differentially expressed in pathology-containing and pathology-free neurons in the brains of AD patients and control donors, (4) the identification of protein kinase targets responsible for phosphorylation of the tau protein which contributes to AD pathology and the use of this information to identify novel therapeutic approaches to the disease, (5) the collaborative discovery of a novel cognitive enhancing agent based on the genetic finding in episodic memory, and (6) the identification of new, cell-free extracellular vesicle biomarkers in the blood of AD patients. Collaborations within Arizona and across the nation have been critical for each of these projects and they included work with Arizona State University, Banner Alzheimer’s Institute, University of Arizona, Banner Sun Health Research Institute, Barrow Neurological Institute, the National Institutes of Health, and many others.

Currently the Division has major areas of focus in the genetic basis of disease in rare AD clinical cases (using next generation DNA sequencing), the characterization of the transcriptome of multiple cell types in the AD brain (using laser capture microdissection and single cell sequencing approaches), cell-free fluid biomarker identification (using extracellular vesicle molecular profiling), and novel drug development for cognitive enhancement and AD. The Division also serves as an AD-related genomics and biostatistics resource for the Arizona Alzheimer’s Consortium and frequently assists in generation and interpretation of genotyping and sequencing data.

Overall, the mission of the Division’s work in AD is to develop improved ways to assess personalized risk for AD before the onset of symptoms, leverage molecular information to identify novel drug targets, and gain deeper understanding of the genomic changes associated with disease onset and progression.
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Researchers at the University of Arizona (UA) are engaged in collaborative, multidisciplinary 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 age-related cognitive impairment and dementia. To accomplish these goals, investigators from across the UA campus are engaged in these research projects, representing fifteen departments and institutes in four colleges, encompassing the fields of neuroimaging, biomedical engineering, cognitive and behavioral neurosciences, neuropsychology, psychiatry, neurology, cardiology, surgery, pharmacology, physiology, and statistics are involved in these research programs. Projects apply a range of scientific approaches from basic neuroscience to cognitive behavioral science to clinical intervention in studies that translate across human and non-human animal models of aging and disorders of aging. 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 are being made available to the entire neuroimaging community. This year, we are excited to report that UA has been awarded a high-end instrumentation grant from NIH that will support the acquisition of a next-generation Siemens Cima.X MRI scanner. The new magnet is scheduled to be installed in fall, 2023. UA will be one of the first sites in the country to obtain this state-of-the-art magnet that promises to significantly enhance our imaging capabilities.

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 novel methods for MRI analyses and creating 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 NIH, NIA, NIHGS, DOD, NSF, NHLBI, NINR, NIBIB, NIDA, SBIR, NBIB, USDA, NIFA, the Flinn Foundation, and the Alzheimer’s Association, among others. Many of these grants derived directly from projects that were begun with funding from the AAC pilot project program. Recent examples include:

- Joint Estimation Diffusion Imaging (JEDI) for Improved Tissue Characterization and Neural Connectivity in Aging and Alzheimer's Disease (NIA, Hutchinson)
- Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults (NIA, Wilson/Alexander)
- Bioinspired optical sniffer based on microtoroid resonators and science and technology convergence (NSF, Su)
• Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation (NIA, Chou/Ryan)
• Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer's disease biomarkers and risk factors in clinically normal older adults (NIA, Grilli/Andrews-Hanna)
• Interleaved TMS-fMRI for Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnestic Mild Cognitive Impairment (NIA, Chen/Chou)
• Angiotensin-(1-7): A Treatment for Neuropsychological and Memory Impairments Following Moderate to Severe Traumatic Brain Injury (DOD, Joseph/Hay)

This program of research is strengthened by our close ties to other research units at UA including the Evelyn F. McKnight Brain Institute, focusing on understanding and preventing age-related memory impairment, and the Center for Innovation in Brain Sciences, focusing on the development of pharmacological interventions for neurodegenerative diseases. 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.** A major strength at UA is our expertise in neuroimaging methods, most notably MRI. We continue to build the resources required for sharing data and standardized analysis pipelines that are made available to the research community through XNAT, a shared online repository for neuroimaging data that is funded by the NIH. The complexity and high cost of collecting and analyzing large-scale datasets highlights the importance of sharing data across laboratories. 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 adult lifespan. Over the past year, pilot funding was provided to:

- establish a neuroimaging acquisition and analysis core at the University of Arizona in Tucson to be a core service to AAC investigators,
- combine novel radial MRI methods for T2 and T1 mapping with deep learning (DL) methods for high-resolution parametric mapping of the hippocampal internal structures,
- implement an integrated set of high-resolution and multi-contrast 3T MR imaging protocols capable of mapping hippocampal subfields of human subjects,
- develop protocols for T2-weighted MRI, multiplexed sensitivity encoded (MUSE) diffusion-tensor imaging (DTI), and T2*-weighted quantitative susceptibility mapping (QSM) at uniform spatial-resolution (0.4 x 0.4 x 2 mm³) and voxel geometry,
- develop enhanced probabilistic tractography analyses for postprocessed DTI data to isolate brainstem-specific white matter tracts for quantitative analyses with respect to age and cognition, and
- develop and refine methods for registering ex vivo MRI data with histologically-prepared brain sections from the same animals for evaluation of hippocampus anatomy and microstructure.
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, in order to:

- determine how physical activity (PA) and sleep quality (SQ) influence cognitive and brain aging in highly active versus typically active older adults with differential risk for Alzheimer’s disease,
- determine the effect of theta-burst stimulation on TMS-evoked potentials in individuals with amnestic mild cognitive impairment,
- determine the impact of inter- vs. intra-generational conversation on the specificity of autobiographical memory in young and older adults, and individuals with objectively-defined subtle cognitive decline or mild cognitive impairment,
- explore novel hypotheses regarding the effect of normal and pathological aging processes on spatial cognition,
- quantitatively assess the directional nonlinear interactions between neural network function and motor task performance using convergent cross mapping in order to assess dysregulation of interactions between motor and brain systems as a novel sign of cognitive impairment,
- measure asymptomatic extracranial carotid atherosclerotic disease and micro-embolic events and their impact on blood brain barrier integrity in older adults using MRI, and
- determine whether manual lymph drainage massage increases cervical lymphatic flow and protein clearance via magnetic resonance imaging of interstitial fluid movement after cisterna magna injection and photoacoustic imaging/ultrasound of cervical lymphatic dynamics.

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 age-related cognitive impairment and/or AD, slow the progression of AD, or ameliorate cognitive impairments associated with normal aging and AD. These pilot studies will:

- develop a fully functional Neuropixels system capable of collecting high-density neural signals from behaving rats to assess cell stability, longevity of recording probe functionality, and the effect of the chronic device on the animal’s behavior,
- validate a tortuosity index in a pre-clinical model of AD to determine effect of vascular morphology on amyloid deposition, using Tg-SwDI mice, a validated pre-clinical model of CAA, using time-of-flight MRI angiography and brain anatomy/microhemorrhages assessed by T1,
- investigate if menopause reduces SKCa/IKCa function in brain arterioles, impairing functional hyperemia and accelerating dementia in menopausal AD mice,
- determine whether gene therapy may rescue SKCa or IKCa function to restore vasodilation in menopausal mice,
- determine the feasibility of detecting the presence of amyloid beta from postmortem serum samples from healthy patients and those with confirmed AD,
- determine whether β-amylloid can directly reprogram astrocyte metabolism, and
- characterize human resistin-related arterial stiffness and tissue changes in novel murine animal models.
### UNIVERSITY OF ARIZONA

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The University of Arizona (UA) has a strong history of academic and medical excellence in the state of Arizona, governed by the Arizona Board of Regents. Two medical school campuses have been established, one located in Tucson at the Arizona Health Sciences Center and University Medical Center, and one located in Phoenix on the Phoenix Bioscience Core (PBC). The UA College of Medicine – Phoenix shares the PBC campus with the UA Coit College of Pharmacy, UA Zuckerman College of Public Health, UA Eller College of Management, and several allied health programs from Northern Arizona University, Arizona State University, the Translational Genomics Research Institute, and the Phoenix VA Research Service. Through these many colleges and institutions, the UA College of Medicine – Phoenix is uniquely positioned to accelerate the biomedical and economic engines in Phoenix and the State by leveraging vital relationships with key clinical and community partners.

The UA College of Medicine – Phoenix mission is to inspire and train exemplary physicians, scientists, and leaders to optimize health and health care in Arizona and beyond. The UA College of Medicine – Phoenix was founded in 2007 as a full, four-year medical program. It was granted full independent accreditation by the Liaison Committee of Medical Education (LCME) in June 2017. At its new class size, the program matriculates 120 new allopathic doctors each year. The UA College of Medicine – Phoenix continues to expand and grow as it also provides graduate training opportunities through the Clinical Translation Science Program. This program offers MS and PhD and combined MD/PhD and MD/MPH degrees.

The UA College of Medicine – Phoenix commits to life-long learning and critical thinking for all trainees, staff, and faculty. One example of this commitment is the requirement for all medical students to complete a Scholarly Research Project over their four years of medical training. Students are paired with physicians and translational scientists to complete projects that culminate in a thesis as part of the graduation requirements.

As part of the overall mission of the university, UA College of Medicine – Phoenix has developed and continues to reinforce cooperative agreements, partnerships, and collaborations with local institutions. Some examples include the development of the Neurotrauma & Social Impact research team, a collaboration between the UA College of Medicine – Phoenix and Phoenix VA Health Care System. The team sets the goal to be the premiere destination for neurotrauma research, training, and collaboration. More recently, this program has engaged with partners from the Maricopa County Attorney’s Office, Mesa and Tempe Police Departments, The Sojourner Center, and The CACTIS Foundation to establish the Maricopa County Collaboration on Concussion in Domestic Violence (MC3DV). Primary research directions for the program include inflammation, rehabilitation, and practical therapies for traumatic brain injury as a causative factor in challenging healthy aging and promoting neurodegenerative disease.
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PROJECT PROGRESS REPORTS
A preclinical evaluation of the impact of estrogen therapy after variations in surgical menopause: Effects on cognition, anxiety, and inflammatory markers. Heather A. Bimonte-Nelson, PhD, Benjamin C. Trumble, PhD. Arizona State University; Arizona Alzheimer’s Consortium.

Specific Aims:
The specific aim of this project is to determine the memory, anxiety-like, and inflammatory impacts of estrogen therapy, comparing effects after two different types of surgical menopause.

Background and Significance:
Menopause occurs naturally at an average age of 52 (Pinkerton et al., 2017). However, the experience of menopause, as well as its etiology, is more diverse than this definition may indicate; indeed, individuals can experience gynecological surgery before this menopausal transition, resulting in a different trajectory with unique indications and treatment plans. For example, oophorectomy, or the surgical removal of the ovaries, performed before natural menopause onset results in the abrupt decline in circulating estrogens and progesterone (Koebele & Bimonte-Nelson, 2016). Coincident with these sharp declines in ovarian hormone levels is the onset of menopause indications including hot flashes, mood alterations, and memory disturbances (El Khoudary et al., 2019; Pinkerton et al., 2017). There is work indicating that women who have had oophorectomy show sustained chronic inflammation post-surgery (Pacifici et al., 1991), and have an increased risk for dementia later in life (Rocca et al., 2007). To combat some of these indications, hormone therapy (HT) may be prescribed. HT typically contains an estrogen, such as 17-beta-estradiol (E2) (Shifren et al., 2019). HT can reduce hot flashes, and has been shown to improve mood and memory outcomes (Pinkerton et al., 2017). When prescribed early after oophorectomy, HT can also improve inflammatory outcomes (Pacifici et al., 1991) and decrease dementia risk (Rocca et al., 2014) associated with oophorectomy surgery. Notably, E2, specifically, has been shown to have anti-inflammatory effects, although systematic evaluations with variations in menopause and cognition have not been tested (Suzuki et al., 2007; Vegeto et al., 2003).

While it has been a main focus of clinical and preclinical research, oophorectomy is not the only form of surgical menopause. Hysterecetomy, or removal of the uterus, is the second most common gynecological surgery (Carlson et al., 1993), with one-third of women experiencing this procedure by the age of 60 in the United States (Carlson et al., 1993; Whiteman et al., 2008). In fact, between 1998 and 2010, in the United States over 7.4 million women underwent hysterectomy, with approximately 600,000 surgeries occurring each year (Carlson et al., 1993; Corona et al., 2015, Wright et al., 2013). This procedure may be performed alone, or in conjunction with oophorectomy. The experience of menopause following hysterectomy can be difficult to operationally define, as menstruation does not occur after surgery because the physical source of menstrual bleeding has been surgically removed, but ovarian hormones still circulate if ovaries are retained. Indeed, even with repeated within-subjects measures, endocrine evaluations can be poor predictors of the menopause transition (Prior, 2005). Rather than the standard clinical criteria of one year of amenorrhea (NAMS, 2014), menopause in hysterectomized women can be indicated by the presence of associated symptoms (Koebele & Bimonte-Nelson, 2016; The Practice Committee of the American Society of Reproductive Medicine, 2004). It is during this period that women who have undergone hysterectomy would be prescribed HT (Haney & Wild, 2007). Notably, clinicians no longer need to be concerned about the risk of endometrial hyperplasia with unopposed estrogen administration for this population, as these individuals no longer have a uterus. Without such risk, hysterectomized women can be prescribed HT in the form of an estrogen without a concomitant progestin, making for a HT profile
distinct from that of uterus-intact individuals (NAMS, 2014). Both clinically and preclinically, this population has been understudied, with even less research being conducted to evaluate subsequent cognitive or physiological outcomes with HT use. In clinical work, hysterectomized and non-hysterectomized ovary-intact women are often pooled together (Wharton et al., 2011; Wroolie et al., 2011); however, some studies that have evaluated these populations separately have found divergent outcomes for estrogen-alone as compared to estrogen plus progestogen containing HT (Coker et al., 2010; Maki, 2013; Resnick et al., 2009). Only recently has a preclinical rodent model of hysterectomy been developed to address such critical questions; we have developed this model. We have shown learning and memory deficits using our novel rodent model of hysterectomy compared to sham controls (Koebele et al., 2019). While the preclinical literature has found that estrogen-containing HT can be beneficial for memory and anxiety-like outcomes in models of ovariectomy (Ovx) (Acosta, Mayer, Talboom, Zay, et al., 2009; Bimonte & Denenberg, 1999; Koebele, Nishimura, et al., 2020), there has yet to be such determination of effects of HT administration following hysterectomy. Here, we propose to evaluate the cognitive and anxiety-like behavioral effects of E2 administration in our laboratory’s novel rodent model of hysterectomy. The current application will also systematically test whether the effects of hysterectomy and E2 impact inflammatory markers in the brain, and whether they correlate with treatment-induced cognitive or anxiety-like change.

**Preliminary Data, Experimental Design and Methods:**
Sexually-inexperienced Fischer-344 CDF rats (N=60) will arrive from the NIA colony. Following one week of acclimation in the vivarium space, rats will undergo gynecological surgery. This will allow for a direct comparison between different forms of surgical menopause, and this will be followed by E2 treatment or Control (Braden et al., 2017; Koebele, Mennenga, et al., 2020), as utilized in the literature for evaluating menopause-related outcomes (Chen et al., 2018; Kirshner et al., 2020). The administration paradigm utilized here more closely mimics the E2 transdermal patch, a commonly prescribed HT more recently evaluated in the KEEPS study (Gleason et al., 2015).

Rats will undergo a behavioral battery to assess spatial working and reference memory outcomes, as well as anxiety-like behaviors. After the completion of behavior testing, rats will be euthanized, wherein blood, remaining reproductive tissues, and brain tissue will be collected for further processing. Brain tissue collected from areas relevant to learning and memory will be analyzed for a variety of inflammatory markers (IL-6, TNF-alpha, and GM-CSF). These inflammatory markers have been related to anxiety-like or depressive-like behaviors in rodent (Erta et al., 2015; Maldonado-Bouchard et al., 2016) and human (Buspavanich et al., 2021) studies.

**Proposed One-Year and Long-Term Outcomes:**
Rats will be ordered immediately. The surgeries will be initiated about a week after the animals arrive to allow for acclimation to the animal facility. Rodent behavior testing will then ensue, and will be completed by the end of the one-year project period. We will score, analyze, and write the data into manuscript form immediately after conclusion of the behavioral battery. To follow, we will perform brain assessments of inflammatory markers to correlate with the behavioral 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, with inflammatory markers as a putative driving mechanism if the current data so indicate.

**Year End Progress Summary:**
Rats were ordered immediately as proposed. The surgeries were initiated, and rodent behavior testing has been completed with the battery as proposed. We have scored all behavioral data and
are analyzing final results currently. We are also undergoing/completing brain assessments of inflammatory markers to correlate with the behavioral data. Regarding long-term outcomes, expected deliverables include a manuscript submitted within two years from study initiation (within the current year), and a grant to study brainbehavioraging/hormone relationships with hysterectomy, with inflammatory markers as a putative driving mechanism if the current data so indicate.

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Determining the impact of RAB10 on Alzheimer’s disease-related phenotypes. David Brafman, PhD. Arizona State University; Arizona Alzheimer’s Consortium.

Specific Aims:
We and others have used human induced pluripotent stem cell (hiPSC)-based models, which are highly complementary to existing animal models, to study AD in a simplified and accessible system. In particular, the use of isogenic hiPSC lines with identical genetic backgrounds that only differ with respect to individual variants has become the gold standard in modeling and analyzing the effects of AD-related risk factors. We recently reported the development of a series of methods that employ a transient reporter for editing enrichment (TREE) which allows for the generation of isogenic hiPSC lines with clonal homozygous editing efficiencies approaching 90%-12-15. In this proposal, we will utilize these TREE-based approaches to introduce RAB10 mutations into isogenic hiPSCs from both non-demented control (NDC) and AD patients. In turn, we will use these isogenic hiPSC lines in a neuronal-astrocyte co-culture model to address the following hypothesis-testing questions: (1) What role does RAB10 play in cell surface amyloid precursor protein (APP) levels and subsequent endocytosis? (2) How does RAB10 modulate APP endosomal trafficking, processing, and secretion? (3) What is the effect of RAB10 on Aβ uptake, endocytic trafficking, and degradation? (4) Does RAB10 modulate tau-related pathologies? (5) Are the functions of RAB10 in modulating disease-related processes dependent upon LRRK2-mediated phosphorylation? To answer these hypothesis-testing questions, we propose the following specific aims:

Specific Aim 1: Use a TREE-based genome editing approach to introduce RAB10 mutations into isogenic hiPSC lines.

Specific Aim 2: Examine the specific effect of RAB10 mutations on the modulation of AD-related phenotypes and molecular processes.

Background and Significance:
In Alzheimer’s disease (AD), the majority of therapeutic interventions are focused on targeting the pathological consequences of AD—the amyloid plaques or neurofibrillary tangles that result from hypophosphorylated tau. Although these amyloid- and tau-centric molecular interventions have shown promise, they have not been successful in later clinical trials. This suggest, in part, that targets associated with later stages of the disease might not prove effective therapeutic interventions. Alternatively, identification of aberrant processes induced earlier and upstream from amyloid- and tau-related pathology, would provide an attractive targets for the development of therapeutic interventions. Indeed, there has been emerging evidence that dysfunction in the endo-lysosomal network (ELN) might induce downstream disease-related pathologies. In fact, numerous genome-wide association studies have identified several genes associated with endo-lysosomal processes. As such, understanding the function of various components of the endo-lysosomal network and the impact these members have on AD-related phenotypes is critical to the development of new therapeutic interventions. To that end, Rab GTPases play many roles in vesicular trafficking, typically with specific roles in distinct endo-lysosomal compartments. Interestingly, one RAB protein, RAB10, is unique as it has been implicated in numerous endo-lysosomal transport steps and is expressed in multiple intracellular compartments. Recently, linkage analyses combined with whole genome sequencing in pedigrees with AD resilience identified a variant in RAB10 that conferred protection against AD. Additional evidence also suggest that RAB10 might modulate amyloid- and tau-related pathologies. Despite these associations of RAB10 with end-point disease-
related pathologies, the precise manner by which RAB10 modulates specific upstream molecular processes has not yet been elucidated.

**Preliminary Data, Experimental Design and Methods:**
Generation of pure populations of functionally mature hiPSC-derived cortical neurons and astrocytes. Using a combination of directed differentiation protocols and magnetic-activated cell sorting (MACS) strategies we have developed methods for the large-scale generation of hiPSC-derived neurons, astrocytes, and microglia. 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 S100β 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.

Rapid and highly efficient generation of isogenic hiPSC lines. The use of isogenic cell lines with identical genetic background that only vary with respect to a particular gene of interest is a powerful approach and the only means by which conclusive genotype-to-phenotype relationships can be made. Currently, most approaches to engineer isogenic hiPSCs utilize the introduction of Cas9-mediated DNA double stranded breaks (DSBs) followed by homology directed repair (HDR) with exogenous DNA templates. However, HDR-based modification of hPSCs has been challenging with efficiencies reported in the range of 1-10% depending on the gene targeted20-22. As detailed most recently in our Nature Protocols and Stem Cell Reports publications we have developed a series of methods that employ transient reporters of editing enrichment (TREE) to facilitate highly efficient (>80%) single base pair editing of human cells at precise genomic loci12-15. In addition, these TREE-based approaches provide for the generation of KO hiPSC lines without the introduction of deleterious DSBs. Critically, our TREE-based approaches allows us to generate isogenic hiPSC lines with unparalleled efficiency and uniquely position us to study RAB10 independent of genomic variability.

Using human induced pluripotent stem cells (hiPSCs) to investigate the mechanisms by which various genetic factors modulates Alzheimer’s disease (AD) risk. We have used TREE-based gene editing methods to introduce genetic risk factors into isogenic hiPSCs derived from a variety of non-demented control (NDC) and AD patients12-15,23. In recent work published in Nature Communications and Acta Neuropathologica with Dr. Guojun Bu's24,25 group, we have used isogenic hiPSCs to investigate the mechanisms by which APOE424 increases AD risk. Along similar lines, we recently published in Molecular Psychiatry our initial work using isogenic APOE hiPSC to investigate the mechanisms by which APOE2 mitigates the presence of AD-related phenotypes26. Briefly, with hiPSC-derived neural cultures we demonstrated that isogenic conversion of APOE4 to APOE3 reduced AD-related phenotypes including reducing levels of Aβ and phosphorylated tau and reversing synaptic loss. By comparison, analysis of co-cultures derived from AD isogenic lines revealed that conversion of APOE3 to APOE2 decreased pathogenic amyloidogenic processing of APP as well as reduced Aβ release and levels of phosphorylated tau. Overall, these experiments demonstrate our ability to use isogenic hiPSC lines to investigate the mechanisms by which various genetic factors modulates AD risk.

**Experimental Designs and Methods:**
**Specific Aim 1:** Using our TREE-based approach, we will generate isogenic sets of hiPSCs that have been modified as follows: (i) An A-to-G conversion of the ATG start codon to ACG to generate a RAB10 knockout (KO), (ii) The introduction of a single nucleotide polymorphism at
Rs142787485 associated with reduced expression of RAB10 and protection against AD6. Since complete knockout of RAB10 might have detrimental effects on cell health and viability, this mutation will allow us to study the effects of reduced RAB10 expression in the context of a risk-modulating variant. (iii) A mutation of the nucleotides encoding amino acid residue threonine 73 to nucleotides encoding valine. Since RAB10 activity is, in part, controlled by LRRK2-mediated phosphorylation at Thr737, mutation of this amino acid to valine will allow us to ascertain the biological significance of this phosphorylation.

For this proposal, we will focus on the generation of such sets from familial AD and non-demented control (NDC) hiPSCs, many of which we have previously used TREE-based genome engineering to modify. In addition, these published and well-characterized hiPSC lines also display robust AD-related phenotypes when differentiated to neural cell types (see 27-29). Importantly, these hiPSC lines are equal in terms of their representation from male and female patients, which is important given the gender-based differences in AD risk.

**Specific Aim 2:** In the strictest form of the amyloid cascade hypothesis, generation and subsequent oligomerization of Aβ is the key step that leads to elevated phosphorylated-tau and subsequent synaptic and neuronal loss. Given the role of RAB10 in various aspects of endolysosomal trafficking, the AD-risk modulating effects of RAB10 could occur at multiple levels of this amyloid cascade, although several amyloid-independent, tau-centric mechanisms could be affected as well. In this aim, we will use the isogenic lines generated in Specific Aim 1 to begin to probe some of these hypothesized mechanisms. Specifically, we will differentiate our isogenic lines to cortical cultures and examine these cultures to test our hypotheses that RAB10 exerts its effects through (i) alteration in cell surface APP levels and endocytosis (ii) modulation of APP endosomal trafficking and processing (iii) regulation of Aβ receptor-mediated endocytosis, endocytic trafficking, and lysosomal degradation and (iv) influencing tau phosphorylation and internalization.

**Proposed One-Year and Long-Term Outcomes:**
This resource-generating (Specific Aim 1) and hypothesis-testing (Specific Aim 2) proposal will enable us to determine the extent to which RAB10 modulates specific AD-related phenotypes. Although the proposed studies will not interrogate all of the hypothesized mechanisms by which RAB10 modulates AD risk, we will uncover clues that will set the stage for future more detailed studies to apply for more comprehensive grants to funding agencies (e.g. NIH, Alzheimer’s Association, American Federation for Aging Research, Brightfocus Foundation) to further mechanistically probe these links. Publication and presentation of results shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. The Brafman laboratory has previously received AAC funds which led to the generation of preliminary used in several successful grant applications (AARG-21-851005, DOD-T0138, DOD-T0042-C, R21AG075612 R21AG070406P R21 AG063358 NIH-NIA, R21 AG056706 NIH-NIA, R21 EB020767 NIH-NIBIB, R01 GM121698 NIH-NIGMS, ADHS16-162401).

**Year End Progress Summary:**
1. Development of new, highly efficient gene editing methods in hiPSCs. The emergence of deaminase fused-Cas9 base editing technologies as well as prime editing technologies have enabled precise chromosomal editing without the need for potentially deleterious double stranded breaks or inefficient homology directed repair. While current base editors are restricted to a limited number of base substitutions, prime editors (PEs) can direct all single base substitutions as well as insertions and deletions. Even so, existing methods to purify edited cell populations are limited and rely on downstream sequencing techniques. Recent reports have shown that PE efficiency is low in cells resistant to genome modification such as human pluripotent stem cells (hPSCs). Previously, we developed a series of methods that employ transient reporters for editing enrichment (TREE) to facilitate highly efficient (>80%) base editing of cells. Briefly, these TREE-
based methods employ a transient episomal fluorescent reporter that allows for identification and 
flow cytometry-based isolation of cells that have had single nucleotide changes at precise 
genomic locations. Over the past year, we have built upon this work to establish a new TREE-
based method entitled prime-induced nucleotide engineering using a transient reporter for editing 
enrichment (PINE-TREE) to detect and report upon prime editing activity with a cell. Moreover, 
we demonstrated at several AD-related loci and across various types of genomic modifications 
(i.e., base substitutions, insertions, deletions) that PINE-TREE allows for the real-time 
identification and purification of edited cell populations. We employed PINE-TREE to modify 
hPSCs resulting in editing efficiencies significantly exceeding those using typical enrichment 
strategies. Finally, we demonstrated that PINE-TREE provides for the efficient generation of 
clonal isogenic hPSCs at loci that are difficult to edit using traditional reporter of transfection 
(RoT)-based PE enrichment techniques. Overall, PINE-TREE is a highly adaptable and easily 
implemented method that will greatly enhance the use of PE technologies for numerous in vitro 
applications. This work has been accepted for publication as a full length manuscript in Molecular 
Therapy. Moving forward, we are using PINE-TREE for the highly efficient introduction of the 
various RAB10 variants into isogenic hiPSCs. In addition, we are using PINE-TREE to generate 
RAB10 knockout (KO) isogenic hiPSCs.

2. Generation of pure populations of functionally mature hiPSC-derived microglia. Building 
upon our previous work to develop methods for the scalable generation of cortical neurons and 
astrocytes, we have adapted current previously published protocols to generate functional 
microglia-like cells from hPSCs. These protocols result in a highly pure population of microglia 
(>80% TREM2 / IBA1-postive) with cells morphologically distinct from monocytes and 
macrophages. More specifically, these microglia-like cells resemble human fetal and adult 
microglia as they display an axial bipolar morphology and express high levels of canonical 
microglial markers such as TREM2 and IBA1. Functionally, these microglia-like cells also display 
the ability to rapidly, uptake fluorescently tagged Aβ42 as measured by real-time fluorescent 
microscopy. Together, our ability to generate pure populations of neurons, astrocytes, and 
microglia that can also be dissociated and re-cultured in defined ratios provides a unique ability 
for control and reproducibility. Such analysis will enable us to determine the extent by which 
RAB10 modulates AD-related phenotypes in a cell-specific manner.

3. Submission of grants to Alzheimer’s Association and NIA. Using the preliminary data 
generated over the past year, we have submitted two funding proposals to further interrogate the 
role of RAB10 in manifestation of AD-related phenotypes. The first proposal was submitted in May 
2023 to the Alzheimer’s Association in response to their call Alzheimer’s Disease Strategic Fund: 
Endolysosomal Activity in Alzheimer’s (E2A) Grant Program. The second proposal was submitted 
in July 2023 to the NIA in response to Notice of Special Interest (NOSI): Genetic Underpinnings 
of Endosomal Trafficking as a Pathological Hub in Alzheimer's Disease and Alzheimer's Disease-
Related Dementias (AD/ADRD).
Video-conference delivery of an evidence-based intervention for people living alone with early-stage cognitive impairment. David W. Coon, PhD, Molly Maxfield, PhD, Dona Locke, PhD, Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

**Specific Aims:**

a) Finalize intervention protocol for video-conference (Zoom) delivery of EPIC Living Alone Virtual (EPIC-LA Virtual; an evidence-based intervention) analyzing (1) focus group data collected during COVID pandemic with people living alone with MCI or early-stage dementia and family members and providers who assist this population; and (2) pre-pilot experience with EPIC-LA.

b) Implement revised screening and interview protocol based on data in Specific Aim “a”.

c) Conduct a single arm pre-post study using the EPIC-LA Virtual intervention with up to 25 participants through a pilot feasibility and acceptability trial.

d) Use appropriate statistical analyses to provide descriptives that characterize the sample and further examine EPIC-LA feasibility and acceptability as well as inferences to describe the impact of the intervention.

e) Disseminate findings through presentations at national conferences such as the Gerontological Society of America and the American Psychological Association.

**Background and Significance:**

There are over 6.5 million people living with Alzheimer’s disease and related dementias (ADRD) in the United States, 85% of these individuals want to remain in their home for as long as possible, and reports suggest up to 26% of them live alone.1 Another 15-20% of people age 65 and older have Mild Cognitive Impairment (MCI), a condition characterized by measurable changes in thinking abilities that are noticeable to both people with MCI and their family/friends. These issues are of particular importance to Arizona as our state is projected to have the greatest increase in its proportion of both people living with ADRD between now and 2025.1

People with MCI or early-stage dementia can still carry out many of their everyday activities and participate fully in legal, financial, and care decision-making.2,4-6 Still, the period initially following a diagnosis can be a challenging time as those with MCI or early-stage dementia as they struggle to understand potential impacts of the disease. With memory and behavior changes, people with MCI and early-stage ADRD report fluctuations in their functional ability, narrowing of their social functioning and contacts, changes in the quality of their relationships, loss of self, feelings of frustration, loneliness, and isolation and are also at risk for depressive symptoms and clinical depression.4,7-14 These are of heightened concern for those living alone. However, people with MCI and early-stage dementia also want to remain significant contributing members in their support network and to expand their network to others in early stage.4,14 Our world is aging and the proportion of people living alone and the proportion of people living with cognitive impairment both increase with age.1,2,15 No evidence-based interventions have been identified to help them manage their ongoing memory changes, associated stressors, and related distress.14,15 The evaluation of EPIC-LA Virtual provides a critical next step to address this gap in research and care.

**Preliminary Data, Experimental Design, and Methods:**

Two of the project’s investigators run intervention programs for individuals diagnosed with MCI and/or early-stage dementia. Dr. Coon developed and has led the evidence-based program, Early-stage Partners in Care (EPIC II)16 in partnership with community-based organizations. EPIC II is a group-based program focused on patients with early-stage dementia and their care partners that includes education and skill-training workshops designed to reduced stress, enhance well-being, and help manage challenges by hearing the patient’s voice in terms of care.
values and future care preferences. Dr. Locke has extensive experience with patients in the early-stages of cognitive decline through her HABIT Healthy Action to Benefit Independence and Thinking program—a cognitive rehab and brain wellness intervention. Using our collective experience, we are responding to partner and sponsor requests (e.g., National Institute on Aging, the Alzheimer’s Association, and the U.S. Administration for Community Living) to test an intervention program for people living alone with cognitive impairment.

EPIC-LA Virtual is a group-based intervention that incorporates care values clarification and care planning components from the EPIC II and psychoeducational skill-building components from CarePRO (Dr. Coon’s evidence-based intervention for ADRD caregivers). EPIC-LA Virtual will be delivered in small groups of 6-8 people living alone with MCI or early-stage dementia. Video-based conferencing in contrast to in-person delivery presents the opportunity to: (1) reach across the nation to urban and rural areas with broadband access, (2) eliminate transportation barriers and driving concerns, (3) meet the needs of homebound participants with health concerns, and (4) better serve participants in the workforce with scheduling constraints.

The proposed study is a single arm, pre-post feasibility and acceptability study that also explores changes in key outcomes for people living alone with MCI or early-stage ADRD just before and shortly after intervention participation. This project will first finalize intervention protocol for video-conference (Zoom) delivery of EPIC-LA by analyzing focus group data collected during COVID with people living alone with MCI or early-stage dementia and providers who assist this population as well as participant experiences in pre-pilot work and then implement a revised screening and interview protocol to conduct a single arm pre-post intervention study with up to 25 participants.

**Proposed One-Year and Long-Term Outcomes:**
The proposed short-term outcomes are described as outputs in the Methods section. In addition, the data analyses would yield both professional presentations at meetings like the Gerontological Society of America, the American Society on Aging or American Psychological Association as well as the submission of the pilot results to venues like The Gerontologist (Practice Concepts Section), the Clinical Gerontologist, or Dementia. Subsequently, the PIs would submit either an R21 or an R01 in 2024, depending on the pilot project’s findings.

**Year End Progress Summary:**
The overarching goal of EPIC-LA Virtual is to create a supportive environment where people living alone with MCI or early-stage ADRD can receive education about memory changes and their impact; learn to manage cognitive, behavioral, emotional and social changes; enhance communication skills and positive coping strategies; clarify personal care values and preferences for future care tasks; and plan for their future. Iterative review of data from 50 focus group members including older adults living alone with cognitive impairment as well as family members and providers who assist them guided initial revision of EPIC II for EPIC-LA Virtual. Thirteen (N=13) participants have completed EPIC-LA to date joining from a variety of states including Arizona, California, Massachusetts, Florida, Idaho, and Hawaii.

Participant feedback after completing EPIC-LA intervention was extremely positive especially in terms of connecting with other people facing cognitive changes, learning ways to incorporate EPIC strategies into their own situations, generating new ways to plan for their future, and feeling understood and supported. Screening and assessment tools were well-received and pre-workshop training about Zoom delivery proved beneficial. In terms of acceptability, participants reported high levels of perceived benefit from EPIC-LA with a 100% of participants reporting some or a great deal of benefit related to: overall benefit, better understanding of memory loss and its effects, and increased confidence in dealing with memory loss. A 100% indicated some or a great deal of benefit in that it made their lives easier, enhanced their ability to care for themselves, and improved their life. All participants also stated that their level of preparation for future care needs
had improved substantially. Over 70% reported at least some improvement in their physical health, satisfaction of support from others, and amount of time in leisure activities. Over 85% saw improvements in their emotional well-being and communication with others. There are plans to enroll more participants to increase the sample size; however, medium effect sizes were found pre/post intervention related to reductions in depressive symptoms and loneliness as well as increases in key quality of life indicators (e.g., relationship with friends and life as a whole).

References:
Peeling back the layers of dementia, a systems approach. Tim Karr PhD, Diego Mastroeni PhD, Ben Readhead MBBS, Thomas Beach MD, PhD. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:
Specific Aim 1 (Dr. Mastroeni): Isolation of protein from frozen: Middle Temporal Gyrus (brain), Eye (retinal quadrant), Gallbladder, Heart, Kidney, Liver, Lung, Pancreas, Skin (abdominal), and Spleen from 4 AD, 4 normal control and 4 amnestic mild cognitive impaired subjects, 12 samples x 10 organs =120 samples.
Specific Aim 2 (Dr. Karr): Proteomic landscape analysis using Liquid-chromatography tandem mass spectrometry.
Specific Aim 3 (Dr. Readhead): Organ Network bioinformatics and layering of existing omics data from the same subjects (e.g., we already have gut microbiome data, transcriptomic data from the MTG and genomic data from the same subjects).

Background and Significance:
A century of research has focused on all the individual parts of late onset Alzheimer's disease (LOAD) but has failed to treat the disease as whole. Reductionist biology was designed to disentangle the tangled, but no individual part is independent, as an engine or tires to an automobile, all are required for the automobile to move. What happens in a fingernail influences the brain. Assuming we are not counting individual teeth or nails as an organ, the human body has 78 organs, five of which are necessary for survival (heart, brain, kidneys, liver, and lungs). To truly disentangle a web of biological processes we need to better understand the stability of the web or how the individual parts effect the whole body.

Over the past several years we have generated a tremendous amount of brain genomics, transcriptomics, and proteomics. We have identified hundreds of biological processes associated with disease pathogenesis, yet we are at a bottleneck in terms of a therapeutic approach to treat. We hypothesize this inability to treat is due to our unilateral approach. LOAD progresses over a long period before clinically apparent, and the physiological and molecular events likely occur years before a clinical diagnosis.

Preliminary Data, Experimental Design and Methods:
Specific Aim 1 has been completed Specific Aim 2 is in progress.

Specific Aim 1 Experimental design and Methods:
Samples: Inclusion criteria: we will only use tissue from subjects that were examined by a neuropathologist and an anatomical pathologist. We will only use samples that are clear from infection or inflammation and have pathological confirmation of disease, mild cognitive impairment, or non-disease. All samples will be matched for age (>65yrs.), sex, a RIN value of 8.5 or greater and PMI < 2.5 hours. Exclusion criteria: we will specifically omit individuals with a clinical diagnosis of brain, heart, liver, eye, gallbladder, kidney, lung, pancreatic, skin or spleen-associated diseases. We will exclude subjects who have presented clinical symptoms of AD greater than 3 years to reduce disease-associated agonal state (e.g., bed ridden). We will omit any individuals with a mutated form of AD, or early onset cases. We will omit ApoE 4 carriers. Future studies will look at the effect of ApoE genotype, considering the effect ApoE has on AD.

Proteomics: As previously described1-3, relative protein abundance differences amongst the various tissues will be using standard methodologies and operating procedures developed in the Mass Spec Core facility at ASU, managed by Dr. Karr. Tissue samples will be thawed and solubilized in 25 microliters of 5% SDS/50mM TEAB containing 50mM dithiothreitol. Solubilized
samples will then be incubated for 10-15 minutes at 95°C and spun again at 15,000 rpm for 15 minutes at 20°C to confirm complete solubilization (i.e., no visible pellets observed). Supernatants will be removed and stored at -20°C or immediately processed as described below. Solubilized proteins will be quantified using EZQ Protein Quantitation Kit (Thermo Fisher) and alkylated with 2.25µg iodoacetamide (Pierce; final concentration 40mM) for 30 minutes in the dark at room temperature. Samples will then be processed using the Protifi S-trap Micro Columns as per manufacturer instructions. Briefly, samples were acidified by addition of 12% phosphoric acid to a final concentration of ~1.2% phosphoric acid. Proteins were digested by addition of 2.0 µg of porcine trypsin (MS grade, Pierce) and incubated at 30°C for 2 hours. S-trap buffer (90% methanol, 100 mM TEAB final) was also added in volumes 7X our total sample volume. Acidified sample and the S-trap buffer was filtered through columns. Columns were washed 3X with S-trap buffer. An additional 0.5 µg of trypsin and 25 µL of 50 mM TEAB was added to the top of each column and incubated for 1 hour at 47°C. Samples were eluted off the S-trap columns using three elution buffers: 50 mM TEAB, 0.2% formic acid in water, and 50% acetonitrile/50% water + 0.2% formic acid. Samples were dried down via speed vac and resuspended in 20-30 µL of 0.1% formic acid.

Liquid-chromatography tandem mass spectrometry: All LC-MS analyses will be performed at the Biosciences Mass Spectrometry Core Facility (https://cores.research.asu.edu/mass-spec/) at Arizona State University. All data-dependent mass spectra will be collected in positive mode using an Orbitrap Fusion Lumos mass spectrometer (Thermo Scientific) coupled with an UltiMate 3000 UHPLC (Thermo Scientific). Label-free quantification (LFQ): Raw files will be searched against the current Uniprot (www.uniprot.org) human database using Proteome Discover 2.5 (Thermo Scientific). Raw files searches using SequestHT will include Trypsin as enzyme, maximum missed cleavage site 3, min/max peptide length 6/144, precursor ion (MS1) mass tolerance set to 20 ppm, fragment mass tolerance set to 0.5 Da and a minimum of 1 peptide identified. Carbamidomethyl (C) will be specified as fixed modification, and dynamic modifications set to Acetylation and Met-loss at the N-terminus, and oxidation of Met. A concatenated target/decoy strategy and a false-discovery rate (FDR) set to 1.0% will be calculated using Percolator (19). Accurate mass and retention time of detected ions (features) using Minora Feature Detector algorithm node in Proteome Discoverer will identify chromatographic features to determine area-under-the-curve (AUC) of the selected ion chromatograms of the aligned features across all runs and relative abundances calculated. The total proteins identified in the study and the differential abundances determined (Benjamini-Hochberg corrected) data from the output will be exported and used for downstream bioinformatic analyses. Gene ontology enrichment: Differentially abundant protein differences within and between tissue/disease state samples will be analyzed initially using DAVID and Cytoscape to provide a global view of the gene ontology (GO) patterns present. We will then use the ClueGO plugin v2.5.8 in Cytoscape to generate enriched GO categories using a right-sided hypergeometric test and P-values, adjusted using Benjamini-Hochberg for multiple testing correction, to determine the overall enrichment of GO categories in each tissue x disease state present.

**Proposed One-Year and Long-Term Outcomes:**
These data will provide the foundational framework for future studies looking at multiple organs with respect to disease process. We believe this will allow us to formulate hypothesis on a systems level that will integrate and compliment traditional bottom-up approaches and provide a deeper overarching view of neurodegenerative diseases.

**Year End Progress Summary:**
1. The acquisition of biological samples from all tissue/organs has been successfully completed.
2. All biological samples have been prepared for mass spectrometry label-free quantitative analysis. 3. Label-free quantitation is currently underway.

Specific Aims:
Evaluate the Biostamp nPoint sensor patch, an FDA 510(k) approved wireless device for collecting physiological data in clinical and home settings developed and commercially available from MC10 for expanded use that also includes external settings with specific application to Alzheimer’s (AD) patients.

Background and Significance:
Clinical need and current gaps: Patients affected by AD have impaired ability to carry out daily activities as they suffer from cognitive dysfunction, memory loss, disoriented movement, and coordination. There is a need for continuous monitoring and assistance to patients and caregivers. Smart wearable devices such as wristbands or smartwatches may provide a certain degree of freedom with the possibility of remote healthcare monitoring throughout the day and night without restriction and discomfort. Existing devices for AD patients are bulky causing discomfort to the wearer. AD patients may forget to wear these devices or forget that they took them off if they found them uncomfortable making them poorly suited for practical applications. Thus, there is a need to fabricate lightweight, stretchable, ultrathin skin-like multifunctional sensing patches for continual wearing with less intervention and more durability. The patch could be attached to the skin surface like a temporary tattoo by soft contact making them mechanically invisible to the user.

Biostamp nPoint sensor patches solve the above challenges because they can be applied to the skin at multiple body locations for remotely targeted data collection. This is a rechargeable sensor patch and is reusable involving up to 24 hours of continuous wear. It is used to monitor vital signs such as heart rate and muscle activity, sleep metrics, and postural classifications with clinically validated accuracy. Data collected is processed and stored in a secure cloud which is synchronized with EDC and CTM third-party app-based systems. This device has been used to monitor motor symptoms in Parkinson’s disease, assessment of postural sway in Multiple sclerosis patients, and measure foot strike angle during running and other physical activities in a normal individual.

Preliminary Data, Experimental Design and Methods:
The pivotal study done by the MC10 company on the Biostamp nPoint device demonstrated the accuracy of physiological data collection such as heart rate, respiratory rate, muscle activity, and movement in both clinic and home environments. Biostamp nPoint devices were supposed to be available for purchase. This device had been tested on healthy individuals, Parkinson’s, and Huntington disease patients.

Proposed One-Year and Long-Term Outcomes:
Throughout one year, the durability, feasibility, and ease of use would be demonstrated. The lifetime of the device, irritability, and if continual monitoring is required would be determined. The device would be configured to the need of AD patients. The long-term outcome of physiological data monitoring would be useful for early biomarker detection.

Year End Progress Summary:
(1) BioStamp Device Evaluation
The first step of this project was to purchase the BioStamp devices. When contacting the company, we received the following reply: “Unfortunately, the BioStamp has reached the end of
its service lifestyle. That said, we have several other wearable/sensor options that may be a fit for your research project/proposal. Would it be possible for you to share some details on your proposal?" from Carmel Rafalowsky, Business Development Specialist, at Medidata Solutions.

We arranged a zoom call that was attended by 7 employees of this company, where we explained our project. We never heard from them again. Thus, we were unable to obtain the device that we were planning to test, and we were unable to source a replacement device.

Since the PI of this project is new to the Alzheimer’s field, she pivoted to exploring opportunities for viable collaborations within the Arizona Alzheimer’s consortium with the long-term goal of identifying molecular biomarkers for future tattoo-like wearable devices to monitor Alzheimer’s patient health. Three avenues were pursued: (i) collaboration with Ramon Velazquez to provide metabolomics data on choline deficiency related to Alzheimer’s disease, (ii) collaboration with Susanta Sarkar to degrade Aβ aggregates as a molecular model system for Alzheimer plaques, (iii) T32 training grant application in Alzheimer’s disease.

(2) Metabolomics of choline deficiency in Alzheimer’s disease

Human serum and mouse serum and brain samples were analyzed by metabolomics and analyzed using the MetaboAnalystR package (PMID: 35999348) and compared to choline levels in the same samples. Four metabolites in particular showed high association with choline levels, L-valine, 4-hydroxyphenylpyruvic acid, methylmalonic acid and ferulic acid. L-valine is an essential amino acid. Elevated levels of L-valine have been linked to a variety of health issues including increased oxidative stress and insulin resistance and a high level of L-valine increases the risk of AD in some studies. We found that higher circulating choline was associated with lower relative abundance of L-Valine. 4-Hydroxyphenylpyruvic acid and ferulic acid have anti-acetylcholinesterase activity, preventing the enzymatic breakdown of ACh. Many of the existing drugs to treat AD are also acetylcholinesterase inhibitors, indicating that elevating these metabolites can be particularly beneficial against AD. Finally, methylmalonic acid (MMA) is a precursor for succinyl-coenzyme A and a buildup of MMA is often interpreted as a deficiency in vitamin B12. Our observed elevation of MMA with higher choline levels was unexpected since choline and vitamin B12 levels typically rise and fall together, and will be a topic of future studies.

Our results have been accepted for publication in Acta Neuropathologica.

Jessica M Judd, Paniz Jasbi, Wendy Winslow, Geidy E Serrano, Thomas G Beach, Judith Klein-Seetharaman, Ramon Velazquez (2023) Inflammation and the pathological progression of Alzheimer’s disease are associated with low circulating choline levels., bioRxiv. 2023 May 8;2023.05.06.539713. doi: 10.1101/2023.05.06.539713.

In conclusion, L-valine may be a suitable candidate of a biomarker to monitor Alzheimer’s patient health for which a skin patch could be developed.

(3) Alzheimer plaque degradation using protease

Irrespective of the debate about whether protein aggregates are the cause or consequence, ~50% of patients with Alzheimer’s disease (AD) show extracellular aggregates of amyloid-beta peptide (Aβ) that are toxic to cells. Aβ is partially cleaved Aβ precursor protein (APP) and prone to aggregation due to fibrillation6 and misfolding. Usually, researchers implicate secretases in the fragmentation of APP9. However, matrix metalloproteases (MMPs) can also fragment APP and Aβ. As such, MMPs are likely to affect aggregation if they come in contact with Aβ because MMPs are broad-spectrum proteases and have intracellular functions. A mechanistic understanding of interactions between MMPs and Aβ may enable controlling MMP activity on Aβ to prevent fragmentation and aggregation and degrade preexisting aggregates. However, a molecular understanding of MMP-Aβ interactions is lacking, and there are no crystal structures of Aβ-bound MMPs. To this end, identification of interaction poses of MMPs with Aβ monomers and aggregates is a logical first step for targeting MMPs to inhibit Aβ aggregation and degrade aggregates. So far, we focused on MMP1 from the 23-member human MMP family. We performed MD simulations and calculated correlations of fluctuations of the interdomain distance of MMP1 with and without
binding to Aβ. We identified exclusive allosteric residues that are altered in MMP1 only when bound to Aβ.
In conclusion, MMP1 interaction with Aβ may be a new avenue to AD patient treatment.

(4) Training grant in Alzheimer’s disease
The PI has been working with over 50 researchers, clinicians and community representatives to develop a training grant in Alzheimer’s disease. Recognizing the exponentially increasing amount of data in all disciplines involved in AD/ADRD research and the critical and often enabling role Artificial Intelligence (AI) plays in data-intensive research, the proposal employs a data-centric approach in organizing the training program, with AI being a bridge serving to connect all the involved disciplines through its role as a data processing and inference engine. This is conceptually illustrated in the figure to the right. The objective of the training program is then to provide the trainees with solid knowledge and skills in the involved disciplines and their intersection with AI so as to prepare them for conducting cutting-edge research for AD/ADRD. The focus of the training grant is on (1) computational disciplines related to AI, (2) mathematical sciences including statistical analytics and decision making, (3) biomedical engineering including multimodal biosensing, (4) molecular science including multi-omics, structural and systems biology. The proposal will be submitted this coming Fall.
Profiling cellular dust in neurodegenerative disease associated microglia and macrophages. Diego Mastroeni PhD, Tim Karr PhD, Beth Stevens PhD, Nader Morshed PhD, Kendall Jensen PhD. Arizona State University; Harvard University; Translational Genomics Institute; Arizona Alzheimer's Institute.

Background:
Neurodegenerative diseases progress over a long period before they become clinically apparent, and the physiological and molecular events which must ultimately be addressed to cure such diseases likely occur years before clinical diagnosis. There is, for example, considerable evidence implicating the early involvement of neuroinflammation in the etiology of Alzheimer's disease and Parkinson's disease.

To understand neuroinflammation, we first need to understand the cells that modulate this pathway. Microglia, the resident immune cell of the CNS constantly patrol the brain, looking for signs of infection or inflammation caused by a host of immune stimulants. As microglia are activated to clear potential threats to the CNS chemical signatures of their presence are released (cytokines). These cytokines activate neighboring microglia initiating a cascade of events that are believed to drive disease pathogenesis. Although cytokines are generally considered to function as soluble molecules, recent efforts have shown that cytokines are encapsulated in extracellular vesicles (EVs). EVs represent a diverse family of lipidic particles pinched off plasma membranes or released from multivesicular bodies (exosomes). These EVs contain mRNAs, miRNAs, and signaling molecules that reflect the physiological state of the cell. The interesting thing about EVs is they are capable of crossing the blood-brain barrier under inflamed conditions, and upon inflammatory stimuli (e.g. TNF-α), microglial cells respond by releasing EVs which are shed into the bloodstream. Why this is so important is that we can potentially detect the physiological state of CNS microglia by analyzing microglial released exosomes in the peripheral compartments (CSF). Currently, a major obstacle in the field is that there is no way to detect brain inflammation in response to neurodegeneration while still alive. We posit that understanding such events, especially in peripheral compartments, may provide important clues to early disease.

Problem statement: Microglia and monocytes share many overlapping genes and membrane-bound proteins, but we are also aware that they are ontogenetically distinct. Currently, there is no method to clearly distinguish EVs isolated from macrophages from CNS microglia. We recently submitted an R21 to the NIH and the grant was scored favorable, but this was the major point of contention. This data will be foundational for the R21 resubmission.

Hypothesis: Human, disease-associated iPSCs, differentiated into microglia will show unique membrane bound proteins, mRNAs, miRNAs, and signaling molecules encapsulated in EVs compared to Human disease-associated iPSCs differentiated into macrophages. To test our hypothesis, we will capitalize on the strengths of different institutions. Dr. Mastroeni has assembled a team of Co-Is to complement his expertise in neurobiology which include experts in iPSC and glial biology: Dr. Stevens & Dr. Morshed, and a member of the NCATS Extracellular RNA Communication Consortium (ERCC), Dr. Jensen, to fulfill the aims below.

Specific Aim 1: Differentiate and characterize disease-associated human iPSC’s macrophages and microglia.
Specific Aim 2: Isolate and analyze EVs from disease-associated human iPSC’s macrophages and microglia.

Experimental Design and Methods:
Specific Aim 1 Experimental design and Methods: For both microglia and macrophages we will profile 4 males and 4 females, all samples will be processed in triplicate, for a total of 24
samples. Differentiation of hiPSC-microglia is routinely performed in our collaborators laboratory at Harvard and will provide the media from such preparation for EV isolation. Briefly, since microglia share a common progenitor with myeloid cells, we first differentiate iPSCs to hematopoietic progenitor cells under hypoxia conditions for 10-12 days, for macrophage differentiation.

Single-cell hiPSCs are cultured in hypoxia (20% O2, 20% CO2) at 37°C with 50ng/ml FGF2 and 50ng/ml BMP4, 12.5ng/ml Activin A, 2mM LiCl during days 0-2 and 50ng/ml FGF2 and 50ng/ml VEGF for days 2-4 in basal HPC medium (50% IMDM, 50% F12, 0.02 mg/ml insulin, 2% v/v ITSG-X, 64µg/ml ascorbic acid, 400 µM monothioglycerol (MTG), 10 µg/ml PVA, 1x GlutaMax, 1x Chemically-defined lipid concentrate, 1x non-essential amino acids (NEAA), 1% v/v Antibiotic-Antimycotic) to generate EBs. EBs are transferred to normoxia for six days in basal HPC media supplemented with 50ng/ml each of FGF2, VEGF, TPO, and IL6, and 10ng/ml of each of SCF and IL3. On days 10-12, HPCs are collected in the absence of FACS, filtered through a 45µm cell strainer, and plated onto Matrigel-coated 6-well plates as described (TCW et al. bioRxiv, 2019). HPCs are further differentiated to microglia by culturing with microglia basal medium (DMEM/F12, 1x Glutamax, 1x NEAA, 2% v/v ITS-G, 2% v/v B27, 0.5% v/v N2, 200uM MTG, 5ug/ml Insulin) with 50 ng/mL TGFβ, 100 ng/mL IL-34 and 25 ng/mL M-CSF for 25 days, and then culturing in microglia basal medium supplemented with 100 ng/mL CX3CL1 and 100 ng/mL CD200 for an additional three days. All fully differentiated cells will be harvested on day 28 for assays.

Because of the cost and time allotted, we plan to purchase fully differentiated macrophages from Axol bio. hiPSC-derived macrophages are derived from iPSCs that have undergone an intermediate differentiation to monocytes prior to directed terminal differentiation to macrophages. This provides a highly pure and consistently reproducible population of macrophages.

**Specific Aim 2 Experimental design and Methods:** Isolation and verification of exosomes: We will enrich for EVs from differentiated microglial and monocytes using the exoEasy kit as previously described. The exoEasy kit was recently found by the ERCC to provide consistent results in replicates and across sites. Briefly, magnetic beads coated with CD63 (binds all EVs) antibody are prepared following manufacturer’s instruction.
20μL of magnetic beads (RNA sequencing: 1 x 106 beads/ mL) are washed in 200μL PBS (0.1% BSA, 0.2 μm filtered). 100μL cell solution containing exosomes are added to the magnetic beads and incubated for 16–20hr at 4°C. The magnet is then applied, and exosome-coated beads are washed in 0.3 mL of PBS (0.1% BSA) and prepared for downstream application, as previously described. Half of the isolated EVs will be sent to our (ASU) Mass Spec core under the guidance of Dr. Karr. Samples will be prepped by the core and a list of differentially expressed and overlapping proteins will be sent to Dr. Mastroeni. The other half of the exosomes will be processed in house by Dr. Mastroeni and Dr. Jensen for RNA sequencing studies, see below.

**Preparation of mRNA from EVs:** Total RNA will be extracted from the exosomes using the Qiagen RNAeasy micro kit. The quality and quantity of total RNA will be assessed on the Agilent bioanalyzer and samples with RIN >8.5 prioritized for analyses. mRNA expression will be quantified using sequencing methods previously described. While most biofluid analysis has focused on small RNAs, we can detect long RNAs and long RNA fragments in EVs. We have a publication drafted, in collaboration with Saumya Das at MGH, comparing long RNA library preparation methods for biofluids. Based on the results of those studies, the Clontech SMARTer pico V2 kit demonstrated a reduced PCR duplicate rate, better rRNA depletion, strandedness, and greater detection of protein coding and non-coding IncRNAs in EVs isolated from biofluids, which will be easier and cleaner in culture.

**Transcriptomic and Biological Pathway Analyses:** Multiomic data generated from both macrophages and microglia will be integrated with the purpose of identifying individual molecular signatures. We will use well-established unsupervised algorithms designed for handing these high-dimensional datasets, such as similarity network fusion (SNF), multiple factor analysis (MFA) or multiple canonical correlation analysis (MCCA). Up-to-date pathway annotations from public databases and curated molecular maps will also be used to facilitate the identification of relevant molecular signatures. We will apply algorithm-based pathway analysis using graph-based statistic network analysis and classical machine learning techniques (e.g., feature selection and sample clustering) to identify discriminative pathway signatures for sample classification. We will address two important issues, 1) selection of features (exRNAs) and 2) design performance evaluation and validation of the classifier. In both issues, the accurate evaluation of classification performance is critical. RNaseq data contains tens of thousands of features or genes, while the sample size is small. The classifier design hence falls into the common high-dimension small sample size category. Design a predictor that has close to optimal performance on independent data, and interpretable components, one must apply feature-selection procedures to greatly reduce the number of features used for prediction. The small feature sizes in the predictor can also help reveal the relationship between the selected features, hence, underlying mechanism that determines the outcome. The constructed predictor will also be close to optimal. Although the optimal predictor might need more features, it has been shown that the classification performance usually becomes stabilized with a small number of features, and will only improve slightly, if at all, with more features. Many studies have exploited the statistical advantage of using multiple markers of disease and have thereby assessed the efficacy of panels of markers using classifier models. Several mathematical models can be applied to evaluate combinations of genes. These include threshold-based methods, decision trees, logistic regression, support vector machine (SVM), LASSO, and Random Forest (RF).

**Future Goals:** The proposed studies will establish the utility of peripheral EVs in predicting CNS microglial activation state which will provide greater insight into one of the earliest phases of neurodegeneration, including methods that are currently lacking and that promise to yield novel insights into CNS inflammation in the living. This new approach will provide a valuable resource for the wider scientific community to pursue a multitude of studies that have not previously been possible due to limitations in understanding the microglial activation state during disease progression.
Year End Progress
Summary:
We are delighted and humbled by the generous support extended to our project by the Arizona Alzheimer's Consortium. Their belief in the potential impact of our research has been instrumental in driving our work forward, and we cannot thank them enough for their crucial contribution.

The backing we received from the consortium has been a game-changer for our research. The preliminary data generated from this support, as presented in Figure 2, has proven to be immensely valuable. Not only has it helped us to lay a strong foundation for our investigations, but it has also granted us a significant competitive advantage within the field.

In light of these advancements, we are thrilled to announce that our recently submitted R21 application has received a favorable score. This achievement would not have been possible without the support and resources made available to us by the Arizona Alzheimer's Consortium. We recognize the responsibility that comes with this opportunity, and we are committed to utilizing the granted funding to its fullest potential. Our dedication to conducting rigorous and impactful research remains unwavering, and we are eager to take the next steps in our project with the utmost enthusiasm.

Once again, we express our deepest gratitude to the Arizona Alzheimer's Consortium for their unwavering support, which has been instrumental in propelling our research to new heights. We are excited about the journey ahead and look forward to sharing our progress and discoveries with the consortium and the wider scientific community.

Previously funded AAC grant:
2014-2015: Project Title: Are Microglia the Same in Different Brain Regions or Poles Apart?
Grants because of the seed money:
2018-2023: Alzheimer's Association: Gender Effects on identified cell population in Alzheimer's Disease

References:
Advanced metabolic and diffusion neuroimaging in apoE4 carriers. Edward Ofori, PhD, Benjamin Bartelle, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:
1) To examine the effects of apoE4 dose on advanced DTI measures from corticostriatal networks and identify aDTI correlates with cognition
1) To discover advanced metabolic neuroimaging measures and metabolic maps that mediate the relation between apoE4 dose and altered aDTI in the corticostriatal networks.

Background and Significance:
The apoE4 allele is the strongest genetic risk factor for late-onset Alzheimer's compared to apoE3, potentially by differentially interacting with amyloid-beta and affecting its metabolism. ApoE4 genotype impacts cognitive and pathological trajectories across the Alzheimer's continuum. This project will leverage advanced DTI metrics, which can assess brain fluid and provide information on microstructural processes like neuroinflammation, along with apoE status to identify corticostriatal tract integrity differences and inform the amyloid cascade hypothesis. The group has shown aDTI measures are more sensitive for detecting neurodegeneration and neuroinflammation than conventional methods. Though studies indicate apoE4 carriers have subcortical changes in caudate, thalamus and medial temporal regions, little is known about aDTI in corticostriatal networks, which may be important in Alzheimer's progression. Metabolic neuroimaging could also provide insight into neurodegeneration timing.

Preliminary Data, Experimental Design and Methods:
Preliminary data shows increased diffusivity in the caudate of apoE4 carriers, suggesting neuroinflammation and associating with cognitive scores. Preliminary metabolic data also shows reduced NAA and choline in apoE4 carriers' striatal regions.

Proposed One-Year and Long-Term Outcomes:
Specific Aim 1 will provide aDTI patterns in apoE4 carriers in corticostriatal and other brain regions where aDTI are elevated in comparison with apoE2 and apoE3 carriers. We will also examine identify where apoE2 have lower aDTI metrics in comparison to apoE2 and apoE4. We will use aDTI signatures of APOE4 carriers to correlate with cognitive scores.

Specific Aim 2 will provide metabolic profiles and maps for apoE4 in older adults, including unique spatial characterization among areas sensitive to altered aDTI metrics and individual metabolite patterns across apoE status. This unique outcome will provide the whole-brain patterns of metabolic alterations with the extended metabolite profile, beyond typically reported metabolite such as NAA, creatine, and choline, e.g., glutamate, glutamine, and gaba-aminobutyric acid. The increased aDTI and decreased ml/Cr profiles for apoE4 carriers in older adults, will lead to further development of biomarkers for early detection of AD pathogenesis, disease status, and for monitoring disease progression and treatment efficacy.

Long-term outcomes will be to leverage these data to submit for a R01 that looks at a large scale these techniques in apoE4 carriers, generate a line of independence and establish these techniques in the understanding of brain health and metabolism.

Year End Progress Summary:
We have drafted a manuscript in regards to Aim 1 leveraging our preliminary data: Here is the abstract:
The ε4 allele of apolipoprotein E (APOE) is a major genetic risk factor for Alzheimer’s disease (AD) compared to the ε3 allele. To examine the effects of APOE genotype on corticostriatal integrity, we performed advanced diffusion tensor imaging (aDTI) in 33 APOE ε4 homozygotes and 64 APOE ε3 homozygotes (mean age 64±8.2 years, 80% female). APOE4 carriers demonstrated significantly increased aDTI diffusivity in the caudate (p<0.01), suggesting greater neuroinflammation. Caudate diffusivity also associated with cognitive scores on verbal comprehension and block design tests (r=0.43, p<0.05). Preliminary metabolic neuroimaging of one APOE4 and one APOE3 carrier found reduced N-acetylaspartate and choline in the APOE4 carrier’s striatum. Together, these aDTI and metabolic differences demonstrate corticostriatal vulnerabilities that may underlie AD risk in APOE4 carriers. Further research into the interactions between APOE genotype, subcortical integrity, and metabolism may elucidate pathways for targeted therapeutic interventions.

Other significant advancements have been made over the past year in our examination of advanced diffusion tensor and metabolic neuroimaging measures in APOE4 carriers. On the diffusion tensor imaging side, we have implemented cutting-edge approaches to improve sensitivity in detecting microstructural alterations associated with APOE4 dose effects. This includes having investigators individually draw precise regions of interest on the substantia nigra to capture subtle diffusivity changes that may be missed with standardized atlases. We have also incorporated advanced fixel-based analysis methods for diffusion tensor imaging, which provides enhanced specificity in identifying white matter tract abnormalities compared to conventional voxel-based approaches.

Through these optimized DTI protocols, we have made progress in elucidating the effects of APOE4 on corticostriatal network integrity. Our preliminary findings of increased caudate diffusivity and associations with cognitive performance suggest APOE4-related vulnerabilities in this subcortical region.

To clarify the mechanisms underlying the DTI-detected microstructural alterations, we have also expanded into metabolic neuroimaging techniques. Thus far, we have successfully collected 3D magnetic resonance spectroscopic imaging data from 20 subjects and are in the process of analyzing their APOE genotype. By integrating information on genotype-specific metabolite profiles with the DTI measures, we aim to gain crucial insights into the interplay between APOE variants, neurodegeneration, and brain metabolism.

Specific Aims:
Aim 1: Directly characterize the spatial, cell-type and neuropathological context of viral transcripts in post-mortem brain tissue samples from subjects with AD who are also infected with an AD-associated virus using an innovative multiplexed in situ RNA profiling approach.

Background and Significance:
The potential influence of pathogenic microbes on the risk of developing, or accelerating the progress of Alzheimer’s disease (AD) was first proposed by Alois Alzheimer1 and Oskar Fischer2 well over a century ago. Since this time, and particularly over the past four decades, hundreds of scientific papers have emerged linking the activity of diverse microbial species with different facets of AD pathophysiology. These reports have accelerated further recently, including reports of Herpesviridae (HHV) induced seeding of amyloid beta (Aβ) fibrillation in transgenic AD mouse and 3D organoid model systems, with increased Aβ42 production also associated with improved survival in a murine viral encephalitis paradigm3. Tzeng et al4 reported an increased dementia risk following severe HSV-1 infection, which is almost completely mitigated by antiviral use. Lövheim et al5 reported an association between HSV-1 carriage and episodic memory decline, particularly within APOE-Ε4 carriers. Our own study in this area described an increased abundance of HSV-1, HHV-6A, and HHV-7 in the brains of subjects with AD, an observation that persisted in two out of three additional patient cohorts surveyed, and which was strengthened during a meta-analysis across available samples6, although alternative quantification approaches did not confirm this same finding7. More recently, an epidemiological study of 265,000 subjects reported an increased hazard ratio (HR) of dementia among subjects with a history of HSV-1 or varicella-zoster virus infection, and a reduced HR for those that received antiviral therapies8. Despite the complex, and at times discordant findings, a wealth of scientific research supports the role of complex interactions between multiple tissue systems and microbes in the context of AD etiopathology.

Preliminary Data:
We will utilize AMAb profiles to identify human Herpesvirus proteins that are enriched among AD cases (HHV-6A, HSV-1, HSV-2, HCMV, see Figure 1) and use these to identify specific subjects with detectable viral nucleic acids upon brain metagenomic profiling. Brain metagenomics that will
be used to finalize this selection is still ongoing and expected to finalize by Q2 2022. Partial results are shown in Figure 2 which summarizes viral transcript abundances for HHV-6, which is observed in approximately ~25% of samples and supports the plausibility of using metagenomic data to efficiently select specific samples for multiplexed in situ profiling.

**Experimental Designs and Methods:**
We propose an RNAscope analysis (RNAscope Multiplex Fluorescent Assay kit, Advanced Cell Diagnostics, Inc.) of FFPE brain tissue samples requested from BSHRI for 12 subjects, each with reference to a specific virus and prioritized viral transcripts. Brain regions of interest will be guided by the regions represented in the informative metagenomics data (and may include superior temporal gyrus, dorsolateral prefrontal cortex, hippocampus, or olfactory bulb). Viral probes for analysis will be selected from available probe-sets distributed by Advanced Cell Diagnostics for use with the RNAscope platform, which currently includes 152 human Herpesvirus probes. We will focus on the detection of viral transcripts that are implicated by the AMAb profiling and/or metagenomics. This work will be lead by Dr. Diego Mastroeni (ASU-Banner NDRC), and will involve the design, development and utilization of approximately five novel herpesvirus probes for which no commercial options exist. Our motivation for this is driven by our preliminary analyses of AMAb data which has implicated specific viral proteins that have not been closely studied, but which offer the possibility of substantially enriching our understanding of the biological context of virus-host interactions in AD. For example, we identified a significant enrichment for antibody titres against the HSV-1 UL4 protein (Figure 1C) within AD cases, and this signal can be observed to be localized to the final 20 amino acids of the protein.

**Proposed One-Year and Long-Term Outcomes:**
Deliverables:
1. Summarized RNA scope results from 12 confirmed virus-positive AD subjects including:
   a. Virus abundance
   b. Cell-type localization
   c. Subcellular localization
   d. Proximity to neuritic plaques and neurofibrillary tangles
2. Novel probes designed for any viral transcripts for which no commercial probes exist

**Year End Progress Summary:**
Successful award of spatial transcriptomic data generation grant We were grateful to be awarded a data generation grant by STOmics, which provides funds for the generation of in situ, spatial transcriptomics for 12 brain tissue samples using their proprietary SpaTial Enhanced RESolution Omics-Sequencing (Stereo-seq) technology. This approach offers unprecedented field-of-view and resolution of tissue transcriptomics, and which promises to leapfrog the planned experimental approach we outlined in our proposal, through the assaying of the entire host cell transcriptome as well as viral sequences that may be present in the samples. We have thus opted to use this opportunity to profile the superior frontal gyrus cortical samples we had planned to evaluate during this project. Tissue has been provided to STOmics and data generation is expected to proceed shortly. Given that our STOmics award is due to generate a superior version of data that we had originally planned to generate, we thus used our allocated AAC funds to advance valuable complementary data generation efforts.

**Increased IgG4 antibody production in the gut of AD subjects with unique microglial subpopulations.** This prioritization leverages findings from single nucleus RNAseq (snRNAseq) data generated at ASU-Banner Neurodegenerative Disease Research Center, which has identified a novel AD- associated microglial subpopulation. Briefly, we performed Chromium 10x snRNAseq on postmortem, superior frontal gyrus (SFG) brain tissue samples from 101 well characterized
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We observed a novel AD-associated microglial subpopulation (MG-1) in 47% of AD subjects (n=31 / 66 AD) profiled within our study. We determined that there is no significant difference in age of death, sex, ethnicity, post-mortem interval (PMI), Abeta plaque density, neurofibrillary tangle burden, clinical dementia rating or ApoE4 carriage rates between AD subjects with and without MG-1 microglia. We also had whole body autopsy results available on 68 (AD n=48, Aged Control n=23) of the 101 subjects, which allowed us to examine potential association with diverse disease comorbidities. We did not identify any difference in rates of Type 2 diabetes mellitus, hypertension, obesity, atrial fibrillation, coronary stenosis, cardiomegaly, atherosclerosis, smoking, or chronic obstructive pulmonary disease as evaluated at the time of autopsy.

We hypothesized that MG-1+ AD subjects may differ from MG-1- AD subjects on the basis of a microbial or immunological perturbation which could be occurring peripherally. We reasoned that such a microbial perturbation may be reflected in the proteome of the transverse colon (TC), which reflects the anatomical site with the highest microbial diversity. We generated mass spectrometry proteomics data from frozen TC samples from a subset of 26 subjects with brain snRNAseq. We then examined whether any proteins are differentially abundant as a function of the presence of MG-1 microglia within the SFG, while adjusting for AD status, age of death, sex and PMI. The most differentially abundant protein in the TC of subjects with MG-1 microglia was IGHG4 (Immunoglobulin Heavy Constant Gamma 4, Figure 2, T-statistic:4.5 P-value: 2.1e-4, Figure 5) which forms the constant region of the IgG4 antibody heavy chain. This observation was suggestive with an increased IgG4 tissue response in the TC wall of subjects with MG-1 microglia, and more broadly, consistent with a potential microbial interaction (whether direct or indirect) between components of the gut microbiome and the presence of MG-1 microglia. To further validate this observation, we performed immunohistochemistry on TC sections from 25 subjects and observed a statistically significant enrichment between MG-1 microglia in the SFG and IgG4 immunoreactivity in the TC (Pvalue: 2.8e-3, Odds Ratio: 24.5, Fisher's Exact Test). Remarkably, IgG4 immunoreactivity in the TC was also frequently associated with IgG4 immunoreactivity in SFG cortical and hippocampal samples, indicating a multisystem presence of IgG4 in subjects with MG-1 microglia.

**MG-1 microglia are associated with increased cerebrospinal fluid IgG4 against Human Cytomegalovirus.** An increased abundance of IgG4 in the TC and brain could reflect a nonspecific increase in general IgG4 antibody production, or alternatively, might reflect antibodies generated against specific antigens. Reprocessing of TC proteomics revealed trace amounts of peptides mapping to several common human Herpesviridae, including HHV-6 and Human Cytomegalovirus (HCMV), but quantities were too low in abundance to be definitive. We thus utilized unused funds from this project to generate IgG4 specific antimicrobial antibody profiles from 96 cerebrospinal Fluid (CSF) samples (MG-1+ microglia AD n=27 and MG-1- microglia AD n=30) using an epitope repertoire analysis approach. These data then allow the detection of specific antigens that the increased IgG4 may be selected for. Using an outlier sum statistical approach, we observed a significantly increased abundance of IgG4 against several HCMV antigens (Figure 3), in particular the Cytoplasmic envelopment protein 3 (CEP3) which is encoded by viral gene UL99 and critical for the envelopment of HCMV virions within the cytoplasm of infected cells9 and thus essential for viral replication. In addition we saw an enrichment for IgG4 antibodies against protein UL13, recently reported as sufficient to directly increase cellular
respiration during infection through targeting of mitochondrial cristae architecture. Remarkably, HCMV is also frequently detectable within the SFG and vagus nerve of these same subjects using an immunohistochemistry approach. These findings and associated data will be summarized in upcoming manuscripts entitled “A public resource of single cell transcriptomes and multiscale networks from the Alzheimer’s disease and aging affected brain” and “Alzheimer’s disease-associated CD83(+) microglia are linked with increased Immunoglobulin G4 and Human Cytomegalovirus in the gut, vagal nerve, and brain” due to be submitted in August 2023.

These findings have been used to inform the selection of 12 superior frontal gyrus cortical tissue samples from AD subjects, with and without the presence of MG-1 microglia, HCMV and IgG4, which are currently undergoing Stereo-seq spatial transcriptomic profiling. It is expected that this data will enable the interrogation of spatial relationships between HCMV, MG-1 microglia, IgG4 deposition and neuropathological markers. Completion of these data generation efforts and subsequent analysis will allow the completion of our project one-year outcomes in the next three months. We also expect that these findings will be used to support several grant applications to further these investigations.

**Figure 3:** Increased abundance of IgG4 antibodies against Human Cytomegalovirus (HCMV) antigens in CSF of MG1+ AD subjects compared with MG1- AD subjects, using an outlier sum based approach.
Establishing feasibility and dose-response of an online visuospatial training program for older adults. Sydney Schaefer, PhD, Michael Malek-Ahmadi, PhD, GStat. Arizona State University; Banner Alzheimer’s Institute; Arizona Alzheimer’s Consortium.

Specific Aims:
The specific aim of this project is to develop an online visuospatial training game for older adults and test its feasibility and dose-response.

Background and Significance:
Visuospatial declines occur even earlier than memory declines in the progression of Alzheimer’s disease, with evidence of up to 20 years prior to the onset of Mild Cognitive Impairment. Although these deficits initially are subtle, they have been shown to significantly affect daily life. Numerous internet-based cognitive training programs have been marketed to older adults, such as Lumosity, CogFit, and NeuroGrow, but none aim to remediate visuospatial deficits or focus on visuospatial rehabilitation specifically. Thus, currently, there are few clinical options for minimizing the functional impacts of visuospatial deficits early in AD progression. The objective of this AAC proposal is to prototype the design of a visuospatial training game that can be done at home on the internet. The cognitive training and assessment market is projected to be valued at $11.4 billion by 2025, with primary growth opportunities in gamification and at home use, but it does not have a clear solution to offer for visuospatial rehabilitation yet. Our preliminary data provide initial evidence of the efficacy of visuospatial training, with improvements in visuospatial working memory and mental rotation after a single session of training. We have not tested yet how persistent these benefits are, and what the ideal dose of training may be for a given training program among older adults. This project therefore aims to 1) design and prototype an internet-based game that targets various aspects of visuospatial function; and 2) test its feasibility among older adults. This proposal will also provide critical pilot data for a larger efficacy trial in the future.

Preliminary Data, Experimental Design and Methods:
For this proposal, we provide two key sets of preliminary data. First, we have shown proof-of-concept that even a single session of visuospatial working memory training can improve visuospatial working memory and mental rotation, compared to an active control group. Specifically, reaction time on the mental rotation task (similar to the Shepard-Metzler task) improved from pre- to post-training by 124 milliseconds (~8% improvement in performance). We tested mental rotation before and after training because this aspect of visuospatial function has been shown previously to be sensitive to AD7 and is malleable with training even in patients with Mild Cognitive Impairment8. Mental rotation is also distinct from visuospatial working memory, allowing us to test the generalizability of this training, in line with recommendations for developing cognitive training tools9. These preliminary data were collected in younger adults with no known visuospatial deficits, demonstrating the possibility for improvement even in an unimpaired sample. Furthermore, these data highlight the clinical potential of visuospatial training in older adults who may be progressing towards AD. The second set of preliminary data shows the feasibility of our research team to create and deploy online training games for older adults. In our previous AAC grants, we developed an internet-based game (called SuperG) that could be played on either a computer or mobile device. In SuperG, participants must implicitly learn a set of physics-based rules that govern the movement of an astronaut on the screen as the participants control how the astronaut travels from planet to planet. As participants learn the rules, they become more accurate, and their response times get faster. We have tested this game in several online cohorts who played remotely and unsupervised, and we have validated the online data against data that
were collected in-lab and supervised. These results are currently under review and have led to a funded NIH award (F32AG071110). These preliminary data also show that as older adults practiced SuperG, the amount they improved on the game was related to APOE ε4 carrier status, such that carriers had faster response times than non-carriers. (These data were recently presented at the American Society of Neurorehabilitation Annual Meeting, and are in preparation as a manuscript.) These data not only show that creating and deploying an online game is feasible, but also that online games can be relevant to AD.

**Proposed One-Year and Long-Term Outcomes:**
Based on our track record, we plan to submit two manuscripts and present one conference abstract at the American Society of Neurorehabilitation during the one-year award period. We will also submit an R03 to NIA to help gather preliminary data on the optimal dose of visuospatial training once the training program is developed through this AAC grant. We are also intentionally developing a visuospatial training program that can be delivered online, as we plan to submit a randomized controlled trial in the future as an R01 to NIA in response to NOT-AG-21-048, a Notice of Special Interest focused on Digital Technology for Early Detection and Monitoring of Alzheimer’s Disease. Specifically, training that is available online and that can be done at any time improves accessibility of digital technology for individuals from diverse socioeconomic and geographical backgrounds, which is one of the goals of this Notice of Special Interest.

**Year End Progress Summary:**
Our prior AAC grant developed and prototyped a visuospatial training game, with a longer-term goal to minimize the functional impacts of visuospatial deficits early in AD progression. Over the last year, we developed and tested a single session of visuospatial working memory using a computerized Corsi Block Tapping Test, which we showed to be efficacious in improving visuospatial abilities (including mental rotation). However, our biggest challenge was that we found that cognitive testing (including visuospatial testing) was stressful, particularly for older adults. While this was anecdotal, based on participant feedback and conversation, this is highly consistent with prior literature. Specifically, older adults have been shown to experience stress and anxiety in response to cognitive testing, particularly in those who are already experiencing cognitive decline. This is also consistent with our high rate of interested participants who did not meet our inclusion criteria of being in the bottom 50th percentile of visuospatial ability, as measured by the Wechsler Adult Intelligence Scale – IV Perceptual Reasoning Index (PRI). This meant participants who had no visuospatial deficits were more likely to volunteer for our study. We have addressed this challenge in four ways: 1) We have expanded our inclusion criteria to include all levels of visuospatial ability (so as not to exclude participants on the basis of PRI scores) to help us further pilot test our visuospatial training protocol; 2) We have begun collaborating with colleagues at the University of Southern California to increase our sample size and study catchment; 3) We have altered our proof-of-principle study design to randomize the number of training sessions across participants, allowing us to better identify an optimal dose of training across a continuum (where we will use a sigmoidal dose-response curve); and 4) We are now quantifying the extent of test-related stress associated with cognitive testing in our next round of AAC funding for AY24, using methods that we have previously tested in young adults. These protocol and design changes in response to our challenges maintain our progress towards our long-term outcomes. In AY23, we met our target of submitting an R03 to NIA (R03AG081743-01; impact score: 50). The major critique from the reviewers was that instead of a proof-of-concept for identifying the optimal dose, this should be identified already, and that the proposal should be a randomized clinical trial involving groups of participants who do and do not receive the visuospatial training. In speaking with my NIA PO, they recommended that this be submitted as an R01 with more preliminary data on the visuospatial intervention itself. Thus, I and my new collaborator (K. Leech, University of Southern California) are in the process of designing this multisite RCT for this new R01 submission for AY24, and collecting the critical pilot data for this (see
Challenge response #2). We also met our goal of submitting two manuscripts as well, both of which are now published. In the first one (published in Experimental Brain Research), we developed and tested a single session of visuospatial working memory training using a computerized Corsi Block Tapping Test. This publication showed that even a single session of visuospatial training was efficacious in improving visuospatial abilities. In the second one (published in Games for Health), we demonstrated that online visuomotor training (in this case, through SuperG) is reliable compared to an in-lab sample. We also presented SuperG at the American Society of Neurorehabilitation (ASNR) Annual Meeting in Charleston, SC in March 2023, as planned.

Project Description:
Our hypothesis is that cellular stress and the resulting disruption in cell proteostasis is a fundamental process underlying neuronal degeneration and a key early feature of AD. Our objective is to identify specific toxic variants of key neuronal proteins that contribute to the disruption of neuronal proteostasis in early stages of AD. A better understanding of the fundamental underlying factors that contribute to disruption of neuronal proteostasis will lead to new and better therapeutic targets that can restore neuronal health and stop progression of ADRDs, especially during early disease stages before significant neurodegeneration has taken place.

Specific Aim: Utilize a panel of over ten novel antibodies developed in our lab that selectively bind AD related protein variants of key neuronal proteins including amyloid beta, tau and TDP-43 to probe post-mortem pathologically validated human AD brain tissue to identify key toxic protein variants that selectively disrupt the ubiquitin proteasome system in early stages of AD.

Background and Significance:
1A) Molecular Mechanisms of Alzheimer’s Disease. Pathologically, AD is characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain. The principle component of the extracellular plaques is the β-amyloid protein (Aβ), while the neurofibrillary tangles are primarily composed of tau, a phosphorylated microtubule-associated protein (1, 2). A vast amount of literature has led to formation of the “Aβ hypothesis” which postulates a central role for Aβ in AD (3, 4); however major weaknesses of the Aβ hypothesis include lack of a good correlation of the presence of amyloid plaques with the progression of AD (5, 6) and clinical therapeutic trials targeting Aβ have had consistently disappointing results. One notable exception is the very recent FDA accelerated approval of Aducanumab for treating AD, although the approval has been very controversial as many consider that the high cost and potential serious side effects of the drug, such as cerebral hemorrhaging (7), offset the limited potential benefits. Many studies now indicate that soluble oligomeric forms of Aβ are the relevant toxic species involved in disease onset and spread (8-10), drugs targeting small oligomeric Aβ in human trials show greater therapeutic benefit than drugs targeting monomeric and larger Aβ aggregates (7, 11), and studies in animal models indicate that even the specific oligomeric Aβ species targeted can have a profound impact on the therapeutic outcome (12). Similar to Aβ, tau also exists in a variety of different forms and aggregate morphologies, soluble oligomeric tau variants are also considered the relevant toxic species involved in toxicity and spread of disease (13-22), and therapeutics targeting tau have also had very disappointing results in clinical trials (23).

1B) Role of cellular stress and cell proteostasis in AD. Even though therapeutics targeting Aβ and tau have largely failed to show clinical benefit, both Aβ and tau clearly play important roles in AD, where oligomeric variants of both proteins can be toxic to neurons and generate an inflammatory response (24-27). Cellular stress in the brain can be induced by a variety of different factors including oxidative stress, lifestyle, environmental toxins, injury, decreased circulation and aging. Cellular stress can disrupt cell proteostasis leading to an increased production and decreased clearance of misfolded and aggregated proteins including Aβ, tau and the stress response protein Tar DNA binding protein (TDP-43) which has also been implicated in neurodegenerative diseases including AD (28-30). The increase in misfolded proteins, some of which are toxic, can overwhelm the ubiquitin proteasome system (UPS), resulting in further generation of toxic protein variants and neuronal degeneration (31-40). Cellular stress induced by misfolding and aggregation of one protein can promote misfolding and aggregation of other proteins in a feed forward cycle, so the
presence of one toxic protein variant such as Aβ, can lead to generation of additional toxic protein variants including tau, TDP-43, and alpha-synuclein (α-syn) resulting in a spectrum of neurodegenerative diseases including AD, Parkinson’s disease (PD), Frontotemporal dementia (FTD), Lewy body dementia (LBD), and amyotrophic lateral sclerosis (ALS) among others. The presence of co-morbidities is therefore an expected feature of neurodegenerative diseases and post-mortem analysis of brain tissue confirms that many neurodegenerative disease cases including AD, PD and FTD share overlapping pathologies (41-43). Therefore, disruption of cell proteostasis and the subsequent generation of toxic misprocessed, misfolded or aggregated protein variants is likely a critical feature involved in early stages of AD and related dementias (ADRDs).

Preliminary Data:
We demonstrated the therapeutic value of targeting intracellularly generated toxic oligomeric Aβ variants to restore neuronal health in an AD mouse model (12). Targeting intracellular oligomeric Aβ restored a WT neuronal phenotype, enhanced neurogenesis and dramatically improved survival to WT levels (12). In contrast targeting extracellular oligomeric Aβ reduced plaques and inflammation, but did not improve neuronal health or survival (12). Immunohistochemical (IHC) analysis indicated that mice treated with the antibody targeting intracellularly generated oligomeric Aβ had a functional ubiquitin proteosome system (UPS) similar to that in WT mice, while extracellular Aβ targeted mice showed a dysfunctional neuronal UPS, similar to the transgenic sham treated mice. Therefore targeting and clearing a toxic intracellularly generated Aβ variant essentially restores neuronal health (12) and a functional UPS pathway, while targeting extracellular oligomeric Aβ decreased plaque loads (12), but did not restore the UPS pathway or improve neuronal health.

We also showed that intracellularly generated oligomeric Aβ disrupts the UPS in human AD brain similarly to what we observed in the AD mouse model. We co-stained brain tissue from a post-mortem human AD case (88 yrs), an age-matched cognitively normal control case (ND, 79 yrs), and a young ND case (38 yrs) with ubiquitin and the C6T antibody generated in our lab that selectively binds the intracellularly generated oligomeric Aβ variant. The ND case had only very limited cytoplasmic C6T staining which always colocalized with robust ubiquitin staining indicating healthy neurons with a functional UPS pathway. In the age matched ND case, there was an essentially similar pattern to that observed in the APP/PS1 mouse brain, the presence of both healthy neurons with a functional UPS and neurons with cytoplasmic C6T and a disrupted UPS. The age-matched ND case reflects the presence of both healthy neurons and stressed neurons, indicating a functional though not optimal UPS system, typical of what should be expected in most elderly brains. The late stage AD case contains primarily extracellular non-ubiquitinated C6T in diffuse plaque like structures with limited cytoplasmic but more axonal ubiquitin staining corresponding to misprocessed tau. The late stage AD case reflects brain tissue with a severely dysfunctional UPS, resulting in accumulation of extracellular non-ubiquitinated Aβ aggregates. This data supports our hypothesis that a functional UPS effectively tags and clears intracellularly generated misprocessed protein variants in healthy neurons, but a disrupted UPS results in cytoplasmic accumulation of toxic variants such as the intracellular oligomeric Aβ variant and subsequent neuronal degeneration.

Experimental Designs and Methods:
A) Methods. Brain tissue samples from the middle temporal gyrus of pathologically confirmed AD and cognitively normal age-matched controls will be obtained from the Banner/Sun Health Brain Bank (BSHBB). Early stage AD cases based on mini-mental state exam (MMSE) scores and Braak staging will be selected in consultation with Dr. Tom Beach, director of the BSHBB. Immunohistochemistry (IHC): Brain tissue samples will be analyzed by IHC as described previously (44-47). We will stain for a panel of ten different ADRD related variants of Aβ, tau, TDP-43 and α-syn using antibodies generated in our lab (48-57). In addition, we will co-stain with
antibodies against ubiquitin, total Aβ, total tau, and MAP2, as described previously (28, 45-47, 50-52, 58-62). Secondary antibodies depend on source of the primary antibodies.

Expected results: We expect to identify protein variants that are associated with neuronal proteostasis dysfunction in early stages of AD. These protein variants represent promising new therapeutic targets for both diagnosing and treating ADRDs. We have utilized our reagents extensively in IHC studies to characterize human ADRD cases and mouse brain tissue samples and do not expect to encounter issues that we cannot address. One limitation is that we can only visualize one scFv on each tissue sample at a time, which can make it difficult to co-localize different protein variant targets. We can overcome this limitation by preincubating different phage particles with different fluorescent tags so we could simultaneously image three or four different phage particles each displaying a different scFv.

**Proposed One-Year and Long-Term Outcomes:**
We expect that seed funding for this project will generate compelling preliminary data to support new grant applications to NIH, DOD and other agencies in at least three different areas. The first area is to utilize the scFvs as powerful tools to selectively label and collect individual cells from human AD brain tissue that have disrupted UPS pathways. Single cell analyses of these labeled cells can provide information on cell mechanisms contributing to neuronal stress and neurodegeneration during early stages of AD and identify novel therapeutic targets. The second area is to determine whether protein variants that disrupt the UPS pathway during early stages of AD are promising new therapeutic targets. The same antibodies that we used to stain brain tissue to identify the protein variants can be used as therapeutics to intracellularly bind and clear the toxic protein variant target from neurons as previously demonstrated. The third area for further funding is to develop mammalian cell models that replicate the key features of UPS dysfunction in early stage AD brain tissue. The cell models can be subsequently used as effective high throughput screening assays for novel therapeutics for treating early stage AD.

**Year End Progress Summary:**
1. We obtained slices of post-mortem human AD brain tissue with different Braak stages (I, II, III, IV, V and VI) from the Brain Bank at Banner Sun Health. Samples contained both male and female AD cases.
2. We stained the human brain tissue samples with (Braak stage I through VI) with a panel of reagents we developed that selectively bind AD related variants of Aβ, tau and TDP-43, three neuronal proteins implicated in the progression of AD. We also stained brain tissue with commercially available antibodies against these same protein variants. We identified several reagents that bind intracellularly generated Aβ, tau or TDP variants during early AD stages. Notably, none of the commercial antibodies show significant staining of neurons in early Braak stage human brain tissue.
3. The panel of reagents we generated showed exquisite sensitivity for early stage AD brain tissue. As an example, a commercial antibody against TDP-43 showed extensive nuclear staining of TDP-43 in early stage AD cases as expected. TDP-43 in healthy neurons is diffusely located in the nucleus, however in stressed neurons such as those in AD brain tissue, TDP-43 begins to accumulate and aggregate in neuronal cytoplasm. Therefore the commercial antibody showed a staining pattern consistent with healthy neurons. However when staining the same tissue with one of our disease specific TPD-43 reagents, we exclusively stain cytoplasmic TDP-43 variants indicative of diseased neurons. Therefore our panel of reagents are very powerful tools to identify protein variants implicated in early stages of AD progression.
4. We identified a panel of nine different AD specific reagents that all selectively stained neurons in early stage AD brain tissue (3 against different Aβ variants, 4 against different tau variants and one against a TDP-43 variant). We used this panel of reagents to characterize the protein variant fingerprints in a blinded set of longitudinal blood samples from control and AD
cases. Using this panel of reagents we were able to differentiate the AD blood samples from the control samples with high specificity and sensitivity. Of particular importance, we were able to identify AD blood samples years before a clinical diagnosis of AD, in most cases presymptomatically. We were also able to identify control cases that showed a decline in MMSE scores. Therefore identification of protein variants implicated in AD has excellent potential as biomarkers for early detection of AD.
Detecting and targeting injury-induced Alzheimer’s disease pathology. Sarah E. Stabenfeldt, PhD, Diego Mastroeni, PhD, Arizona State University; Arizona Alzheimer’s Consortium.

Specific Aims:
1) Specific Aim 1: Characterize the neurodegenerative molecular signature of neural injury targeting motif on mouse TBI sections.
2) Specific Aim 2: Test whether neural injury targeting motif recognizes neurodegenerative pathology in vivo.

Background and Significance:
An increased risk for Alzheimer’s disease (AD) and neurodegenerative disorders (NDDs) 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 60% increased risk of developing dementia (2,6). Professional athletes in contact sports such as boxing, American football, and soccer are particularly vulnerable to developing NDDs due to head injuries (7,8). Commonalities exist between TBI and AD/NDDs pathologies including a dysfunctional blood-brain barrier (9–11), neuroinflammation (12–15), 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 leverage our prior TBI biomarker research to detect and target AD/NDD degenerative processes. We previously developed an innovative discovery pipeline that involved in vivo phage display biopanning, next generation sequencing analysis, and subsequent proteomic analysis that identified novel spatiotemporal TBI targeting motifs (16). Of particular interest is a targeting motif that recognizes key regulators of AD/NDD degenerative process.

Preliminary Data, Experimental Design and Methods:
Our recent study with in vivo phage display biopanning performed in a pre-clinical murine focal TBI model discovered two novel targeting motifs with affinity and specificity to either acute (1 day) or subacute (7 day) TBI neuropathology (16). These targeting motifs are comprised of stable cyclic peptides based on the critical antibody epitope recognition domain of the complementarity determining region 3 (CDR3), termed CDR3 Loop Assembly via Structured Peptide (CLASP). Bacteriophage (phage) display is a powerful technique to identify motifs (e.g. peptides, antibody fragments) capable of targeting cell surface receptors and features of the extracellular environment unique to specific injury/disease pathology (17–20). We demonstrated such power of phage display by identifying CDR3 motifs with a domain antibody phage library (dAb) that recognize temporal alterations in the neural injury microenvironment (16). We conducted three in vivo phage display biopanning screens with the dAb phage library in mice that sustained a focal TBI (controlled cortical impact; CCI) at three different time points post-injury (1, 7, and 21 days post-injury; dpi). Using next-generation sequencing and bioinformatics analysis, we then compared and identified enriched phage populations for each time point post-injury. The bioinformatic analysis focused on ranking by CDR3 as this region imparts high diversity and specificity for dAb/antigen recognition compared to CDR1 and CDR2 (21–23). This analysis pipeline enabled selection of prominent CDR3 targeting domains for either acute injury (1 dpi) and subacute (7 dpi). After applying strict selection criteria, we used the CLASP system to generate CDR3
mimetics for validation testing. Ultimately, we successfully identified and validated two CLASP targeting domains that recognize acute (1 dpi) or subacute (7 dpi) TBI. The IHC based assessment on post-mortem murine TBI tissue demonstrate the stark temporal and spatial localization to neural injury by the acute and subacute CLASP motifs (16).

Relevant to this proposal, immunoprecipitation and mass-spectroscopy proteomic analysis revealed the subacute TBI CLASP may target AD/NDD associated cellular signaling molecules such as heat shock cognate 71 kDa and endoplasmic reticulum chaperone binding immunoglobulin protein (ER chaperone BiP) were identified as potential protein targets (16). ER chaperone BiP, a monitor of endoplasmic reticulum stress, is induced in AD in response to protein misfolding and cell death (24). Recent studies also suggest that heat shock cognate 71 kDa, a cytosolic facilitator of protein folding and degradation, may have a strong interaction with Tau protein, a hallmark of AD (25).

**Experimental Designs and Methods:**

Aim 1: We will use a mix of adult male and female mice with no genetic predisposition to neurodegenerative disease subjected to a unilateral CCI to the primary motor cortex (IACUC approved). Animals will be sacrificed at 1 and 4 weeks post-injury (n = 3 per sex per time point), brains processed, sectioned, and mounted for Nanostring analysis; naïve tissue will serve as negative controls. Working with Dr. Diego Mastroeni, we will stain the tissue with biotinylated acute and subacute CLASP motifs in addition to the neuronal marker, NeuN, to identify regions for Nanostring analysis; Nanostring enable spatial selection of distinct single cell analysis immunostained with the CLASP motifs. Transcriptomic analysis will focus on neurodegenerative and AD related processes and pathways.

Aim 2: Dr. Stabenfeldt’s team will use an established platform to fabricate polymeric nanoparticles with biorthogonal surface chemistry to immobilize CLASP motifs and near-infrared (NIR) and fluorescent fluorophores. We will use a mix of adult male and female mice with no genetic predisposition to neurodegenerative disease subjected to a unilateral CCI to the primary motor cortex (IACUC approved). At 1 and 4 weeks post-injury (n = 5 per sex per time point), animals will receive intravenous injections of CLASP-nanoparticles and biodistribution will be evaluated via IVIS NIR in vivo scanner at 1hr, 6hr, and 24hr after injection. Following the 24hr time point, animals will be sacrificed, brains processed, sectioned, and mounted for immunohistological assessment. Immunohistochemical analysis will be performed to determine TDP-43 pathologies that we have previously observed in our TBI model that indicate substantial neurodegenerative processes.

**Proposed One-Year and Long-Term Outcomes:**
The results from this study will determine the utility of our novel neural injury targeting motif to recognize neurodegenerative pathology following TBI. Data and findings from this proposal will be disseminated at the appropriate national conferences and journal publications. With prior support from AAC, Dr. Stabenfeldt and current/prior AAC collaborators have been awarded an NIH R03 and submitted multiple NIH and DOD proposals focused on the role of TBI in AD/NDDs (see list below). The potential future outcome of the proposed neurodegenerative detection/targeting strategy coupled with therapeutic drug delivery (a strength of Dr. Stabenfeldt) will address injury-induced neurodegeneration early after injury thereby potentially reducing AD/NDD risk for millions. Additionally, this project is very attractive for external funding agencies such as NIH, Alzheimer’s Association, and American Federation for Aging Research.

**Year End Progress Summary:**
Progress on this project were in two main areas: 1. Further characterization of TDP-43 pathology in our mouse preclinical model of TBI, and 2. Generation of targeting nanoparticles. Details on the progress for each of these areas is outlined below.
1. TDP-43 pathology progression in mouse preclinical TBI model. Here, we expanded on prior AAC funding and projects to characterize TDP-43 proteinopathies following a single moderate TBI event over 180 days post injury. Analysis revealed a temporal-dependent and significant increase in neuronal TDP-43 mislocalization in the cortical forebrain rostral to and distant from the primary injury site up to 180 DPI. TDP-43 mislocalization was also detected in neurons located in the ventral horns of the cervical spinal cord following a TBI. Moreover, a cortical layer-dependent affect was identified, increasing from superficial to deeper cortical layers over time from 7 DPI up to 180 DPI. Lastly, RNAseq analysis confirmed an injury-induced misregulation of several key biological processes implicated in neurons that increased over time. Collectively, this study demonstrates a connection between a single moderate TBI event and chronic neurodegenerative processes that are not limited to the primary injury site and broadly distributed throughout the cortex and corticospinal tract. Our results are currently under review at Acta Neurologica Communications (revised manuscript currently under review).

2. The second area of progress was on reproducibly generating CLASP peptides and targeting nanoparticles. Admittedly, this portion of the project took considerably more time than anticipated as a collaborator that had previously made the CLASP peptides moved and therefore, PI Stabenfeldt's lab group had to learn this process. The lead technician Amanda Witten was able to learn the conjugation, HPLC purification, and MALDI analysis pipeline to readily generate the CLASP peptides. In parallel, several manufacture delays and nanoparticle preparation methods stalled progress. We were able to generate serum stable, endotoxin-free, nanoparticles that present CLASP peptides on the surface and demonstrate no adverse effects on mice with injected intravenously. This milestone was reached in mid-June 2023. Therefore, we are poised to pursue studies moving forward.

This project strengthened the collaboration between Drs. Stabenfeldt and Mastroeni, that will be instrumental as they have just received an NIH R01 with co-collaborator Jonathan Lifshitz. Additionally, the results generated from this funding will be used for upcoming NIH and DOD submissions over the 2023 and 2024 cycles.

Project Personnel SUPPORTED by Funds:
Name Degree Project Role
Witten, Amanda MS Research Technician
Sex-dependent changes in learning and flexibility during aging in mice. Jessica Verpeut, PhD; Heather Bimonte-Nelson, PhD. Arizona State University; Arizona Alzheimer’s Consortium.

Specific Aims:
The specific aim of this project is to determine how learning and flexible cognition changes across the lifespan in both male and female mice. Behavior during task performance in juvenile and aged mice will be quantified by clustering joints using machine learning software.

Background and Significance:
Mapping biological pathways 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.

Preliminary Data, Experimental Design and Methods:
The preliminary data to support this project analyzed juvenile (postnatal day 21) male and female C57BL/6J mice. Animals were trained to discriminate between two shapes on a digital touchscreen. The pairwise touchscreen task has high translational value, as it has been previously used to assess learning and reversal in rodents, non-human primates, and humans (Izquierdo et al. 2017). The correct shape is paired with a liquid reward of 20% sweetened condensed milk. In our preliminary results, juvenile females were quicker to initiate the task (p < 0.01), but males and females equally were able to learn the task. In reversal learning, we initially saw that juvenile females had greater reversal performance, indicated by the number of correct trials, compared to male juvenile mice (p < 0.01).

In the proposed study, cognitive performance was assessed in C57BL/6J juvenile (P21) and middle-aged (10 months old) mice using a visual discrimination touchscreen apparatus (Med Associates). A subset of juvenile mice were aged to 10 months to analyze cognition across the lifespan. 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) using machine-learning programs (Pereira et al. 2022; Klibaite et al. 2021). Behavior tracking is critical to assure that animals are able to perform the task and are not hindered by a confounding variable, such as an inability to move about the apparatus. A control task for vision was included at the beginning of all trials to assure that animals could complete the task. After testing, mice (n = 12 per group; see Table 1) were euthanized for a future project analyzing neural structure (dendritic complexity and spine morphology) in cognitive-associated
brain regions, including the medial prefrontal cortex, infralimbic cortex, and anterior cingulate cortex.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of males</th>
<th>Number of females</th>
<th>Age at testing onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile</td>
<td>24</td>
<td>24</td>
<td>21 days</td>
</tr>
<tr>
<td>Aged Juvenile</td>
<td>12</td>
<td>12</td>
<td>10 months</td>
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<tr>
<td>Aged</td>
<td>12</td>
<td>12</td>
<td>10 months</td>
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Proposed One-Year and Long-Term Outcomes:
Our laboratory maintains a colony of C57BL/6J animals and has both juvenile and mice aged to several months old for experiments to be completed by the end of the one-year project period. The lab has already collected preliminary data in juvenile mice; for the current project, we spent the last year studying animal cognition from the juvenile period through middle-age. It is expected that female juvenile mice would have better cognitive flexibility compared to males, and that this effect would wane in aged females. All behavior will be quantified during this one year period. Following the end of the study, all mice were euthanized for future analysis (beyond the scope of the current proposal) of neural structure using Golgi-Cox staining techniques. For long-term outcomes, a manuscript will be submitted within two years of study completion to allow for analysis of neural structure. 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 detriments in collaboration with Dr. Bimonte-Nelson and others. As well, 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.

Year End Progress Summary:
One-year outcomes: Over the past year my lab has examined cognition in juvenile (P21, n=24 total) and middle-aged (10 months, n=24 total) male and female C57BL/6J mice using the pairwise touchscreen task. To begin the task, animals first have to learn to interact with the screen and that the opposite side of the apparatus contains a dipper with 20% sweetened condensed milk. Animals learn through trial and error how to initiate their reward. To continue through each shaping stage, animals have to increase the amount of times they correctly interact with the screen. Both male and female juveniles initiated and responded faster to trials during early stages of shaping (p< 0.05). Then, a second shape appears on the touchscreen during visual discrimination. Through trial and error, animals have to learn which shape initiates a reward. Both juvenile and middle-age animals were able to learn this task to criteria, but juveniles demonstrated significantly more correct choices during visual discrimination (p < 0.05, Figure 1A). After 10 days, the correct shape is switched so that the previously correct shape no longer initiates a reward to test reversal performance, a measure of cognitive flexibility. As expected, juvenile mice demonstrated more correct trials during reversal (p<0.001, Figure 1B) although both ages reached criteria by day 15. Interestingly, female mice, regardless of age, were faster to initiate each trial (p < 0.01, Figure 1C) and choose an image (p < 0.001, Figure 1D). Trial number was not a predictor of performance.
Figure 1. Performance outcomes of the pairwise touchscreen task. Juvenile animals had a significantly increased performance compared to aged animals in both (A) visual discrimination and (B) reversal learning. Females, regardless of age, had a faster (C) initiation and (D) response latency. *p<0.05, **p<0.01, ***p<0.001.

The current work establishes age-related changes in both males and females on the two-choice pairwise touchscreen task. It is anticipated that 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.

**Long-term outcomes:**
Video recordings of animals performing the task were collected to be analyzed using machine learning software to quantify locomotion, velocity, attention, and non-task related behavior. We are currently in the process of analyzing this data. In addition, animals have been euthanized to undergo neural structure analysis using Golgi-Cox staining techniques to assess dendritic complexity and spine density (measures related to cognition). As we proposed, the manuscript will not be submitted until neural structure has been analyzed or within two years of study completion. We expect this analysis to be finished in the fall to submit the manuscript by early spring. This work will be presented as a poster at the fall Society for Neuroscience and ADRC conference by the undergraduate lead, Vincent Truong.

Challenges encountered: As older animals were required, some animals (n=3) tested at a juvenile age did not live until middle-age. We added more mice into the study to solve this problem. In addition, animals needed more than 10 days to re-reach criteria (75%) in reversal learning stages, so we extended the time to 75% correct or 15 days.

Future grant applicants and collaborations: This work will be submitted for a future NIH grant on sex-differences in aging with Heather Bimonte-Nelson. I am developing a separate study to analyze fine motor behavior in an Alzheimer’s disease rat model with Sydney Schaeffer and Scott Beeman. As a team, we are submitting a R21/R33 this fall 2023.
Reducing recruitment costs in preclinical Alzheimer’s disease clinical trials with geometric machine learning: Yalin Wang, PhD, Richard J. Caselli, MD, Kewei Chen, PhD. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer’s Institute; Arizona Alzheimer’s Institute.

**Project Description:**
Alzheimer’s disease (AD)-related dementia (ADRD) is a significant public health concern, affecting 6.2 million Americans and costing US ~$239 billion in 2021. These numbers are expected to grow to nearly 50 million and $1.1 trillion by 2050. Current evidence supports that AD prevention at the preclinical phase before symptom onset is likely to be the most effective but will require the establishment of sensitive and cost-effective biomarkers to identify high-risk individuals and serve as endpoints for AD/ADRD randomized controlled trials (RCTs). While the Positron Emission Tomography (PET), cerebrospinal fluid, and emerging blood biomarkers for AD hallmark pathology of amyloid (A) and tau (T) have significantly advanced the field, they are expensive, invasive, or need additional validations. In contrast, structural magnetic resonance imaging (sMRI) has long been embedded in AD/ADRD RCTs to serve as screening tool and/or to measure neurodegeneration (N) outcome (e.g., hippocampal volume). There is an emerging research interest in increasing the sMRI utility in estimating Aβ/tau burden for screening to reduce RCT recruitment costs compared to expensive PET techniques.

**Specific Aim(s):**
To develop an attention-based self-supervised deep learning (SSDL) method, leveraging >10,000 sMRI images (6235 of them are paired with amyloid or tau PET) from 7 existing projects (ADNI, AZ APOE, WRAP, OASIS, NACC, AIBL, and ADCP) to train and validate our methods in cognitively unimpaired (CU) populations to examine their comparability for determining eligibility to the A/T screening criteria.

(a) Develop Three-dimensional HiErarchical Mesh Encoder (THEME) to estimate Aβ/tau burden for RCT screening; (b). Validate the THEME screening in 2715/721 CU Aβ/tau-MRI data pairs (ADNI, AZ APOE, WRAP, OASIS). Hypothesis: THEME will better assess A/T positivity than the prevailing standard techniques, including the hippocampal volume.

**Background and Significance:**
AD is a significant public health concern, with the number of affected individuals expected to reach 14 million by 2050 in the U.S. alone. Current therapeutic failures were at least partially attributable to the interventions being initiated too late or targeting non-AD etiology. Measuring brain biomarkers and intervening at its preclinical stages improve the likelihood of therapeutic success. Aβ plaque and tau deposition are the hallmarks of AD and appear in the preclinical stages. However, analysis of Aβ biomarkers in two phase 3 clinical trials revealed that 27% of subjects meeting clinical inclusion criteria for mild AD were Aβ negative. The development of advanced brain biomarkers to improve the screening efficiency will benefit AD randomized controlled trials (RCTs) and expedite AD treatment development.

The A/T/N system (Aβ, Tau, and Neurodegeneration) is a research framework to define the biological AD. Under the A/T/N hypothesis, an imbalance between Aβ production and clearance occurs early and is followed by the accumulation of tau protein tangles. Aβ and tau cause damage to the brain in the form of neurodegeneration. Assessment of Aβ/tau pathology using cerebrospinal fluid (CSF) or positron emission tomography (PET) scans can easily become inefficient due to the degree of their acceptance, invasiveness, costs, and/or PET facility availability. While blood-based biomarkers (BBB) are more affordable alternatives for inferring Aβ/tau burden in the brain, BBB measurement variabilities reduced their clinical usability.
Structural magnetic resonance imaging (sMRI) is another alternative that is noninvasive, broadly accessible, cost-effective, and widely used as a standard-of-care procedure. SMRI scans can detect N very early around the time of Aβ initiation and tau appearance. Prior findings support that Aβ pathology correlates with sMRI-based atrophy measures in multiple brain structures, including total cortical and grey matter volumes, hippocampus, accumbens, thalamus, and putamen volumes. Similarly, patterns of tau pathology are mirrored by entorhinal thickness, hippocampal and ventricular volumes. Therefore, the development of sMRI biomarkers with strong A/T specificity is an emerging research area and will be advantageous in AD RCT recruitment. However, neuroimaging labeling is expensive or invasive (e.g., PET data collection), time-consuming, expert knowledge required, and labor-intensive. To tackle this contradiction, exploiting unlabeled data (potentially including clinical neuroimaging data) via unsupervised learning approaches becomes an imperative demand.

**Preliminary Data, Experimental Design and Methods:**

Preliminary data. With our previously introduced hippocampal surface MMS and surface sparse coding research, we attempted to classify individuals with different Aβ statuses in ADNI and OASIS cohorts, including (1) Aβ+ AD vs. Aβ- CU; (2) Aβ+ MCI vs. Aβ- MCI; (3) Aβ+ CU vs. Aβ- CU. Experimental results suggested that our MMS and sparse coding approach can discriminate Aβ positivity in people with MCI (Accuracy (ACC)=0.89) and CU individuals (ACC=0.79 (ADNI) and ACC=0.81 (OASIS)). These results compared favorably relative to state-of-the-art research. Our recent work also applied our framework to study regional tau depositions in different Braak stages. With 925 ADNI subjects, our results suggested that our framework predicted early Braak stage and later Braak stage tau depositions more closely to the Tau PET measures than other approaches such as hippocampal volume, hippocampal surface area, and shape morphometry features based on spherical harmonics (SPHARM).

**Experimental Design and Methods:**

We propose a self-supervised learning model in which the hippocampal surfaces either have or do not have label information. We chop the mesh into different blocks. We concatenate the class block at the beginning of the sequence and pass the class-attached sequence through a transformer network to obtain a global representation of the input sequences. The latter is used for brain amyloid burden estimation. 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:**

TetCNN: Convolutional Neural Networks on Tetrahedral Meshes

Convolutional neural networks (CNN) have been broadly studied on images, videos, graphs, and triangular meshes. However, it has seldom been studied on tetrahedral meshes. Given the merits of using volumetric meshes in applications like brain image analysis, we introduced a novel interpretable graph CNN framework for the tetrahedral mesh structure. Inspired by the ChebyNet, our model exploited the volumetric Laplace-Beltrami Operator (LBO) to define filters over commonly used graph Laplacian which lacks the Riemannian metric information of 3D manifolds. For pooling adaptation, we introduced new objective functions for localized minimum cuts in the Graclus algorithm based on the LBO. We employed a piece-wise constant approximation scheme that used the clustering assignment matrix to estimate the LBO on sampled meshes after each pooling. Finally, adapting the Gradient-weighted Class Activation Mapping algorithm for tetrahedral meshes, we used the obtained heatmaps to visualize discovered regions-of-interest as biomarkers. We demonstrated the effectiveness of our model on cortical tetrahedral meshes from patients with AD, as there is
scientific evidence showing the correlation of cortical thickness to neurodegenerative disease progression. Our results showed the superiority of our LBO-based convolution layer and adapted pooling over the conventionally used unitary cortical thickness, graph Laplacian, and point cloud representation. The work was honored with a podium oral presentation in one of the most prestigious medical conferences, Information Processing in Medical Imaging (IPMI) 2023.

Pre-Training Graph Attention Convolution for Brain Structural Imaging Biomarker Analysis and Its Application to Alzheimer’s Disease Pathology Identification We developed a method, pre-training graph attention convolution, taking MRI to predict A\beta positivity. The proposed self-supervised learning architecture refined feature extraction from mesh representation via pre-training and fine-tuning, resulting in more powerful biomarkers for A\beta identification. We obtained subjects from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and use our method to discriminate A\beta positivity. Theoretically, we provided analysis toward the understanding of what the network has learned. Empirically, our method showed strong performance on par or even better than state of the art. Our work proposed a self-supervised transformer-based surface analysis framework and may open new opportunities for brain shape analysis.

A Surface-Based Federated Chow Test Model for Integrating APOE Status, Tau Deposition Measure, and Hippocampal Surface Morphometry We proposed a surface-based federated Chow test model to study the synergistic effects of APOE, a previously reported significant risk factor of AD, and tau on hippocampal surface morphometry. Using data obtained from different institutions, we demonstrated that our model could detect differences between APOE subgroups in patterns of tau deposition and hippocampal atrophy without sacrificing data privacy. Specifically, we illustrated that the APOE-specific morphometry features correlate with AD progression and better predict future AD conversion than other MRI biomarkers. For example, a strong association between atrophy and abnormal tau was identified in hippocampal subregions cornu ammonis 1 (CA1 subfield) and subiculum in e4 homozygote cohort. Our model allowed for identifying MRI biomarkers for AD and cognitive decline prediction and may uncover a corner of the neural mechanisms of the influence of APOE and tau deposition on hippocampal morphology. The work was published in Journal of Alzheimer’s Disease.

Improved Prediction of Beta-Amyloid and Tau Burden Using Hippocampal Surface Multivariate Morphometry Statistics and Sparse Coding Our previous work showed that MRI-based hippocampal multivariate morphometry statistics (MMS) was a superior neurodegenerative biomarker for group analyses. We applied the framework with the ridge regression model to quantitatively predict the amyloid and tau measurements. We evaluated our framework on amyloid PET/MRI and tau PET/MRI datasets from the ADNI. Each subject had one pair consisting of a PET image and MRI scan, collected about the same time. Experimental results suggested that amyloid/tau measurements predicted with our PASCP-MP representations were closer to the real values than the measures derived from other approaches, such as hippocampal surface area, volume, and shape morphometry features based on spherical harmonics (SPHARM). The work was published in Journal of Alzheimer’s Disease.
Effects of dynamic lighting on improving sleep and mood in older adults with dementia.
Nastaran Shishegar (Nina Sharp), PhD, Shawn Youngstedt, PhD, Molly Maxfield, PhD, Dongwoo (Jason) Yeom, PhD. Arizona State University; Arizona Alzheimer’s Consortium.

Specific Aims:
1. To investigate the effect of a dynamic lighting condition on circadian activity rhythms and selected sleep parameters in older adults with dementia.
2. To evaluate the effect of a dynamic lighting condition on mood.

Background and Significance:
Sleep disorders and the associated behavioral disturbance are very common symptoms experienced by older adults with dementia. These symptoms may be further exacerbated when residing in a long-term care facility as the design of these institutions supports inactivity and reduces adequate daily light exposure. Light is the most important environmental element that is not only necessary to fulfill visual tasks but also is the main stimulus that regulates circadian rhythms. Daily exposure to proper lighting at the right time is reported as an effective non-pharmacological treatment to improve sleep disorders in various age groups including older adults. Several clinical studies have demonstrated the benefits of bright light therapy to improve sleep duration and sleep efficiency at night and reduce daytime sleepiness and behavioral disturbance (i.e., agitation, depression) in older adults. The lighting design in long-term care facilities does not necessarily provide adequate intensity and spectrum to stimulate circadian rhythms in elder residences. Studies reported poor lighting conditions in nursing homes. According to these studies, daytime lighting in these institutions is not even sufficient to fulfill older adults’ visual needs, while light at night is relatively often excessive.

Experimental Design and Methods:
The study was conducted as a within-subject study design over 7 days of conventional lighting (Baseline) followed by 21 days of either dynamic lighting (Treatment) or room lighting (Placebo) in a counterbalanced order. Sleep, circadian activity rhythms, mood, and light exposure were tracked in each condition. The human-lighting interaction occurred in the common areas of the selected memory care facilities where older adults with dementia spent most of the daytime hours under the supervision of facility caregivers. The participants of this study should be older adults diagnosed with dementia based on the recommendation of facility’s management. Exclusion criteria included major organ failure, major diagnosis other than dementia, history of head injury, obstructing cataracts, macular degeneration, and blindness. Individuals taking antidepressants or light therapy will also be excluded.

Lighting conditions: Conventional Lighting (Baseline). Once participants were screened and consented through their legal representatives, the baseline measurement was performed to monitor patterns of sleep, circadian rhythms, mood, and light exposure for 7 days under the conventional lighting condition in the facility. Participants were asked to wear an actigraph continuously for seven days on their non-dominant wrist to track sleep/wake and circadian activity patterns. Wrist actigraphy is a validated, low burden technique for estimating the timing of sleep and wake. Participants also wore a light tracker (Blue Iris mobile sensor) that captured a spot measurement of full spectral power (350 nm-780 nm) every five minutes throughout the daytime (wake until bedtime). To assess mood and agitation in participants, two questionnaires, Cornell Scale for Depression in Dementia (CSDD) and Cohen-Mansfield Agitation Inventory (CMAI), were completed by caregivers on the day 7th of the Baseline. Intervention. The Intervention period started right after the Baseline and continue for 42 days. We examined two lighting conditions, dynamic lighting and an active placebo; Each last for 21 days. The order of conditions was
counterbalanced. The dynamic lighting condition will provide a blue-enriched high intensity lighting in the morning (6:00 – 12:00) for circadian stimulation. The color and intensity of the light changed gradually throughout the day to deliver neutral white medium intensity lighting in the afternoon (12:00 – 16:00) to maintain alertness without exerting substantial circadian effects, and a yellowish low intensity lighting in the evening (16:00 – 18:00) to minimize any circadian effect. Between 18:00 and 6:00, the experimental lights turned off and the lighting returned to conventional condition which delivered a low-circadian lighting dosage. The placebo condition exposed participants to a static lighting condition that was equivalent to the average room lighting from morning to evening. Customized direct/indirect LED luminaires (floor lamps, broad-spectrum white light) were placed in the common areas of the selected facility to create the intervention conditions. Similar to our previous and current field studies, we paired the luminaires with smart control systems to change the lighting automatically based on the defined preset schedules. Participants and caregivers were not told about the structure of the lighting conditions, just that the lighting could change daily. As during Baseline, actigraphy was used to monitor sleep/wake behavior and circadian activity rhythms. Since the lighting can take several days to impact sleep, and to minimize burden on participants and caregivers, actigraphy was conducted only on the last 7 days of each condition. Light spectrum and intensity will be tracked continuously throughout the waking day (Blue Iris mobile sensor). Moreover, caregivers completed CSDD and CMAI every seven days to assess the short and long-term effects of each condition on mood and agitation.

**Proposed One-Year and Long-Term Outcomes:**
Successful study completion provides initial guidance to the designers and administration of senior living facilities as to the lighting design recommendations of greatest benefits to the sleep, mood, and well-being of institutionalized older adults diagnosed with dementia. The outcomes of this study are a quantitative solution (i.e., illuminance levels, CCT, EML), rather than a qualitative one (i.e., brighter, cool light), which could foster public awareness and encourage designers and developers to have a more inclusive approach towards lighting in the design of living spaces for older adults. In terms of long-term outcomes, we hope to increase the likelihood of compliance for accurate measurements of light and potential health outcomes to demonstrate that a practical well-designed light delivery system can improve sleep, mood, and thereby the quality of life in older adults with dementia as well as to reduce burden of caregiving.

**Year End Progress Summary:**
Our team commenced work on the project promptly after securing the funding. The Principal Investigators (PIs) received assistance from two research assistants throughout the project. Later, a third graduate assistant joined the team to expedite data collection and analysis. Due to our target population's vulnerable status and their residence in specialized facilities that prioritize privacy and caregiver involvement, the Institutional Review Board (IRB) process required a considerable amount of time for processing. Furthermore, within the project's designated timeframe, we spent approximately five months reaching out to memory care facilities to identify suitable candidates for our study. Two facilities, namely Sunshine Village and Mirabella at ASU, expressed interest. However, only Sunshine Village presented an adequate number of residents to proceed with the study. Initially, the facility managers introduced 17 potential participants who met our inclusion/exclusion criteria. Out of this group, 14 initially expressed interest, and their legal representatives (LAR) followed up with us. Eventually, the LAR of 11 participants provided consent for their involvement in the study. Among these 11 participants, 10 adhered to the study protocol, while one participant was excluded. The participants were recruited from two cottages at Sunshine Village. The first cottage (comprising 6 participants) began the experiment under the placebo lighting condition, followed by the dynamic condition. The second cottage (comprising 4 participants) started with the dynamic condition and then transitioned to the placebo condition. Data collection was started in January 2023. A total of 9 experimental lights were installed in the common area of each cottage to implement the interventional conditions. All lighting setups and
measurements were conducted in the common room of the selected cottages to ensure the target intensity and spectrum were met. Prior to the baseline measurements, we dedicated one week to training caregivers on survey completion and how to monitor the Actiwatch and light tracker. Following the training period, the baseline measurements were conducted for one week. The interventional condition commenced immediately after the baseline, with participants assigned to either the dynamic or placebo condition. On the first day of the dynamic week, participants exhibited some discomfort under the morning lighting condition, which had the highest light intensity. In response, we promptly took action and modified the interventional condition by reducing the light intensity and implementing a two-hour fading period from 6:00 to 8:00. This gradual increase in light intensity allowed participants' eyes to adapt to the bright lighting. This alteration in the dynamic condition yielded positive feedback from both residents and caregivers. Each intervention lasted for 3 weeks, and the CMAI and Cornell surveys were printed and delivered to the caregivers every week on the last day of their shift. Actigraphy was conducted during the final week of each intervention. Once data collection was completed in the first cottage following the designated procedure, we proceeded to initiate the study in the other cottage. One challenge we encountered was ensuring participants' compliance with wearing the wearables (Actiwatch and light tracker). To address this issue, we developed a tracking sheet for caregivers to monitor the usage of these devices every 2 hours, verifying whether participants were wearing them or not. This approach aimed to ensure the validity of the collected data. As a result, 6 out of 10 participants completed wearing the Actiwatch, while only 4 out of 10 participants completed wearing the light tracker throughout the study period. Throughout the study, our research team maintained close collaboration with caregivers, scheduling regular meetings to gather feedback regarding the measurement tools, experimental lighting conditions, and participants' interactions with the study equipment. We found this feedback to be invaluable, as it provided insights for designing future studies and developing our external funding proposal. Overall, caregivers reported that both intervention lighting conditions were well-received by residents, who tended to spend more time in common areas when the lights were activated. The introduction of the lights transformed the caregivers' perception of the environment, creating a livelier and happier atmosphere. Additionally, the lighting had a positive impact on the perception of residents' families, fostering increased trust in the care provided to their loved ones. The data collected from Cottage 1 was analyzed, revealing a trend of improvement in sleep duration and efficiency during the intervention conditions compared to the baseline. However, no statistically significant differences were detected. Furthermore, the descriptive analysis indicated an improvement in mood and reduction in agitation during the intervention conditions, although again, no statistically significant differences were found. The initial results from the six participants were presented at the 2023 Sleep Conference held in Indianapolis. Data collection were completed June 2023, and we are currently in the data analysis stage for both cottages.
Outreach, recruitment, and ongoing engagement of Latino and Native American research participants. David W. Coon, PhD, Jessica Langbaum, PhD, Richard Caselli, MD, Thomas Beach, PhD, Alireza Atri, MD, David Weidman, MD, Anna Burke, MD, Steven Rapcsak, MD, Eric Reiman, MD. Banner Alzheimer’s Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute; Barrow Neurological Institute; University of Arizona; Arizona State University; Arizona Alzheimer’s Consortium.

Project Description:
This proposal requests complementary support to enhance ongoing efforts for participant recruitment and outreach efforts as part of the Arizona Alzheimer’s Consortium’s ADC and ancillary programs with a focus on Latino and Native American Communities. The Arizona ADC is part of a multi-institutional state-wide consortium that links together the major research institutions in Arizona to advance effort in the early detection, tracking of progression, and evaluation treatments and prevention therapies for Alzheimer’s disease and related disorders. The ancillary programs include the Arizona BBDP and Arizona APOE4 Gene Dose Program. The Arizona Brain and Body Donation Program (BBDP) provides an invaluable scientific resource of longitudinal cognitive, motor, clinical, and genetic data from >800 living older adults who have standardized annual assessments, consent to brain (and frequently body) donation, and provide a resource of unusually high-quality brain tissue, postmortem CSF and blood samples (which differ in some respects to samples that are acquired in life) and neuropathological data after they die. The program includes but is not limited to research participants with the clinical features of Alzheimer’s disease (AD) or related disorders and cognitively and neurologically unimpaired older adults with support from the National Institute on Aging (NIA)-supported Arizona ADRC 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 over 200 participants who were initially late-middle-aged participants with a first-degree family history of dementia who are followed every two years with a battery of clinical ratings, cognitive tests, FDG, amyloid and now tau PET scans, and MRIs, who have provided plasma, serum and PBMC samples that are stored at Mayo Clinic, and who have begun to provide CSF samples with support from a longstanding NIA grant. It also includes more than 200 other participants, with or without a family history and through youngest to oldest adult ages, who are followed using state and organizational Arizona Alzheimer’s Consortium funds, and who have not yet provided CSF, plasma and serum samples.

Latino and Native American Recruitment, Enrollment: The inclusion of Latino and Native American participants from a variety of backgrounds and different characteristics (e.g., level of educational attainment, race, country of origin, family history of AD) will assist investigators in providing answers to questions about dementia diagnosis, treatment, and management strategies that are likely to be applicable to the broad U.S. population. Additionally, a more diverse participant pool will facilitate investigations of different risk factors, health disparities and the neuropathology and genetics of AD and related dementias as well as studies of caregiving and family burden in diverse groups. As part of increasing outreach to families facing dementia, this project develops and implements a Spanish language media/marketing campaign to complement current English campaign underway. The campaign will include print, video testimonials, social media campaign and local TV (e.g., Univision). It expands the marketing campaign and related
assets that leverage traditional media (e.g., radio, TV, and print) and social media venues to help engage, recruit, and retain Latino participants in ADRD research. Examples include the following: (a) commercials with on-camera spokesperson with spokesperson; management of social media campaign with curated social media posts; look live video messages for social media stories; (b) boots on the ground staff (Promotores/CHW staff as encouraged in NIA Listening Group ASU-HOPE network); (c) develop, design and print collateral focused on brain imaging procedures, brain donation, LP (feedback from BAI ADRC coordinator is that participants, especially Native Americans, are hesitant to do study procedures that are unfamiliar to them); (d) Integration of qualitative feedback collected through other funding with feedback from community advisory board to advance additional research/retention strategies; (e) funding to cover targeted messages through Alzheimer’s Prevention Registry; and (f) support for new outreach strategies to increase engagement, enrollment, and retention efforts of Latino and Native American participants.

**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:**
Our outreach efforts are a combination of in-person events, traditional media, and social media strategies. The COVID-19 pandemic required us to adapt many of our activities to include video conferencing (i.e. Zoom), Facebook and Facebook Live events, texting, and the like to reach these populations. Still many 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 9,000 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, trainings, and annual conference in partnership with a variety of community-based organizations (e.g., local area agencies on aging, the Alzheimer’s Association). These activities were combined with individualized Zoom-based and in-person presentations to numerous organizations such as Molina Healthcare, Blue Cross Blue Shield, Valle del Sol, La Libre Initiative, Unlimited Potential, Chicanos por La Causa, Salud en Balance, El Rio Health, Muhammad Ali Parkinson’s Center, the Parkinson’s Foundation, Consulado Mexicano, Tempe Action Alliance, American Heart Association, Si Se Puede, United Health Care, Equality Health, Well-Connected Español, and local church and senior centers. The Promotores HOPE Network Conference drew over 250 participants and AAC clinical partners were present at information and networking tables to provide additional outreach support. 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., Conexiones, Entre Mujeres, La Onda Radio, Frequencia A Radio, 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. We worked with a local professional marketing firm with established experience in the Latino community to continue to develop a campaign and related assets that leverage both traditional media and social media venues to engage, recruit, and retain Latino participants in ADRD 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 and a future campaign in Spanish. Through other funds, the AAC’s logo was refreshed to reflect more of its Arizona roots and we are incorporating the launch of the new logo as part of our new campaign efforts. During this year, we also began the establishment of a Native American Advisory Board to gather additional input from the community about community engagement, outreach, recruitment and retention activities and advanced plans for the 17th Annual Alzheimer’s and Dementia in Native Americans Conference and its complementary pre-conference to be held October 18 and 19.
Arizona Alzheimer’s Consortium (AAC) website updates. David W. Coon, PhD, Jessica Langbaum, PhD. Banner Alzheimer’s Institute; Arizona State University; Arizona Alzheimer’s Consortium.

**Project Description:**
The Arizona Alzheimer’s Consortium (AAC), including through website operations (azalz.org), 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) (azadrc.org), 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: development and publishing of branding and design guidelines for all web and video/print media (including art direction, font selection, graphic design, video production, video editing, user experience testing, backend database functions, web security, and multi-platform optimization); development of a new logo that honors diversity, heritage, history, outreach, and our extremely broad and deep scientific platform; integrate this logo with both the AAC and ADRC for comprehensive branding across all media and by all users (member institutions, contractors/vendors, media outlets, social media, etc.); continuing web development work, such as usability, platform, and scalability testing to ensure the sites work on common browsers and devices (desktop, laptop, and mobile); establishing contact and data intake methods for the public to express interest in participating in research studies; fostering interoperability between the AAC and the ADRC websites; liaising with AAC Communications Committee members and institutional subject matter experts to review (and edit as needed) new
original content and to help source additional content; curating and updating a Vimeo social media channel with more than 351 minutes (5.85 hours) of new content in addition to 630 minutes (10.5 hours) of existing content related to key categories (Alzheimer’s Treatment and Management, Brain Health and Alzheimer’s Prevention, Caregiving, and Conversations with Our Scientists) embedded into the websites; sourcing images to reinforce AAC, ADRC, and member institution commitments to reach across the diversity of our state and its communities; circulating content on a non-public staging server for review before public-facing publish testing including “platform breaking” to ensure performance and that the site is publication-ready.

Video content on the AAC and AZADRC platforms achieved 12,086 impressions (meaning at least partial views) from July 1, 2022 – June 30, 2023. Additional content that is currently under review and being published to the websites includes recent presentations from our scientists; more than 100 new graphics and images sourced for use; and new drone footage of our communities to emphasize the far-reaching effect of our multi-site statewide presence. Video footage and interviews from the upcoming 2023 AAC Scientific Conference will be published as well.

Key content has been translated from English to Spanish (and in some cases is produced in Spanish and translated to English) to continue engaging our underserved Latino/Hispanic community. Content is also available for repurpose into additional social media campaigns.

Ongoing services include ongoing work with AAC member institutions to source additional video content and develop new original content; the development of fresh, dynamic, bilingual material that will meet the informational needs of our communities, including our underserved Latino and Native American communities; ongoing art direction and graphic design that strengthens branding between the AAC and the ADRC sites and our member institutions, and enhances community engagement; and collaboration with additional contractors/vendors to distribute content into target markets. Content will continue to be developed and refreshed in future years—making this not a one-off effort, but instead a substantial and ongoing push to expand public engagement, publicize research opportunities, and deepen institutional collaboration and connections.
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, Thomas Beach, PhD, Jeffrey H. Kordower, PhD, Petra Fromme, PhD. Arizona Alzheimer’s Consortium; Arizona State University; Banner Sun Health Research Institute.

Specific Aims:
1) Specific Aim 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) Specific Aim 2 - Study the effects of tau polymorph seeding on cellular proteostasis. We will use advanced structural imaging methods and our cellular models to study the effects of aberrant tau polymorphism on cellular organization for protein complexes.
3) Specific Aim 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 Alzheimer’s disease (AD) brain.

Background and Significance:
Classical stages for neurodegenerative tauopathies can be clocked by distinct cellular and neuroanatomical distribution of the pathological tau protein inclusions. With the recent structure determination (resolution 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 has also been found that recombinant tau protein induced by heparin, micelles, or small molecules to aggregate in vitro form 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. Hyper-phosphorylation or other post-translational modifications increase polarity distribution along intrinsically disordered tau and may drive hydrophobic regions to condense and form hydrogen bonds between 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 aspect of cellular environment drive the conformational variants of tau protein aggregates in a disease specific manner?

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. Understanding what drives unique conformational variants of tau aggregation will reveal pathways of molecular dysregulation occurring in disease.

Preliminary Data, Experimental Design and Methods:
First, we are developing 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, cryo focused ion beam (cryoFIB), and cryo-EM. We 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, microED, 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. Cryo-FIB will allow for direct visualization of tau aggregates and cellular interaction partners in our models and AD brain samples after vitrification and subsequent ion-beam milling.

Proposed One-Year and Long-Term Outcomes:
Establishing a collaborative effort between the Banner Neurodegenerative Disease Research Center (NDRC) and Center for Applied Structural Discovery (CASD) has ignited long-term commitments between the two Centers adding a new dimension toward understanding neurodegenerative diseases here at ASU Biodesign Institute. As a result, a multi-PI T32 Postdoctoral training grant was submitted to NIH for support of up to four Postdocs training to use structural methods aimed toward tackling the problem of neurodegenerative diseases. An additional smaller grant was submitted between NDRC and CASD to examine structural outcomes of tau aggregation in a new NHP model of AD.

We continue working together 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. We are also excited about the commissioning of three new instruments at ASU Spring of 2023. First, a new Leica EM ICE high-pressure freezer allowing cryo-tissue preparation of thicker samples for cryoFIB milling and slice-and-view serial imaging at a resolution up to 10 nm each image while moving through brain tissue or cells. Second, a new cryoEM pre-screening instrument Talos L120C G2 cryo-ready transmission electron microscope (TEM) was added to improve our cryoEM workflow. Lastly, a Leica EM GP2 plunge freezer allows specific environmental settings and the option of single-sided blotting optimal for cryoFIB milling. An additional new cryo plasma FIB instrument is planned at ASU to benefit the whole ASU life sciences community and we are actively seeking funding.

Year End 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 including all six isoforms of human brain tau protein. We experienced a contamination problem in both cell culture rooms in Fall 2022 for the insect cells and then Winter 2023 for the mammalian cells. Once discovered, it took a few weeks to confidently eradicate the problem. Additionally, the supply of baculovirus system used to express plasmids in Sf9 insect cells was discontinued. An alternate expression system was explored before finding a new vendor with the original baculovirus to continue the optimization and exploration of tau isoforms in an insect cell model. We will continue to develop our cryoEM workflow for aggregate core solutions which will be used to measure tau aggregate structural outcomes after microenvironment changes in the cellular models. We have succeeded in obtaining low-resolution structures of recombinant 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.

Specific Aim 2: Observe Tau aggregate polymorphs interactions within a cellular context. Using direct imaging of tau aggregates within 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 protein complex interactions, ribosomal induction and phase transitions. We can accomplish this by high-pressure freezing brain tissue or plunging cultured cells on gold TEM grids in liquid ethane. A gallium ion beam in Helios cryoFIB can be used to then mill out thin lamellae which are carefully shuttled still under cryo conditions to the Titan Krios cryoEM for tomography and subsequent 3D reconstruction of the intracellular space captured. Through our development of our cryoFIB pipeline suitable for our specific needs, we discovered that the instrumentation here is geared more toward use by the material scientists with little regard for life sciences. Challenges we encountered include limited ‘cryo’ time (life-sciences) allowed per month, no automatic eucentric stage adjustment, no fluorescent targeting, transfer of cryo samples into the chamber is not under anti-contamination vacuum, no in-chamber sputtering to protect biological samples from electron beam charging, and no cryo lift-out arm for extraction from thicker samples. These items are not necessary for material science work using FIB or cryoFIB and therefore were not included in the commissioning unfortunately for the life scientist.

To overcome these challenges, we traveled to the Thermo Nanoport in Hillsboro, OR to use the new advanced Hydra cryo-pFIB more suitable for use in life sciences. The Hydra cryo multi-ion species plasma FIB has the most advanced electron column, detectors and camera for high contrast/resolution SEM imaging through tissue and cellular models. The use of a plasma ion beam for milling will increase efficiency and greatly reduce cutting artifacts. Before the trip, human brain EGFP-tagged tau protein was transiently expressed in human neuroblastoma cells cultured on gold TEM grids. A small molecule tau protein aggregation inducer (Congo Red) was added to the cell media for five days after transfection. The nuclei were quickly stained with Hoechst before vitrification of the cells on grids in liquid ethane using the new Leica EM GP2 plunge freezer and shipped to the Nanoport under dry cryo conditions. The Hydra cryo-pFIB has in-chamber fluorescent imaging for exact targeting and overcomes all the fore-mentioned challenges we experience using the Helios cryoFIB. We successfully collected high-contrast tomography and scanning electron volumetric imaging through our mammalian cell model in a native state revealing large multivesicular bodies, multilayer autophagosomes, excessive mitochondrial fusion, and nuclear envelope expansions (Fig. 1).

**Specific Aim 3: Study of phosphorylation forces key to tau polymorph formation.** We are studying 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 mapped phosphorylation modifications occurring within the Sf9 cells expressing one isoform as a baseline landscape before we begin to study intracellular microenvironment changes. Spodoptera frugiperda Sf9 cells are derived from the immature ovaries of fall armyworm moth pupae and widely used for eukaryotic protein expression having advantages of high expression of human protein, easy manipulation, and posttranslational modification landscape similar to mammalian cells. Our mass spectrometry analysis of human brain tau protein expressed and purified from Sf9 insect cells reveals almost 100% occupation by phosphorylation at the two sites T231 and S235 (2N4R).

Specific Aims:
Specific Aim 1 – Rank the propensity for Tau peptides to self-aggregate and/or induce full-length Tau aggregation. It is hypothesized that some proteolytic cleaved Tau peptides are prone to aggregation and induce full-length Tau to aggregate. Using a Thioflavin dye assay, we will determine which peptides self-aggregate and/or induce/inhibit full-length Tau to aggregate.
Specific Aim 2 – Identify peptide reactions leading to filamentous structures using TEM. It is hypothesized that some Tau-derived peptides capable of inducing full-length Tau protein to aggregate will have filamentous straight or helical aggregate structures like those in AD.

Background and Significance:
The involvement of tau protein self-assembly and stereotypical pattern of spreading along human brain neuronal networks correlates with loss of neurons and is central to clinical progression and staging in Alzheimer’s disease and other neurodegenerative diseases. Under certain conditions permissive to disease in brain, tau molecules can begin to assemble into a rigid β-sheet rich core. Although some tau fragments can spontaneously misfold and begin to accumulate in aggregate form, full-length tau produced in vitro or when expressed in situ does not spontaneously misfold and aggregate even at supersaturation. The initiation of tau to aggregate results after overcoming some unknown energy barrier forbidding aberrant misfolding. Inducing tau monomer to form a small oligomer nucleus leading to filamentous elongation can be a heterogenous association such as with a membrane, small molecules, or peptides stabilizing the misfolded species for subsequent elongation steps to filamentous tau aggregates. Proteolysis is a process of protein degradation which can also control multiple cellular functions. The longest isoform of tau protein contains more than forty known proteolytic cleavage sites resulting in hundreds of possible peptides from tau. Peptides have been shown to rapidly induce the misfolding and aggregation of tau in vitro. Because many known proteolytic cleavage sites on tau protein remain uncharacterized, this study aims to collect preliminary data for future funding and will establish groundwork for a long-term research of proteolytic post-translational modification to identify those sites on tau which may produce toxic, aggregate prone or alternatively, protective peptides preventing tau aggregation in neurons. Toxic peptides and/or protective tau peptides point to proteolytic pathways which will ignite future exploration and collaborations to investigate as therapeutic targets.

Preliminary Data, Experimental Design and Methods:
The study is designed to test and rank the propensity of tau aggregation induction or the prevention thereof by each protease-cleaved tau peptide after incubation with full-length recombinant tau isoforms. We mapped cleavage sites of nineteen known and other yet to be discovered proteases along the longest human brain tau isoform. Tau-derived peptides were designed, ordered from commercial peptide synthesis services with greater than 95% purity. Thioflavin dye fluorescent assays were used to test for β-sheet aggregate formation of a peptide alone as well as ability of the peptide to induce and incorporate into aggregates with full-length human tau protein isoforms. Triplicate reactions including nonspecific protein and dye controls were incubated >24 hours after which fluorescent intensity of ThT is measured in BioTek Synergy H1 microplate reader using excitation wavelength 440nm and emission wavelength 490nm. A fluorescent signal of ThT at 490nm indicates the presence of β-sheet aggregates. Statistical differences were analyzed for fluorescent intensity between wells containing positive tau
aggregate control and wells containing peptide alone, peptide with aggregation inducer, peptide mixed with full-length tau protein, and peptide with full-length tau protein and aggregation inducer. Filter-trap assays and sucrose gradient assays are used to confirm incorporation of peptide with full-length tau protein in aggregates. Reactions positive for β-sheet aggregates by thioflavin assay are adsorbed to TEM grids, negative stained, and imaged using the 2010F JEOL TEM or the Talos L120C TEM housed in the ASU Eyring Materials Center for validation of filamentous aggregate morphology.

Proposed One-Year and Long-Term Outcomes:
The study has a high probability of successful identification of new targets for discovery of the etiology of AD as well protective therapeutic targets. The first several weeks after receipt of funding will be dominated by ordering and receiving peptides and continue throughout most of the pilot study. Thioflavin assays and TEM will begin in the second quarter and continue for the duration of the study. After successful acquisition of preliminary data, a grant proposal to NIH will be submitted to continue characterizing additional peptides. Peptides identified as toxic aggregation inducers or peptides found to inhibit tau aggregation in vitro will deserve their own funding mechanisms and include additional expert collaborators to explore how the protease enzymatic reactions and other factors may be involved in Alzheimer’s disease. Future questions will require answers including whether the identified aggregate prone peptide is present in human brain, what properties of the peptide drive its aggregation or inhibition propensity, explore how other PTM may affect the aggregation or inhibition propensity, comparison of the resulting tau protein core structure to known human disease tauopathy structures, and differential expression and pathway analysis within cells expressing peptides of interest.

Year End Progress Summary:
From the proteolytic cleavage map sites along the longest isoform of human brain tau protein, we chose 90 different peptides resultant from the nineteen known and other yet to be discovered proteases. We started with the shorter peptides to maximize the number of peptides that could be tested with pilot study funding. One challenge encountered was an unknown delay in the setup of the funding account here at ASU. As soon as the funds were made available in October 2022, the 90 tau-derived peptides were ordered to be synthesized and received over several months from GenScript commercial peptide synthesis services with greater than 98% purity.

Aim 1 - The thioflavin analysis shows that in this group of 90 peptides, some fragments of tau protein can form spontaneous β-sheet aggregate structures in vitro while many others do not in 37C reactions of less than 72 hours. We found that when some peptides were mixed with full-length tau along with an aggregation inducer, the peptide enhanced the aggregation process. Although some peptides were able to aggregate spontaneously alone and/or enhance the aggregation of full-length tau with inducer, there were no peptides in this initial set of 90 peptides that acted alone as an inducer of full-length tau aggregation. However, we did identify two peptides which inhibited the aggregation of full-length tau when mixed with aggregation inducer. As a result, we are preparing a grant proposal submission to NIH to extend characterization of these peptide tau aggregation inhibitors and their associated protease pathways in cellular and animal models as potential therapeutic targets to use in neurodegenerative tauopathies.

Aim 2 – Transmission electron microscopy is used to check that the aggregates are in the form of filamentous structures like that seen in Alzheimer’s disease and other tauopathic neurodegenerative diseases. Some peptide aggregates form small non-filamentous aggregate-like structures while others are filamentous. A grant proposal was submitted to NIH/NIA to continue this study and resulted in a competitive score well within the payline. Funding is anticipated Summer 2023.
Alzheimer’s Disease Research Center (ADRC) Internal Scientific Advisory Committee (ISAC) support. Jeffrey Kordower, PhD. Arizona State University; Arizona Alzheimer’s Consortium.

**Specific Aims:**
1. To provide administrative ISAC support to Dr. Jeffrey Kordower, the interim chair of the ISAC during Dr. Carol Barnes’ 2022-2023 sabbatical.
2. To perform grant application management for the ADRC’s Developmental and Pilot Grant programs.

**Background and Significance:**
Our ADRC has implemented an effective program for the solicitation, competitive review, and monitoring of an NIA-sponsored two-year ($60K/year) Developmental project, a state-sponsored two-year Developmental project and several one-year state-sponsored Pilot Project grants each year. Management of activities to support these grant programs were performed by Dr. Winnie Liang, under the purview of Dr. Jeffrey Kordower (ASU). Dr. Liang is versed in grant processes as a result of over 10 years of experience in grant writing and running a research lab, and also has over three years of dedicated experience in scientific operational support. Dr. Liang coordinated the distribution of Requests for Funding Proposals, receipt of all applications, management and identification of external reviewers, organization and collation of reviews, supported ISAC review of applications, communication of funding decisions, and management of the distribution of reviewer honorariums.

**Year End Progress Summary:**
This year, our ADRC received 21 Developmental Grant applications from five institutions, including ASU, BAI, Mayo Clinic AZ, Midwestern, and UA, and 18 Pilot Grant applications from seven institutions, including ASU, UA, BNI, BAI-Tucson, BNI, and Mayo Clinic AZ. Grant reviews were performed by 42 external reviewers for the Developmental Grant, and 36 reviewers for the Pilot Grant. The ISAC Developmental Project review meeting occurred on February 24, 2023, and the Pilot Project review meeting occurred on April 25, 2023.

For the NIA-sponsored Developmental project, funding was recommended to Dr. Qi Wang (ASU), and for the state-sponsored Developmental projects, funding was recommended to six researchers, including Dr. Ying-Hui Chou (UA), Dr’s Aaron Guest and Allie Peckham (ASU), Dr. Oana Dumitrascu (Mayo Clinic AZ), Dr. Emily Edmonds (BAI-Tucson), and Dr. Candace Lewis (ASU). For the Pilot Grant program, funding was recommended for five investigators, including Dr. Zonghui Ding (Mayo Clinic AZ), Dr. Josiane Fernandes da Silva (UA), Dr. Elizabeth Hull (Midwestern), Dr. Eleni Panagiotou (ASU), and Dr. Justin Snider (UA).
BANNER ALZHEIMER’S INSTITUTE
PROJECT PROGRESS REPORTS
Specific Aims:
Aim 1: To identify distinct subgroups of cognitively normal (CN) and MCI within the AAC participant sample using a cluster analysis of baseline neuropsychological data, and to compare resulting subgroups on baseline characteristics, including demographic variables and available AD biomarkers. Hypothesis 1a: Multiple subgroups of MCI will be identified, including those with single-domain impairments (e.g., amnestic, dysexecutive), and those with multi-domain impairments. In addition, multiple CN groups will be identified, including one with above-average cognitive performance, and one with average performance. Hypothesis 1b: Race/ethnicity will differ between cluster-derived groups, with a greater number of non-white participants falling into the MCI subgroups. Hypothesis 1c: The multi-domain MCI group(s) will have a lower education level, and higher rates of apolipoprotein E (APOE) ε4 and AD biomarker positivity relative to less impaired subgroups. The above-average CN group will have a higher education level, and lower rates of APOE ε4 and AD biomarker positivity relative to the average CN group.

Aim 2: To assign neuropsychological diagnoses at an individual level by classifying CN, Obj-SCD, or MCI, and examine baseline characteristics. Hypothesis 2a: Race/ethnicity will differ across the cognitive continuum, with a greater number of non-white participants falling into the Obj-SCD and MCI subgroups relative to the CN group. Hypothesis 2b: Obj-SCD participants will be older, have a lower education level, and will be more likely to report subjective cognitive complaints relative to the CN group. Hypothesis 2c: Prevalence of APOE ε4 and AD biomarker positivity will increase across the continuum (CN<Obj-SCD<MCI).

Aim 3: To examine discrepancies between neuropsychological diagnoses and conventional classification methods (e.g., consensus diagnoses). Hypothesis 3a: Participants classified as CN by conventional methods but MCI by neuropsychological methods will show a higher rate of non-amnestic impairments relative to those classified as MCI by both methods, and a higher rate of racial/ethnic diversity relative to those classified as CN by both methods. Hypothesis 3b: Participants classified as MCI by conventional methods but CN by neuropsychological methods will have lower CDR scores and higher rates of subjective complaints and depressive symptoms relative to those classified as CN by both methods.

Background and Significance:
Early and accurate diagnosis is key for identifying individuals who are at risk for progression to AD for the purpose of early intervention or enrollment in clinical trials aimed at modifying the disease process. Despite the widespread use of conventional criteria for amnestic MCI, there are a number of limitations, including reliance on subjective report, minimal cognitive testing, and clinical judgment. By applying statistical techniques such as cluster analysis, previous studies have identified considerable heterogeneity in MCI samples diagnosed using conventional methods with respect to cognitive and biomarker profiles.

Another method of diagnosis that is utilized by research studies, including Alzheimer's Disease Research Centers (ADRCs), is a “consensus” diagnosis, in which a team of experts use subjective
and objective assessment to arrive at a diagnostic impression. Similar limitations apply to this method, including the necessity of clinical judgment to make a diagnosis, which can vary across clinicians, timepoints, and sites, thus limiting standardization.

In addition to the use of statistical methods (e.g., cluster analysis) for identifying MCI, another method is through the application of neuropsychological criteria for MCI at an individual level. Our actuarial neuropsychological criteria have been shown to produce MCI samples with stronger associations between cognition, CSF biomarkers, hippocampal volume, and stroke risk compared to conventional MCI criteria. We also developed criteria that employ sensitive and reliable neuropsychological tests to define “subtle cognitive decline” (SCD), a feature of “preclinical AD.” Our objectively-defined SCD (Obj-SCD) classifications are associated with future amyloid accumulation, neurodegeneration, and progression to MCI/AD.

A limitation of previous studies is that they were conducted in samples that were largely white. Thus, less is known about the utility of data-driven approaches to define cognitive diagnoses in more diverse samples. This is of critical importance given increased prevalence rates of dementia in minoritized populations. The identification of more precise classifications of prodromal AD is consistent with the field’s movement toward a precision medicine approach to healthcare, which focuses on individualized risk stratification.

**Preliminary Data:**
We applied our data-driven methods to neuropsychological data from 738 non-demented ADRC participants and identified two cognitively normal groups and three MCI subtypes. Progression to dementia over an average of 6 years differed across MCI subtypes. Our data-driven methods outperformed consensus diagnoses in capturing individuals who had abnormal biomarkers, progressed to dementia, or had AD pathology at autopsy.

In a preliminary study looking at differences across race, we examined neuropsychological vs. consensus-based diagnoses in Black vs. White older adults in the National Alzheimer’s Coordinating Center (NACC) cohort. Results showed that, relative to the White sample, Black participants had nearly double the percentage of participants with a neuropsychological diagnosis of MCI despite a consensus diagnosis of CN.

**Experimental Designs and Methods:**
We will conduct a secondary data analysis of data from AAC participants. All participants will have met inclusion/exclusion criteria of the AAC. For this project, additional inclusion criteria are: (1) completion of neuropsychological battery at baseline, and (2) no diagnosis of dementia at baseline. If analyses are underpowered, data from the larger NACC database will be utilized. The neuropsychological measures that will be examined cover five cognitive domains (memory, attention, executive function, language, visuospatial). Raw scores will be transformed into demographically-adjusted z-scores. **Aim 1:** Z-scores will be entered into a hierarchical cluster analysis. Analysis of variance (ANOVA) and chi-square will examine group differences in age, sex, education, race/ethnicity, APOE ε4, and biomarker positivity. **Aim 2:** Participants will be diagnostically reclassified as CN, Obj-SCD, or MCI based on their neuropsychological scores. Diagnostic groups will be compared on demographic and biomarker variables. **Aim 3:** Discrepancies between conventional and neuropsychological diagnostic methods will be examined by comparing discrepant groups to consistent groups.
**Proposed One-Year and Long-Term Outcomes:**
One-year outcomes will include reclassifying AAC participants using neuropsychological methods and characterizing groups on baseline characteristics. Pilot data generated from this project will be instrumental for future grant applications aimed at using longitudinal data to improve the detection of early cognitive changes in those at risk for dementia in diverse samples. Specific aims will include (1) refinement of our methods to improve the detection and staging of prodromal dementia in non-white populations, (2) determining whether cognitive classifications are predictive of future biomarker status, longitudinal clinical outcome, and neuropathological findings, and (3) examining how changes in neuropsychological performance over time relate to longitudinal biomarker changes and risk for progression to MCI/dementia.

**Year End Progress Summary:**
We conducted analyses focused on the larger NACC dataset in order to increase the overall sample size. For Aims 1 and 2, we reclassified participants into subgroups of cognitively normal and MCI using data-driven neuropsychological methods. Cluster analysis was performed with baseline neuropsychological test data from participants age 50+ (mean=71.6 years) without dementia in the NACC Uniform Data Set (UDS) (n=26,255). Results revealed five distinct neuropsychological subgroups: (1) **Optimal CN** (oCN; 13.2%) with above-average to average cognition in all domains; (2) **Typical CN** (tCN; 28.0%) with average cognition across domains; (3) **Amnestic MCI** (aMCI; 25.3%) with isolated low memory performance; (4) **Mixed MCI-Mild** (mMCI-Mild; 20.4%) with low performance across domains; and (5) **Mixed MCI-Severe** (mMCI-Severe; 13.0%) with more severe multi-domain impairment and significant executive dysfunction.

The most impaired subtype, Mixed MCI-Severe, was the oldest and had the fewest years of education. The proportion of non-White participants was lowest in the oCN group and increased across the declining cognitive continuum, with the exception of similar proportions in the tCN and aMCI groups. The proportion of Hispanic participants also increased across the groups. The oCN group had the fewest number of APOE ε4 carriers, followed by the tCN group, followed by the three MCI groups which did not differ. The **extent of cognitive impairment across the CN and MCI groups was related to risk of progression to a diagnosis of dementia.** Survival analyses revealed significant differences across all five groups ($p<.001$); with mMCI-Severe showing the highest rate of progression (mMCI-Severe > mMCI-Mild > aMCI > tCN, > oCN).

We also explored subtle cognitive decline by restricting our sample to only those participants classified as “normal cognition” by NACC’s consensus diagnosis (n=16,005). Cluster analysis in this subsample revealed five subgroups: (1) **High-All** (16.7%) with above average performance across domains; (2) **Low-Attention/Working Memory** (Low-WM; 22.1%) with low scores in verbal attention and working memory; (3) **Low-Memory** (36.3%) with low immediate and delayed verbal memory; (4) **Amnestic MCI** (aMCI; 16.7%) with impaired memory; and (5) **Non-amnestic MCI** (naMCI; 8.3%) with impaired processing speed, executive functioning, and language.

The naMCI group was significantly older and had less education than the other subgroups. The proportion of non-White and Hispanic participants was lowest in the High-All group and increased across the five groups. The aMCI group had a higher proportion of APOE ε4 carriers than the High-All, Low-WM, and Low-Memory groups. **Across the “normal cognition” groups, the extent and pattern of cognitive weaknesses was predictive of progression to MCI/dementia** (naMCI > aMCI > Low-WM = Low-Memory > High-All). Importantly, the finding that progression rates did not differ between the subgroups with weaknesses in attention/working memory versus weaknesses in memory emphasizes that there are different initial presentations.
For **Aim 3**, results showed that our neuropsychological methods classified a greater number of MCI cases than the NACC consensus approach. Our approach also outperformed the consensus approach by providing more precise information about risk for future progression. Consensus diagnoses closely corresponded to CDR scores which may explain the considerable discrepancy between diagnostic methods. Additionally, we identified NACC “normal cognition” participants whose performance was categorized as MCI by the cluster analysis; these participants were at increased risk of progression but were missed by the consensus approach.

**A manuscript with these results is currently under review at Alzheimer’s & Dementia.** Pilot data generated from this project will be included in a **NIH R01 grant application** aimed at examining the utility of our neuropsychological classifications vs. consensus diagnoses, and their relationship to plasma biomarkers, across multiple ADRCs with broad racial/ethnic representation. This application was planned for the summer of 2023; however, submission has been delayed until late 2023, per guidance of the program officer. The overarching goal of this work is to determine which cognitive phenotypes, biomarkers, and other risk factors are most predictive of clinical outcome.

**References:**
The role of alcohol in progression to mild cognitive impairment and dementia: Planning for a biomarker study. Pallavi Joshi, DO, MA, Yinhua Chen, Yi Su, PhD, Ganesh Gopalakrishna, Mentor: Eric M Reiman, MD. Banner Alzheimer’s Institute; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: To characterize the relationship between reported alcohol use and progression from no cognitive impairment to MCI.

Aim 2: To characterize the relationship between reported alcohol use and progression from MCI to dementia.

Aim 3: Set the stage for a grant application to characterize the impact of reported alcohol use on clinical and AD biomarker progression in a much larger cohort of persons with or without plasma ptau evidence of AD.

Background and Significance:
With 55 million people worldwide suffering from dementia and 139 million expected by 2050, there is a pressing need to identify risk factors that prevent or delay its onset. Mild cognitive impairment (MCI) is considered the clinical stage before dementia characterized by cognitive impairment without significant functional decline. Progression to dementia in people with MCI (PDM) is conservatively estimated between 5-10% per year. There is a critical need to identify those at high imminent risk of clinical progression.

Intervening during preclinical AD, before significant neuronal damage has occurred, is more likely to modify the disease course. It is crucial to identify modifiable risk factors and their neuronal impact during the preclinical stage. Alcohol use is a risk factor for dementia with high potential for early identification and intervention. Despite low prevalence of substance abuse, there is a trend of increasing alcohol use among older adults. The 2019 National Survey on Drug Use and Health (NSDUH) found that 5.6 million (10.7%) adults aged 65 years and older engaged in past-month binge alcohol use, and an estimated 1.5 million (2.8%) engaged in past-month heavy alcohol use. Chronic, heavy alcohol use is associated with increased risk of dementia. However, several aspects of the effect of alcohol use on cognition are unclear. First, some studies suggest a nonlinear dose relationship between alcohol consumption and progression to dementia from MCI (PDM) whereby modest alcohol intake (≤ 12.5 g/day) was associated with a reduced risk of dementia, while heavy drinking (≥ 23 drinks/week or ≥ 38 g/day) increases the risk; other studies found that alcohol use (>14 drinks/week) is associated with higher risk of PDM. Second, consensus is lacking on how alcohol use among cognitively unimpaired adults affects progression to MCI. Some studies found that people drinking no alcohol and those drinking >1 time per month were both twice as likely to have MCI as those who drank infrequently, whereas other studies found no significant association between any amount of alcohol intake and MCI. Third, self-report is the typical method of assessment for alcohol use and is inherently susceptible to underreporting and heterogeneity of quantity.

Low amounts of ethanol was protective against Aβ synaptotoxicity in hippocampal neurons in previous cell studies. However, alcohol exposure was found to exacerbate Aβ pathology in mouse models. A cross sectional study found increased CSF p-tau/Aβ42 and tTau/Aβ42 in cognitively unimpaired adults who consumed alcohol ≥1 times/week compared to those who consumed...
alcohol <1 times/week. Brain imaging studies of older adults who consume alcohol have yielded inconsistent results. Some studies found that moderate alcohol consumption in cognitively unimpaired older adults was associated with reduced brain volume, increased ventricle size, grey matter atrophy, reduced frontal and parietal grey matter density, whereas others found a larger total brain volume in older adults who consume light to moderate amounts of alcohol.

Little is known about the impact of alcohol use on CU MCI, MCI dementia, and A/T/N biomarker progression in persons with and without biomarker evidence of AD. The primary purpose of this small pilot study is to explore the association between alcohol exposure and progression in cognitively unimpaired adults and those with MCI and start planning for a larger, longer and more comprehensive study in cohorts with available blood samples, supporting the use of emerging BBBMs to address our over-arching questions (Aim 3).

**Preliminary Data:**
NACC data was filtered for individuals over age 55 years with initial diagnosis of MCI and CU with at least 3 years of follow up data. Individuals with an initial diagnosis of dementia were excluded. Alcohol use was selected for data asking about alcohol use within the past 3 months (ALCOCCAS variable) and frequency of alcohol use (ALCFREQ) which are only available in the initial UDS 3 questionnaire (implemented in 2015). 1348 distinct individuals had a baseline diagnosis of CU. Of these, 373 (27.6%) reported no alcohol use and 975 (72.3%) reported alcohol use within the past 3 months. 510 individuals had a baseline diagnosis of MCI. Of these, 160 (31.3%) reported no alcohol use and 350 (68.6%) reported alcohol use within the past 3 months.

**Experimental Designs and Methods:**
For aims 1 and 2: Within CU and MCI and given our hypothesis based on the literature, we will consider the use of the Cox’s proportional hazard model and Kaplan-Meier survival analysis to assess the progression odd-ratio and time to conversion (survival time) differences between the alcohol users and non-users as the primary statistical method, and simple Chi-square test to secondarily examine prevalence differences. In performing these analyses, statistical inference will aim to test the monotonic trend assuming the risk ranking as infrequent use<no use<frequent use in terms of the conversion time and conversion prevalence. To be conservative, however, we will use two-tailed p=0.05 and adjust for multiple comparisons. We will account for effects of several covariates - age, gender, education and presence or absence of the APOE4 allele in the general linear model.

**Proposed One-Year and Long-Term Outcomes:**
Baseline data will be acquired in the first half of the one year study period. Statistical analysis and development of abstracts, presentations and manuscripts will be in the second half of the one-year study period. Data from this pilot study will inform the feasibility, design, and size of a larger, longer term study looking at the impact of alcohol on clinical progression to dementia and the trends in BBBM over time to validate use of BBBM as a minimally invasive diagnostic tool in cognitively unimpaired individuals.

**Year End Progress Summary:**
NACC data was initially filtered for individuals over age 65 years with initial diagnosis of MCI and CU with 84 months of follow up data. Individuals with an initial diagnosis of dementia were excluded. Initial alcohol use variables were defined based on the NACC database descriptors (nonuser, infrequent use, moderate use, heavy use). In the initial analysis, the difference between these alcohol use groups is not significant. The cox model showed that heavy users/moderate users have a difference compared with nonusers (p=0.0976/p=0.0849), and no difference
between infrequent user with non-user. Being an infrequent alcohol user increased the hazard by a factor of 0.8556 compared with non-users.

We subsequently refined our search by reducing the alcohol frequency groups to 1) none/infrequent: CU = 520, MCI = 153; and 2) moderate/heavy: CU = 916, MCI = 229. Data was controlled for age, sex, education, APOE4 status, and ethnicity (Hispanic vs not). We also did a head-to-head comparison of alcohol use by none/infreq vs moderate/heavy in cognitively unimpaired vs impaired (MCI and AD) groups. There was no significant difference in alcohol use in CU and MCI impaired groups at baseline level. After controlling age, sex, education, APOE4 and Hispanic(yes/no), the cox model output showed no difference when we without adding covariates (results in ppt). Moderate use of alcohol was not more protective in the CU group and more harmful in the MCI group. There was a slight trend for more alcohol associated with less survival from MCI and the opposite for survival from dementia.

A limitation of the field of substance use research is that self-report is the typical method of assessment for alcohol use and is susceptible to underreporting and heterogeneity of quantity. The NACC database includes frequency of alcohol use, but not quantity, quantity per drinking episode, or type or concentration of alcohol use. However, BBBMs have the potential to differentiate between the impact of AD and the effect of alcohol on clinical progression to dementia in high-scale studies. To confirm the value of these measures as markers of preclinical disease progression, determine how early they start to increase in MCI and dementia, and define their role as outcomes for prevention studies, we need larger and more inclusive research cohorts, available longitudinal data, and available blood samples. We examined the NACC ADRC biomarker dataset for feasibility of available BBBMs. Initial diagnosis were CU=1493 or MCI=536. Of these, CU=100 and MCI=23 had at least 1 CSF ptau result and CU=222 and MCI =76 had at least 1 plasma NCRAD sample. The biospecimen did not include all visit numbers but the majority seemed to be done at a follow up visit (visit # > 1). We also considered the ADNI dataset. However, it does not include any alcohol use variables; the only alcohol related questions are at the screening visit to exclude anyone with a substance use disorder. Based on this limitation, despite the potential of the ADNI dataset for legacy BBBMs, we did not consider the ADNI dataset to be helpful in confirming or extending our specific research question. However, the ADNI dataset does have extensive data on amyloid PET and hippocampal volume analyses which could inform neuroimaging correlates of alcohol related neurocognitive progression.

The results of this project were accepted for a poster presentation at the upcoming Alzheimer’s Association International Conference in July 2023. We have also submitted the poster for presentation at the Arizona Alzheimer’s Consortium Annual Meeting in September 2023.
Alzheimer’s Prevention Registry and its GeneMatch Program. Jessica B. Langbaum, PhD, Eric M. Reiman, MD, Pierre N. Tariot, MD, Nellie High, Cassandra Ochoa, David Gordon, Hayley Salata, Banner Alzheimer’s Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: To increase enrollment into the Alzheimer’s Prevention Registry and its GeneMatch program, particularly within Arizona.

Aim 2: To increase the number of study opportunities available to Alzheimer’s Prevention Registry members and GeneMatch participants, particularly within Arizona, by expanding a pilot test a program to help promote studies led by Arizona ADRC and/or AAC researchers.

Aim 3: To provide initial metrics of success at connecting Alzheimer’s Prevention Registry and GeneMatch members with study opportunities, particularly within Arizona.

Background and Significance:
The suffering caused by Alzheimer’s disease (AD) remains one of the greatest unmet medical needs of our times. Interventions that delay onset even by 1 or 2 years would have a major public health impact(1). Considerable effort, attention and funding has been placed on accelerating efforts to prevent and treat the disease, requiring an unprecedented number of healthy older adults to step forward and participate. Enrollment and retention of participants to fill these trials is considered to be the biggest challenges researchers face. Current processes are generally inefficient, contributing to the expense and duration of trials. In the US, recent reviews show that 85-90% of all studies have delays in recruitment and enrollment(2), with 30% under-enrolling and only 7% of sites enrolling the projected number of participants in their originally stated timelines(3). Delayed or inefficient recruitment has scientific, financial, and ethical consequences(4). Moreover, even when trials do meet their enrollment goals, individuals from diverse populations, particularly Black/African Americans and Hispanics/Latinos, are often underrepresented due to a multitude of reasons including mistrust and insufficient dissemination of information. As the field of AD shifts emphasis from recruiting symptomatic patients for treatment studies toward recruiting cognitively unimpaired healthy adults for prevention trials, it is imperative that we understand how to effectively and efficiently recruit, engage and retain participants, with particular attention to recognizing the needs of underrepresented diverse populations. The Banner Alzheimer’s Institute launched the web-based Alzheimer’s Prevention Registry (www.endALZnow.org) in 2012 as a mechanism to keep the general public informed about the latest news in Alzheimer’s prevention research and notify them as study opportunities become available in their communities. The Registry is intended to be a resource to the entire scientific community, helping researchers quickly and efficiently enroll participants into Alzheimer’s prevention related studies(5). In 2015, we launched GeneMatch, a program of the APR. GeneMatch is a novel, trial-independent research enrollment program designed to recruit and refer cognitively healthy adults to AD prevention studies based in part on their APOE test results (NCT02564692)(6).

Preliminary Data, Experimental Design and Methods:
As of April 2022, more than 375,000 individuals have joined the Registry. Most members have provided some additional demographic information, but the actual number varies from question to question. To achieve Aim 1, we will work to expand Registry and GeneMatch enrollment in
Arizona through community outreach efforts, promotion on social media, and other advertising methods as appropriate. For each strategy/tactic, we will track its success. Concerted efforts will be made to increase the enrollment of individuals from underrepresented populations, particularly of individuals who identify as Hispanic/Latino and Black/African American. To achieve Aim 2, we will work with Arizona ADRC and AAC researchers to promote their studies to APR (and if appropriate, GeneMatch) members, with a particular emphasis on promoting pilot studies (for which the results will be used to support a future grant application) and studies led by junior investigators or researchers new to the AD field. We will develop a “scholarship” for these researchers to waive or substantially reduce the normal listing fees associated with promoting studies to APR / GeneMatch members. We will track the number of Arizona-based researchers who apply for and use our recruitment services. To achieve Aim 3, we will provide initial metrics of success at connecting Registry and GeneMatch members with study opportunities, particularly within Arizona. We will track referral and enrollment numbers and time to fill sites’ enrollment goals to assess the ability of the recruitment programs to accelerate enrollment.

**Proposed One-Year and Long-Term Outcomes:**
Results from this effort will help demonstrate the effectiveness of the Registry and its GeneMatch program at helping studies meet their enrollment goals. In addition, results will be submitted for publication in peer-reviewed journals and presented at scientific meetings. Lastly, data and findings will be used to inform future goals of the Registry. We will continue to seek additional external, non-state funding from NIH, industry and philanthropic organizations to support our efforts to expand the Registry and study the “science of recruitment” leveraging the Registry.

**Year End Progress Summary:**
As of June 2023, over 391,000 individuals have joined the Registry, of whom 29,482 reside in Arizona. During the funding period we used a mixture of online advertising (e.g., Banner ads on websites), social media advertising (e.g., Facebook), and mailings to increase enrollment in the Registry and GeneMatch, with a particular focus in Arizona. Social media advertisements were the most successful at enrolling new members. Most Registry members have provided some additional demographic information, but the actual number varies from question to question. Based those who provided additional demographic information, members are predominantly women (75%), report a family history of dementia (54%) (12% are unsure and 14% prefer not to answer) and self-report not having a diagnosis of cognitive impairment (94%). Most members do not provide their race and ethnicity. We are in the process of revising the Registry website with the hope that more members will provide their demographic information, including race and ethnicity. The Registry email newsletters are well-received, with an average open rate of 34%, and unique click rate of 9.47% 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 36.5% and unique click rate of 7.2%. As of June 2023, the Registry has helped 170 studies with their recruitment needs and is currently assisting with recruitment for 34 studies, including 11 Arizona-based studies. As of June 2023, 109,256 have joined GeneMatch, of whom 9,477 live in Arizona. GeneMatch participants are predominately woman (70%), have a mean age of 69 years. As of June 2023 GeneMatch has helped recruit for 19 studies, including 9 studies led by Arizona investigators with several other being multisite studies with AAC partner institutions serving as performance sites. During the past year, we had 5 Arizona ADRC / AAC researchers / studies submit requests for low to no-cost assistance with their participant recruitment needs. Together the Registry and GeneMatch have referred/invited 19,784 potential participants to Arizona-based studies during the July 1, 2022-June 30, 2023 funding period.

In 2019 we received a 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. 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 form underrepresented racial and ethnic groups in AD-focused registries and studies. In August 2021 we received a R33 grant from the NIA (R33AG070604-01A1; Optimizing research infrastructure of registries to accelerate participant recruitment into Alzheimer’s-focused studies) which will greatly improve the website functionality of both the Registry and its GeneMatch program for both members and researchers who use the programs for their recruitment needs.

Several manuscripts based on data collected from the R01 program were published or accepted for publication during the funding period. We published results from 60 semi-structured interviews among Black, Hispanic, and White adults ages 49-79 years to identify underlying beliefs associated with signing up for a registry related to brain health research studies.(7) Here we found very few racial, ethnic, or sex group differences in underlying beliefs. Overall participants were most concerned that if they were to join a registry, they would be asked to participate in experimental studies. Most reported that advancing science was a positive belief about joining a registry. Barriers to enrollment focused on logistical concerns related to joining (e.g., using a computer to enroll). Building off this work, we published results from a national, online survey of 1501 adults ages 50-80, oversampling for Black and Hispanic respondents, assessing intention to join a generic “brain health” registry in the next 30 days (on a scale of 1 to 7, with 1 being the lowest) and to join a registry that required completing specific tasks.(8). Intention to join a registry was low (mean 3.48, SD 1.77) and lower than intention to join a registry that required specific tasks. Intention was greatest for registries requiring completing surveys (M 4.70, SD 1.77), and lowest for registries that required providing a family member’s contact information (M = 3.90, SD 1.93) and those requiring a DNA sample (M = 3.87, SD 1.93). In general, there were few differences between racial, ethnic, or sex groups in overall intention to join a registry. The differences that did exist were primarily between White females and Black females, and in each instance, White females expressed higher intention than Black females. There were also few differences in mean intentions between those reporting a family history of AD and those who did not. Those with a family history were more willing to join a registry that required giving a blood sample or getting a brain scan. Together the results suggest there is general uncertainty about what a registry is, its purpose, and/or the concept of “brain health.” We are currently building off these results, using the Reasoned Action Approach, to develop evidence-based outreach messages describing a registry and required tasks with the goal increasing diversity of enrollees. We also published two companion manuscripts based on data from the R43 program during the funding period. The first paper presents data from four focus groups and an online survey which explored barriers and facilitators to signing up for an AD participant recruitment registry, with an emphasis on the needs of Black and Hispanic adults.(9). Barriers to joining a registry with a mobile device included complex or multistep enrollment processes, beliefs that studies are primarily for people with a diagnosis or specific disease (as opposed to adults without cognitive impairment) and confusion about how studies can prevent AD. The focus groups also revealed that Black participants expressed more hesitation than Hispanics in joining the registry due to greater distrust in government and scientific community. We built off these results to develop and evaluate the usability of a prototype mobile-first participant recruitment registry for AD studies.(10). Other manuscripts detailing findings from the R01 and R43 grants are under review or are in various stages of preparation for submission. Efforts are underway to build off the data collected in the R01 program to submit a R01 grant application to the NIA in 2024 focused on developing
evidence-based messages to increase enrollment of minoritized individuals into AD-related clinical trials.

References:
Alzheimer’s Prevention Initiative and Arizona Alzheimer’s Disease Research Center. 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; Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 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, analyze trial data, prepare for trial data and sample sharing, and plan for future trials in the kindred.
Aim 2: To support efforts to analyze data and samples and share trial data and samples from the recently discontinued API Generation Study 1 and Generation Study 2 trials
Aim 3: To support efforts to conduct a preclinical AD trial of gantenerumab in cognitively unimpaired adults with elevated brain amyloid and the associated ancillary studies
Aim 4: To plan and secure funding for other API led preclinical treatment trials programs/surrogate marker development programs in cognitively unimpaired individuals who are at risk for ADAD or LOAD.
Aim 5: To continue to support registries designed to assist with participant recruitment, including efforts to increase participant diversity and bolster registry infrastructure.
Aim 6: To continue to support the Arizona Alzheimer’s Disease Research Center (ADRC), particularly the Administrative Core and ORE Core, which have provided the foundation for API efforts.

Background and Significance:
Alzheimer’s disease (AD) is the most common form of dementia. This devastating illness takes a significant toll on clinically affected persons and family caregivers, and will take an overwhelming financial toll on society. Results from observational studies suggest that the pathophysiological process of AD begins years, if not decades, before the diagnosis of clinical dementia. It is possible that at least some therapeutic interventions, particularly those that target amyloid pathology need to be started before the clinical onset of AD, when there is already extensive neuropathology, in order to exert their maximum effects. We and others have shown how biomarkers could be used to detect and track the progression of AD, including in ADAD mutation carriers, providing a foundation for use in evaluating AD-modifying treatments(1-3). In May 2012, BAI was awarded a 5-year grant from the NIH to support a preclinical treatment trial of crenezumab in 300 PSEN1 E280A kindred members in Colombia; a second 5-year NIH R01 grant was awarded in April 2017 to complete the 5-year trial, add tau PET to the trial at 30- and 60-month visits, and implement the data and sample sharing program. In September 2013, BAI was awarded a $33.2 million grant from the NIH to support a preclinical treatment trial of two anti-amyloid therapies from Novartis, an active immunotherapy (CAD106) and an BACE inhibitor (umibecestat), in a trial in approximately 1,300 APOE4 HM ages 60-75. In 2017, Novartis, Amgen and Banner announced the API Generation Study 2, a study of umibecestat in approximately 2,000 APOE4 carriers ages 60-75 (HMs and HTs with elevated brain amyloid). Recruitment in the Generation Program and treatment with umibecestat was terminated in July 2019 after an early signal of mild worsening in some measures of cognitive function with umibecestat. Participants were followed off treatment to examine whether the effects observed are reversible. Efforts are underway to anonymize the trial data for sharing with scientific community and transfer biological samples to NCRAD for sharing. In 2018, API and A4 leaders were awarded a grant from the NIA to help support a
proposed prevention trial of an anti-amyloid therapy in cognitively unimpaired adults with elevated brain amyloid. The grant also included an aim to develop a program evaluating self-directed disclosure of amyloid and APOE results to participants during screening compared to provider mediated disclosure. In May 2012, we launched a web-based Alzheimer’s Prevention Registry to keep individuals informed about the latest news in Alzheimer’s prevention research and to notify them as prevention studies become available in their communities(5). In November 2015, we launched the GeneMatch, a program of the Alzheimer’s Prevention Registry, which allows individuals to submit a sample of DNA for APOE genotyping, the results from which are used in part to help match people to studies(6). To date, >375,000 have joined the Registry and >90,000 have joined GeneMatch. In September 2019, BAI was awarded a R01 grant from the NIH to study the science of recruitment of registries to increase diversity of participant recruitment. In August 2021, BAI was awarded an R33 grant to bolster the infrastructure of our API registries to better meet the needs of both members and researchers who use the programs to assist with their recruitment needs. In September 2021, we were awarded a grant from the NIA for the Arizona Alzheimer’s Disease Research Center (ADRC); BAI leaders have leadership roles in the ADRC Administrative Core and ORE Core. The API program has capitalized and benefited from the infrastructure, resources, and data from the ADRC.

Preliminary Data, Experimental Design 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 data and samples after the trial is completed in 2022. For Aim 2, we will work with our Novartis and academic colleagues to analyze data and samples from the Generation Program and to implement a data and sample sharing program, following the “Collaboration for Alzheimer’s Prevention” (CAP) data and sample sharing principles(20). To accomplish Aim 3, we will continue to work with our A4 and Roche colleagues to develop plans for a prevention trial with gantenerumab and associated ancillary studies, aiming to begin enrollment in the ancillary studies by end of 2022. To accomplish Aim 4, API leadership will continue conversations with pharma companies regarding other potential prevention trials for ADAD or LOAD. To accomplish Aim 5, we will continue to continue to support API-led registries designed to assist with participant recruitment, including efforts to increase participant diversity and bolster registry infrastructure. To accomplish Aim 6, we will continue to support the Arizona Alzheimer’s Disease Research Center (ADRC), particularly the Administrative Core and ORE Core, which have provided the foundation for API efforts.

Proposed One-Year and Long-Term Outcomes:
For Aim 1, we anticipate presenting initial results from the API ADAD trial at scientific conferences, will prepare manuscripts for submission, determine next steps for the trial following the clinical readout expected later in 2022, and prepare for trial data and sample sharing. For Aim 2, Banner will work with Novartis and Amgen to analyze trial data and samples, prepare manuscripts for publication, and launch the trial data and sample sharing program following CAP principles. For Aim 3, we will work with our colleagues from A4 and Roche to finalize the collaboration agreement and begin enrollment in the ancillary studies, ideally by end of 2022. To accomplish Aim 4, we will continue to engage in discussions with pharma companies with the goal of finalizing plans for the next trial in the Colombian kindred by early 2023. To accomplish Aim 5, we will analyze initial data from the Registry science R01 grant, prepare manuscripts for submission to peer-reviewed journals, develop evidence-based messaging to increase diversity among registry enrollees, and complete the first phase of the infrastructure improvement detailed in the R33 grant. To accomplish Aim 6, we will continue to serve as leaders in the Arizona ADRC and meet its stated
goals in the next budget year. 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:**
For **Aim 1**, we presented clinical and biomarker data from the API ADAD Trial at AAIC 2022 and CTAD 2022. The primary publication describing the results was submitted to NEJM in June 2023. Efforts are underway to meet the original stated goal of sharing all trial data and remaining biological samples with the scientific community within 18 months after trial completion. Banner and GNA submitted a R01 grant to the NIA in June 2023 for the next trial in Colombia.

For **Aim 2**, we published a manuscript describing the efforts to recruit, screen, and enroll participants into the API Generation Program (21). Manuscripts describing data from the CAD106 and CNP520 programs are currently under peer review. A manuscript describing the impact of APOE and amyloid disclosure among Generation Program participants is currently being prepared for submission to a journal. Generation Program data and samples are available for request by members of the scientific community.

For **Aim 3**, following the announcement by Roche to discontinue the development of gantenerumab and the SKYLINE program, we pivoted to developing plans with Eli Lilly to collaborate on the longitudinal, observational study and randomized trial of disclosure modalities. Efforts are underway to finalize the study protocols and begin enrollment in late 2023 or early 2024.

For **Aim 4**, we engaged with several different pharma companies to develop plans for the next trial in Colombia and submitted our grant to the NIA to support the conduct of this trial. We proposed a two-part clinical trial in 200 cognitively unimpaired and mildly impaired PSEN1 mutation carriers and 40 placebo-treated non-carriers from the Colombian kindred. In Part 1, carriers will receive up to 18 months of a plaque-clearing antibody (PCA) treatment (exemplar: donanemab from Eli Lilly), permitting us to compare the magnitude of Aβ PET and plasma pTau reductions in this ADAD kindred to that observed in trials of the same drug in Aβ+ mildly impaired LOAD patients and cognitively unimpaired older adults. In Part 2, carriers will be randomized to receive 1) continued PCA treatment, 2) an oral gamma secretase modulator (GSM) treatment (exemplar: RG6289 from Roche) with the potential to minimize the re-accumulation of Aβ aggregates in a complementary, potentially less expensive, and more scalable way, 3) combined PCA/GSM treatment, and 4) placebo treatment for 18 months. This seamless, double-blind, placebo-controlled, double-dummy study of a PCA and a GSM in cognitively unimpaired and MCI/mild AD PSEN1 E280A mutation carriers will efficiently address a number of key questions including (1) determining the efficacy of a PCA in reducing brain amyloid levels in ADAD; (2) examining the relative efficacy of combination treatment following PCA treatment versus PCA monotherapy versus GSM monotherapy versus placebo to further lower or maintain low brain amyloid levels as well as on downstream biomarkers; (3) estimate how long placebo-treated mutation carriers remain amyloid negative following PCA-induced amyloid clearance; (4) provide a foundation for understanding the longer term clinical impact of the interventions leveraging the Colombian API Registry; and (5) provide invaluable data and samples for the field. In addition, we continue to make great progress in the effort to find and support the accelerated approval of the intravenous Aβ PCA therapy donanemab in cognitively unimpaired older adults with plasma pTau217 biomarker evidence of Aβ plaques in partnership with Eli Lilly. With the recent demonstration of the treatment’s clinical benefit and biomarker changes in the early clinical stages of AD, we are cautiously optimistic about our chances to demonstrate the treatment’s efficacy and support its approval as early as 2025. We are also exploring ways in which to demonstrate and
support the efficacy of a second-generation subcutaneous PCA in cognitively unimpaired persons with and without plasma pTau217 biomarker evidence of Aβ plaques (i.e., in the secondary and primary prevention of AD) as early as 2027.

For **Aim 5**, we continued to enroll new members into the Alzheimer’s Prevention Registry and its GeneMatch program, use the registries to assist with recruitment into studies in and outside of Arizona, and publish from our efforts to understand facilitators and barriers to joining a registry, particularly for minoritized individuals (22-25).

For **Aim 6**, we continue to leverage learnings from the API program, applying them to the Arizona ADRC. For instance, we are leveraging API learnings from the Registry and GeneMatch, applying them to development of the new ADRC website and related outreach/recruitment materials. We are also leveraging learnings from various API-led APOE and amyloid risk disclosure programs and will be applying those to our ADRC’s efforts to develop a return of results program that is a new requirement in the new ADRC Funding Opportunity Announcement (FOA) that we will apply under in 2025.

**References:**


Enhancements to a centralized data management system for the Arizona Alzheimer’s Disease Research Center (ADRC), Brain and Body Donation Program (BBDP), and APOE Biomarker Core. Don Saner, MS, Ricardo Amador, MS, Robert Bauer, BS, Matthew Huentelman, PhD, Thomas Beach, MD, Richard J. Caselli MD, Eric M. Reiman, MD, David Coon PhD, Banner Alzheimer’s Institute; University of Arizona; Arizona State University; Mayo Clinic Arizona; Banner Sun Health Research Institute; Translational Genomics Research Institute; Barrow Neurological Institute; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: Work closely with ADRC Outreach, Recruitment, and Engagement Core (ORE) and Clinical Core to implement reporting that includes additional key time points: 1) When a visit has occurred, 2) When data are uploaded to the National Alzheimer’s Coordinating Center (NACC) and 3) When data are finalized in NACC.

Aim 2: Continue work with BSHRI to adopt REDCap as an Electronic Data Capture (EDC) tool for a subset of their Clinical Core participants, and create a new export feature that enables the export of data to csv files for participants enrolled in the BBDP.

Aim 3: Modify existing online reports to include ADRC/BIFB imaging (MRI and PET) submission to SCAN and biospecimen collections sent to NCRAD as well as tracking availability of blood based biomarkers.

Aim 4: Assist with projects requiring data from our long standing BBDP, which leverages a SQL server backend with an MS Access front end and begin the construction of a Data Warehouse from these data.

Background and Significance:
The Arizona Alzheimer’s Consortium supports three longitudinal research programs that are internationally recognized for their productivity, impact, and value to researchers inside and outside of Arizona in the scientific fight against Alzheimer’s Disease (AD), Parkinson’s Disease (PD), and related disorders, and the study of normal brain aging. These programs include common data elements, are administered through separate data management programs, and could provide even greater value under a common data management program that is optimized to fulfill the programs’ common and complementary research goals.

1. With support from the National Institute on Aging (NIA), the Arizona ADRC Clinical Core is the nation’s first NIA-sponsored AD Center with multiple clinical core sites (including those at Mayo Clinic Arizona, BSHRI, UA, BNI, and BAI). The Core provides annual assessments in ~500 research participants with AD, related disorders, and cognitively unimpaired older adults; it includes individuals who are enrolled in BSHRI’s BBDP, cognitively unimpaired individuals with two, one, and no copies of the APOE4 allele (the major genetic risk factor for AD), members from Arizona’s understudied Latino and Native Indian communities, and other clinically affected and unaffected research participants; and it provides a shared resource of participants and data for researchers to generate new findings, publications, and grants.

2. The BBDP includes >800 annually assessed research participants from the ADRC, the National Institute for Neurological Disorders (NINDS)-supported National Brain and Tissue Resource for PD (NBTR-PD), and other longitudinally assessments from older adults who consent to brain donation after they die, neuropathological data, and exceptionally high quality
brain and body tissues from >1,500 expired BBDP participants. It has been the world’s leading resource of neuropathology data and brain and other body tissue samples for AD, PD, and other neurodegenerative disease researchers around the world, has contributed to hundreds of research publications and grants, and continues to make major contributions to the study of AD, PD, related disorders, and brain aging.

3. With support from the NIA, the state of Arizona, Mayo Clinic and BAI, the Arizona APOE Biomarker Core provides a longitudinal cohort of research participants and data with two, one, and no copies of the APOE4 gene, reflecting three levels of genetic risk for AD, including a sub-set of subjects with extensive brain imaging and other biomarker data. This program has made pioneering contributions to the conceptualization of “preclinical AD,” established a foundation for the Alzheimer’s Prevention Initiative (API) and the accelerated evaluation of prevention therapies, and includes an invaluable resource of data and samples to help researchers detect and track the earliest biomarker and cognitive changes associated with AD, contribute to the understanding of genetic and non-genetic risk factors, develop data analysis techniques with improved power to detect and track AD and evaluate promising but unproven AD prevention therapies. Consortium researchers lead other valuable longitudinal research programs, which despite fewer common data elements, may benefit from either a shared data management program and/or mechanisms to find other relevant data in the future.

**Preliminary Data, Experimental Design and Methods:**
We have a robust collection of online reports that were developed to monitor enrollment based on finalized packets in NACC; however, with the increased enrollment targets for minorities in our various NIA funded studies, we have realized the need to capture visit data near real time. We have expanded our REDCap Header Information Form to capture completed visit information including visit date, coordinator, race, and ethnicity. We will leverage this information to include new time points in our reporting (visit date, site, race, and ethnicity) when the data is initially uploaded to NACC and when it is finalized on NACC. During the past year, our team has assisted Dr. Robert Alexander with his AARC funded project investigating participants who experience a rapid decline from Alzheimer’s disease. Dr. Alexander’s project leveraged data from the BBDP and was an opportunity for our team to better understand the data structure and nuances of the data, which we believe will be valuable in supporting other researchers and beginning the construction of a Data Warehouse from these data.

As the consortium continues to focus on meeting enrollment targets for our NIA funded trials, and with new, successful enrollment strategies to increase Hispanic and Native American enrollment, it is imperative that we capture and report visit data in near real time. This is reflected in our modified workflow in figure 1.

**Figure 1:** Showing the workflow from visit to pack finalization.

Step two in the diagram is new and will enable us to report on visits that have occurred well in advance of being present at the DCC, uploaded to NACC with error/alert correction, and finalization. In addition to modifying our reports to include earlier time points, our new protocols have additional biospecimen collections including blood and CSF as well as MRI and PET imaging. A subset of these biospecimens will have blood based biomarker assays performed on them and we will need to track these in our updated reporting.
A subset of participants recruited into the Clinical Core from BSHRI have their visits tracked in REDCap and we are actively working with the BSHRI team to make changes to REDCap, including a recently developed scheduling module, to accommodate workflows that are unique to BSHRI. We will build a data export function into our portal that will benefit the BBDP in two ways: 1) participants that are co-enrolled at BSHRI in the Clinical Core and the BBDP will be able to have their finalized NACC data downloaded and incorporated into other operational databases and 2) participants enrolled in the BBDP at sites other than BSHRI, the BBDP will be able to download UDS data on autopsied participants in a CSV format for import into their databases. Currently this data is transferred in PDF and manually transcribed into BSHRI databases.

During the past year we have been working with data from the BBDP program to support Dr. Alexander’s AARC funded project investigating rapid declines in Alzheimer’s patients, which has given our team a better understanding of how these data are currently structured. There is interest from the consortium to make these data more structured to support analyses. In the coming year, we would like to continue to work with researchers to support projects utilizing the BBDP and also begin to use some Data Warehousing methodologies to model the data in a way that makes it easier to analyze. We will utilize Banner’s enterprise data warehouse solution, Teradata, for this effort, leaving the source data in the BBDP MSAccess/SQL server untouched, but authoring Extract, Transform, and Load (ETL) to populate the Teradata database. The Data Warehouse will initially include the following domains: Neuropathology, Neurocognitive testing, Movement testing, Uniform Data Set, Demographics and Genetic (APOE) information. We will continue to work with investigators while constructing the database to drive use cases and work with domain experts in the BBDP program to ensure proper interpretation of the data.

**Proposed One-Year and Long-Term Outcomes:**

By capturing and reporting data at earlier timepoints in our UDS finalization workflow, we will be able to provide more valuable information for the Clinical Core, ORE Core and other sites to ensure we are meeting enrollment targets, including Under Represented Groups. e.g. Native American and Hispanic populations (Note that active Native American outreached has been paused due to data sovereignty issues). We will continue to partner with BSHRI operations and clinical staff to tailor our REDCap project to accommodate their workflow with the possibility of providing new features to other sites (such as the recently implemented scheduling system) and provide export tools from our central database of UDS data to better support the BBDP programs by reducing and/or eliminating duplicative data entry. With our newly awarded ADRC, APOE, and continuing Brain Imaging and Fluid Biomarkers (BIFB) Core, there are new datapoints from Biospecimen collection and analysis and expanded imaging sessions that need to be tracked and reported. This includes tracking of images uploaded to SCAN as well as the somewhat complex reporting on which funding sources are used for image acquisition (recent request for monthly report from Dr. Gene Alexander, PI for the BIFB). The data collected from the BBDP program contains a rich, valuable source of longitudinal data that we propose to leverage to create a new Data Warehouse by authoring ETL code and leveraging Data Warehousing methodologies to organize the data in a more analytic friendly format.

**Year End Progress Summary:**

During the past funding period we have focused on creating enrollment reports that include data from packets earlier in the workflow to better understand what is in progress versus what has been uploaded to NACC. We attended and presented these reports at Outreach, Recruitment and Engagement (ORE) Core meetings (figure 2). Additionally, we added these data to the individual site reports in our central reporting web site to both inform sites of their visit volume and identify when participants are overdue for visits. As in previous years we disseminated information on our data and tools through several pathways including 1) presenting two posters at the fall AAC Scientific conference at ASU in the fall of 2022; 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.

![Clinical Core Active](image)

**Clinical Core Active**

Redcap=Data entry started, not uploaded to NACC.

Working=Uploaded to NACC, not finalized, pending error correction.

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<th>White Hispanic</th>
<th>NW Hispanic</th>
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</table>

**Figure 2:** Report presented at ORE meeting showing where packet are in the process

In addition to managing and transmitting data to NACC, we continued to transfer imaging sessions from BAI-T and BAI-P to the national SCAN site. We also completed the transfer of our legacy imaging data to SCAN. An audit was recently conducted for all sites submitting to SCAN and our site had no findings.

The Data Management Team continues to track and reconcile biospecimens stored locally as well as those transferred to the National Centralized Repository for Alzheimer’s and Related Dementias (NCRAD). During the reporting period we assisted with four NCRAD sample requests which are in various stages of completion. We have also been assisting investigators to obtain data from our local ADRC consortium as well as the larger data set from NACC. During the reporting period we assisted with six requests for data in support of research projects.

We have created a request for proposals document for a biospecimen and data storage system that we will be distributing to vendors. This will be a critical component as we track, share and analyze biospecimens for newly arising fluid based biomarkers.
Advanced imaging and data analysis in Alzheimer’s research. Yi Su, PhD, Hillary Protas, PhD, Javad Sohankar, 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, Qi Wang, PhD, Teresa Wu, 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 Aims:
Aim 1: To further develop and validate machine learning (ML) and deep learning (DL) techniques for the investigation of normal/pathological aging and the development of accurate diagnosis/prognosis models.
Aim 2: To develop ML and DL techniques for multi-omics data analysis
Aim 3: Continued development of robust and high throughput image analysis pipelines that allow large scale data analysis.
Aim 4: Service AAC and the broad scientific community through data and analytical tools sharing.

Background and Significance:
AD is a complex disease characterized neuropathologically by extracellular amyloid accumulations and intracellular tangles of hyperphosphorylated tau protein with strong influence from genetic factors [1-3]. Imaging plays an important role in the characterization of AD and related dementia by providing in vivo measurements of amyloid and tau pathologies [4, 5] as well as other AD related changes of the brain such as reduction in glucose metabolism, inflammatory microglia activation, synaptic density changes, and global and regional brain structural changes that can be measured and monitored in vivo using either PET [6-8] or magnetic resonance imaging (MRI) [9-13]. With the development of sequencing and bioinformatics techniques in recent years, we are also gaining substantial understanding of the genetic underpinning of this disease and the complex genotype-to-phenotype relationships [2, 14]. The ever-expanding imaging and multi-omics datasets call for the development of advanced analytical approaches that can leverage these datasets to improve our understanding of AD and ADRD and facilitate the development of effective treatment and prevention strategies. The Computational Image Analysis program at BAI and our collaborators have a long history of developing advanced statistical and analytical methodologies to advance AD and neuroscience research [15-23]. In this project, our team will continue these efforts in the directions outlined by the four aims.

Experimental Designs and Methods:
Aim 1: a) We will further investigate the use of ML and DL techniques for age prediction based on imaging data to better characterize both normal and pathological aging; 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 prediction of disease progression and differential diagnosis models based on imaging data.

Aim 2: We will further develop and apply ML/DL techniques to the analysis of multi-omics dataset to better characterize the underlying molecular mechanism of AD pathogenesis and progression and examine the quantitative phenotype-genotype relationship that can help establish personalized models of disease progression.

Aim 3: 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 4**: We will work closely with the DMSC core of Arizona ADRC and facilitate the sharing of the derivative imaging data our lab generated through our integrated and standardized pipelines from multiple cohorts including ADNI, Arizona APOE, and Arizona ADRC.

**Proposed One-Year and Long-Term Outcomes:**
In the upcoming year, for Aim 1, we anticipate generating at least one peer reviewed publication and the necessary preliminary data to help secure next phase of funding for our ongoing collaborative STTR project. For Aim 2, we anticipate at least one manuscript and preliminary data for future grant proposals. For Aim 3, we will continue our imaging analysis methodology and pipeline development efforts and continue to generate high quality image analysis results for local and publicly accessible cohorts. For Aim 4, we will provide regular data release of image analysis results from our ongoing analysis 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**, with complementary support from RF1AG073424, R01AG069453, P30AG072980, R42AG053149, in collaboration with Dr. Teresa Wu’s team at ASU, we assembled and processed a large set of imaging scans (15000+ MR, 7500+ PET) and compiled the matching data from multiple cohorts including ADNI, AIBL, NACC, OASIS, NIH APOE, Arizona ADRC to continue our effort of development and application of ML/AI techniques in AD and ADRD research. Leveraging this dataset, we previously trained a deep learning (DL) model that can estimate brain biological age based on T1-weighted MRI data and demonstrated that leveraging the predicted biological age and a patient’s chronological age with a high level of accuracy. We later further demonstrated that the difference between the model predicted brain biological age and chronological age ($\Delta_{age}$) increased along the AD continuum: NL (-1.2yrs) < NL-MCI (-0.7yrs) < MCIs (-0.3yrs) < MCI-AD (0.7yrs) < AD (1.5yrs) controlling for sex, education, and APOE4 gene dose ($F=11.24$, $p<0.0001$) (presented at AAIC 2022). Continue this line of work, we recently further applied this model to the data from the Colombia kindred, the world’s largest autosomal dominant AD kindred with a PSEN1 mutation. We found the age prediction model is able to differentiate PSEN1 carriers from noncarriers, and the two group diverge in the predicted age difference at an age of 44, about the same age when PSEN1 carriers become cognitively impaired. We are also currently exploring the same model in a Native American cohort with additional support from U54MD000507. We also recognized that DL based regression models often lead to systematic biases associated with regression to the mean (RTM), including overestimation of brain age in younger persons and underestimation in older persons. Hence, we recently transform the task of predicting age as a continuous variable to predicting probabilities of discrete age values where age is discretized to closest integer values, i.e. reformulating the age prediction task as a classification problem. With the classification model, the mean absolute error in age prediction improved from 3.76 to 2.41 and R2 improved from 0.93 to 0.96 same test set when compared to regression model. We also observe significant decrease in systematic bias using the classification model - for younger (age<30) and older (age>70) subsets, average $\Delta_{age}$ improved from 3.17 to 0.2, and from -2.49 to -0.97 respectively. This work will be presented at the upcoming AAIC 2023 conference. In a related collaboration with Dr. Jing Li’s team at Georgia Tech with complementary support from R42AG053149, we further develop ML/AI techniques for early diagnosis and prediction of AD progression using imaging data. A high-dimensional (HD) incomplete-modality transfer learning
(IMTL) method was developed using ADNI T1MRI, FDG-PET, and amyloid PET data. To handle high-dimensional features, we employed feature screening to remove noise features, performed modality-wise partial least squares (PLS) to condense remaining features into principal components (PCs), and used correlation test to select PCs. To jointly train the 4 ML prediction models, IMTL was used, which is a generative model that uses expectation-maximization (EM) in joint parameter estimation to facilitate transfer learning. To account for sample imbalance in training, the Synthetic Minority Over-sampling Technique (SMOTE) was used. When the model is used to identify MCI to AD converters, the AUCs by HD-IMTL were 0.802, 0.840, 0.868, and 0.880 for sub-cohorts with MRI, MRI+FDG, MRI+amyloid, and MRI+FDG+amyloid, respectively. The AUCs by existing methods were lower, with ranges of 0.749-0.793, 0.769-0.826, 0.816-0.863, and 0.832-0.868. This work will be presented at AAIC 2023. An extension of this work titled “Uncertainty-driven modality selection for data-efficient prediction of Alzheimer’s Disease” has also recently been published in IIE Transactions on Healthcare Systems Engineering.

For **Aim 2**, in collaboration with Drs. Qi Wang and Teresa Wu’s teams at ASU, we apply cutting-edge machine learning methods to the bulk tissue and single nucleus gene expression data collected from multiple clinical cohorts of AD, for better elucidating the dysregulated gene network in a cell-type specific fashion, to obtain new insights into the disease etiology and possibly, to identify novel drug targets. Built upon our preliminary work, we aim to 1). Identify gene networks implicated in AD from the snRNAseq data obtained in-house from Banner Brain Bank; 2). Identify gene networks implicated in AD from the bulk and snRNAseq data from the ROSMAP study of the AMP-AD consortium. Dr. Wu’s team is engineering the versatile deep learning framework to decipher gene expression data and interpreting the model to obtain the most salient features contributing to AD, and Dr. Wang’s team works on the bioinformatic analysis of raw RNAseq sequencing data as well as gene network analysis based on the features extracted from deep learning model interpretation. This effort helped Dr. Wang to secure her Arizona ADRC developmental award which will start July 2023 to further expand this effort. In addition, an abstract titled “Interpretable deep learning framework towards understanding molecular changes associated with neuropathology in human brains with Alzheimer’s disease” will be presented at AAIC 2023 to summarize the work as a result of this collaboration which demonstrated the potentials of deep learning methods to multi-omic data to characterize the molecular networks associated with increasingly severe clinical and neuropathological stages of neurodegenerative diseases like AD. This offers the opportunity to discover drug targets and/or biomarkers. Further research is ongoing and a manuscript is in preparation.

For **Aim 3**, we continue to refine our streamlined image analysis pipelines which was used to preprocess the large dataset described in Aim 1. We are also exploring a collaborative effort with Gates Venture to co-develop an integrated and expandable computational platform that improves data analysis efficiency and facilitates data management and sharing to better support ongoing research effort at BAI as well as the broader research community. We anticipate this collaborative effort to start in the second half of 2023.

For **Aim 4**, we continue to work with the DMSC core of Arizona ADRC and facilitate the sharing of the derivative imaging data our lab generated using the pipeline described in Aim 3. We have been working with Dr. Alireza Atri’s team at BSHRI and the clinical core of ADRC to facilitate the incorporation of imaging results into their clinical workflow.
ARIZONA ALZHEIMER’S CONSORTIUM
2022-2023 Scientific Progress Report

Statistical and Neuroimaging Data Science Core resources serving the Consortium members. Yi Su, PhD, Michael Malek-Ahmadi, PhD, Hillary Protas, PhD, Yinghua Chen, MS, Ji Luo, MS, Wendy Lee, MS, Valentina Ghisays, PhD, Gene Alexander, PhD, Rui Chang, PhD, Blake Langlais, MS, Ben Readhead, PhD, Ignazio Piras, Kewei Chen, PhD, Don Saner, MS, Eric M. Reiman, MD. Banner Alzheimer’s Institute; Arizona State University; University of Arizona; Mayo Clinic; Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: 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 (including Biomarker Core and the ADCC BIFB Supplement), ADNI and other projects

Aim 2: Offer comprehensive statistical, image analysis, and training services to investigators and students inside and outside Arizona based on the common interest and their needs.

Background and Significance:
The lack of disease-modifying therapies for AD (1), after a variety of treatment strategies being explored (2), mostly in patients who already have clinical symptoms, emphasizes the importance of intervention in its preclinical stage. The development of effective interventions to prevent or delay the onset of AD requires an in-depth understanding of the underlying mechanisms that lead to neurodegenerative changes, subsequently cognitive decline, and dementia. Such efforts are greatly enhanced by the joint team efforts by the investigators in our Consortium and collaborators inside and outside Arizona, with comprehensive datasets of imaging, fluid biomarkers (blood based especially), cognitive, and clinical measurements from multiple projects. A major local effort is the long running Arizona APOE study, which has collected neuroimaging data from 400+ cognitively unimpaired individuals, with more than 1500/2100 MRI/PET scans that characterize the structural, metabolic, and pathological changes of the brain. Supported by newly awarded NIH funding, our Arizona APOE study will now investigate 6-levels of AD risks related to the varying carriages of APOE e2, 3, or 4 gene doses. Another local effort is led by Alzheimer’s Disease Research Center (ADRC) with biomarker, neuropathology, and clinical cores aimed at acquiring imaging, fluid biomarker, cognitive, and clinical data from ADRC and Brain and Body Donation Program participants. Additionally, ADNI, ADNI-DOD, and several clinical trials, among others, are significant and relevant data sources 1) on which we have relied to inform our sample size estimation for our prevention trials or to develop new methodologies; and 2) to which we provided high quality data services to advance our AD research.

Over the years, the CIAL team has continued to serve as a core resource for imaging and statistical expertise to facilitate AD research and collaboration, with the Arizona Alzheimer’s Consortium providing much needed funding for our analytical team, supplementing the NIH funded ADRC/ADCC Data Management and Statistics Core (DMSC). Our lab helped collaborating investigators perform imaging and statistical analysis using state-of-the-art methodologies developed by our lab and elsewhere. Additionally, various educational training activities partially supported by the State have had great impacts for our young scientists and our colleague and students. The important research and analyses performed through this grant have had lasting impact on the AD field and have generated numerous publications that otherwise would have been impossible, with examples listed in (3-24). 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 and keep supporting the research advancements of our Consortium investigators and those inside and outside Arizona with common research interests.

**Experimental Designs and Methods:**

Aim 1. We will continue our efforts to organize and share systematically high-quality image derived measurements from the Arizona APOE cohort, ADRC Biomarker Core and ADCC BIFB Supplement, 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 data access and imaging and statistical services in working and supporting ADRC DMSC.

**Proposed One-Year and Long-Term Outcomes:**

In the upcoming year, we will continue organizing and curating imaging derived measures and integrate them into our database for our local cohorts and large open-science databases and make them available to collaborators. We will closely work and support ADRC DMSC to provide imaging and especially statistical services to ADRC investigators, and those inside and outside Arizona Alzheimer’s Consortium. We anticipate high quality publications and grant submissions as part of the collaborative effort. In the long term, we anticipate being able to help grow the research portfolio of Consortium investigators through our methodology development, statistical service, and assistance.

**Year End Progress Summary:**

In this project year, CIAL worked closely with the Arizona ADRC DMSC to serve as a core resource for the consortium and local, national, and international investigators. With complementary funding support from the Arizona ADRC DMSC and Biomarker Core in addition to related NIH grants RF1AG073424 and R01AG069453, we continue to process and analyze imaging data from Arizona ADRC, the BI-FB project from the previous Arizona ADCC, and the current ongoing NIH APOE 2.0 project (R01AG069453), 445 T1 weighted MR has been pushed through our streamlined structural MR analysis pipeline, 399 amyloid PET and 391 tau PET scans were pushed through our streamlined PET analysis pipeline. The analysis results were archived in our in-house database and are made available to consortium investigators upon request. With the initiation of our recently funded Tracer Harmonization Project (RF1AG073424), we continue to investigate strategies to improve amyloid PET harmonization techniques leveraging publicly available datasets from the Centiloid Project, and our collaborating partners. This core resource will facilitate the dissemination of methods/models/algorithms developed in RF1AG073424 to investigators upon request and will also incorporating these techniques to generate harmonized PET results from ADRC, BIFB, and NIH APOE projects. In addition to data from local cohorts, we are also processing and analyzing data from public AD/ADRD data archives such as ADNI, NACC, AIBL, and OASIS. These data and results are also made available to local and external collaborators through collaborative research.

With complementary support from the DMSC, our team continue to provide imaging and statistical services to collaborators inside and outside of the Arizona Alzheimer’s Consortium. Representative accomplishments from these efforts are summarized below.

We continued our collaboration with Dr. Caselli and his colleagues at Mayo. In a recent project, we sought to determine whether milder COVID-19 disease in older vulnerable individuals is also
associated with cognitive and behavioral sequelae. Neuropsychological, behavioral, and clinical outcomes before and after contracting COVID-19 disease, were compared in members of two ongoing longitudinal studies, the Arizona APOE Cohort and the national Alzheimer's Disease Research Center (ADRC). 152 APOE and 852 ADRC cohort members, mean age overall roughly 70 years, responded to a survey that indicated 21 APOE and 57 ADRC members had contracted COVID-19 before their ensuing (post-COVID) study visit. The mean interval between test sessions that preceded and followed COVID was 2.2 years and 1.2 years respectively for the APOE and ADRC cohorts. The magnitude of change between the pre and post COVID test sessions did not differ on any neuropsychological measure in either cohort. There was, however, a greater increase in informant reported cognitive change in the APOE cohort (p = 0.018), but this became nonsignificant after correcting for multiple comparisons. Overall members of both cohorts recovered well despite their greater age-related vulnerability to more severe disease. This research was recently published in J. Alzheimers Dis.

In our continued collaboration with Dr. Blair Braden (ASU), we helped with the investigation of relationship between visual/verbal memory and structural brain changes such as hippocampal volume and free-water in adults with autism spectrum disorder. Our preliminary findings in a small middle-age autism sample suggest a key memory brain structure, the hippocampus, may shrink faster over 2-3 years compared with control, and short-term memory may become more challenging for some. Our study suggests vulnerabilities for accelerated long-term visual memory decline, compared to matched NT adults. Further, baseline hippocampal free-water may be a predictor of visual memory change in middle-age and older adults with ASD. These preliminary findings lay the groundwork for future prognostic applications of MRI for cognitive aging in middle-age and older adults with ASD. These studies were recently published in Front Aging Neurosci and Autism Res.

We continued collaboration with Dr. Sydney Schaefer (ASU)'s team providing statistical and image analysis support to better understand the motor function and structural brain change in older adults with and without cognitive impairments. In a sample of 121 older adults, intrasubject standard deviation (ISD) across six trials of a novel upper-extremity motor task was predicted with volumetric regional gray matter and neuropsychological scores using classification and regression tree (CART) analyses. Both gray matter and neuropsychological CART models indicated that motor task ISD was related to cortical regions and cognitive test scores associated with memory, executive function, and visuospatial skills. CART models also accurately distinguished motor task ISD of MCI and probable mild AD from CU. This research was recently published in Exp. Gerontol.

We continue to work with Dr. Yalin Wang’s team at ASU to provide/facilitate access to imaging data, imaging, and statistical analysis expertise to facilitate their development and investigation of advanced MRI analysis techniques to detect structural changes related to and predictive of AD specific pathology. A recent effort was to develop a non-invasive and widely available structural MRI-based framework to quantitatively predict the amyloid and tau measurements. With MRI-based hippocampal multivariate morphometry statistics (MMS) features, a Patch Analysis-based Surface Correntropy-induced Sparse coding and max-pooling (PASCS-MP) method combined with the ridge regression model was applied to allow individual amyloid/tau measure prediction. Experimental results suggest that amyloid/tau measurements predicted with our PASCP-MP representations are closer to the real values than the measures derived from other approaches, such as hippocampal surface area, volume, and shape morphometry features based on spherical harmonics. We also continue to support Dr. Yalin Wang’s effort in seeking NIH funding to support ongoing methodological development for AD research.
We also continue to support many other collaborators inside and outside of the consortium to provide statistical and analytical expertise to facilitate their research and grant proposal development, including Dr. Weise (University Hospital Halle), Dr. Suchy-Dicey (Washington State University), Dr. Quiroz (MGH), Dr. Benzinger (WashU), Dr. Pruzin (BAI-Phoenix) and Dr. Edmonds (BAI-Tucson). With complementary support from the DMSC, our team directly supported/participated in 9 additional research grant applications to provide statistical, image, and data analysis expertise, with 3 of them recently funded. Our Core investigators also led 4 recently awarded NIH/NIA grants and another recent submission to develop novel statistical and data analysis techniques and investigate Alzheimer’s disease and related dementia.
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, 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:
Aim 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.

Aim 2: To support the work of a newly formed American Indian/Native American AD Research Advisory Committee, whose work will help establish policies related to Indigenous Data Sovereignty for our ADRC and affiliated studies.

Aim 3: 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 or not they participated in research studies. In 2022 we paused our efforts to recruit new Native American participants, including pausing our partnership with Medstar's Strong Heart Study site in Phoenix, while we formed an American Indian/Native American AD Research Advisory Committee for our ADRC and affiliated programs. The Committee is tasked with working with Native American Community Leaders to create an Indigenous Data Sovereignty and data sharing plan, after which we could re-open research enrollment to American Indian and Native American individuals interested in participating in the Clinical Core or other studies.

Preliminary Data:
A cumulative 117 Native Americans have been enrolled across the consortium as of April 2023; of those 117, 68 have been included in the NACC database. There are 53 active NA ADRC participants, 6 active NA participants in affiliated studies, and 58 are inactive. There are 39 actively enrolled NA ADRC participants 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 then took place in October 2022 at the Ak-Chin Community in
Maricopa, AZ. The Native American outreach team trained more than 30 professional care providers during this time through virtual programs including a Native American and Alzheimer’s disease toolkit training. As conditions are improving, the outreach team plans to resume in person programming 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 3350 professionals, family caregivers, and community members; 2) 5800 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 reaching 118; 4) 31 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 collaborated with tribal partners, Sunshine Music therapy 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.

In October 2022 we formed an American Indian/Native American AD Research Advisory Committee for our ADRC and affiliated programs. The Committee will be working with Native American Community Leaders to create an Indigenous Data Sovereignty and data sharing plan, after which we could re-open research enrollment to American Indian and Native American individuals interested in participating in the Clinical Core or other studies.

**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. Prior to the October 2022 pause in Native American recruitment of new participants, the 2022-2023 Scientific Project had a proposed aim to continue to recruit Native Americans into the ADRC Core, such that our site was following at least 50 participants. While we were ultimately on track to enroll 75 Native American participants in our clinical core, helping to clarify the generalizability of plasma biomarkers compared to amyloid PET in this under-represented groups, we temporarily halted the enrollment of new participants until we could begin to establish a newly formed American Indian/Native American AD Research Advisory Committee. We now plan to resume enrollment in this previously approved project, while deferring future studies to the review and potential approval of this new committee.

3. Refine methods to reach more Native Americans from youth to elders to raise community awareness by offering quarterly virtual and onsite 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 and resume the 16th annual Native American Conference in Alzheimer’s disease.

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 2022 calendar year, prior to the pause in recruiting new Native American participants, across the consortium, we enrolled 8 new participants. Through the 2022-2023 budget year, 36 initial and follow-up assessments were conducted, no participants were withdrawn, and 1 participant died. We will continue to work with the ADRC Education Core and collaborators from the Strong Heart Study, and our newly formed Native American Research Committee to enroll, retain, and study Native American participants in our in our longitudinal research program in highly productive ways that adhere to Indigenous Data Sovereignty Principles.

**Aim 3:** We have continued to reach Native Americans 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 productive study of Native American research participants.

**Aim 4:** Available research data was used at the annual BAI Native Americans and Alzheimer's disease: Tools for the Care Provider toolkit training and the 16th annual Native American Conference in Alzheimer's disease, in October 2022.

BAI Native American Outreach 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. We have also worked with a community partner, the Inter-Tribal Council of Arizona, Inc. – Area Agency on Aging, Region 8 (Grant ID: 90ADP10077-01-00), to support this development and advancement.
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, PhD, Geidy Serrano, PhD, Thomas Beach, PhD, Kewei Chen, PhD, Michael Malek-Ahmadi, PhD.

Specific Aims:
Aim 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.
Aim 2: Blood collection and biospecimen banking of 30 cc of plasma from study participants to be made available for collaborative research opportunities and for preliminary data investigations for grant applications; and referral and co-enrollment of participants in other cognitive aging and biomarker studies.
Aim 3: 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:
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, facilitates and supports recruitment, dual/co-enrollment and retention of cognitively unimpaired (CU) participants into other impactful studies such as the Brain and Body Donation Program (BBDP). For example, continuing to facilitate and support dual enrollment between LCS and BBDP serves to support continued enrollment of CU elderly participants, particularly the oldest old, into the BBDP, provides critical cross-validation between these programs, and allows additional opportunities for exciting and impactful science to be undertaken in the subset of dually-enrolled participants who are highly characterized by psychometric, biological, clinical, psychosocial, and, ultimately, pathological (autopsy) data. Additionally, as some participants change cognitive-functional status from CU to mild cognitive impairment (MCI) or dementia, or when potential candidates for enrollment (during initial contact or enrollment) are identified with potential MCI or dementia status awareness and referrals (clinical and research) can be facilitated, including referral to other research studies and clinical trials.

Preliminary Data:
The LCS has 502 active participants (enrolled 1,574 since inception). We conduct approximately 45-60 different types of study visits were per month, and new participants are enrolled to mitigate attrition, which is 4.5% per year (annualized over the 15-years; mostly due to death and moving
from AZ). Approximately 70% of participants are female, 311 are ≥80 years of age, 170 are ≥85, 80 are between 90-99, and 4 are 100 years or older. Our publications represent the diversity of LCS research, and of the PI’s research on explicating factors related to cognitive reserve. We had one manuscript from the LCS published (e.g. Melikyan et al. Norms and equivalences for MoCA-30, MoCA-22, and MMSE in the oldest-old. Aging Clin Exp Res. Epub 2021 May 29) 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.

**Experimental Designs and Methods:**

**Aim 1:** Clinical Phenotyping (adapted to COVID-19 measures and restrictions using tele/video 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 tele/video or hybrid formats as needed. To mitigate for attrition, we will continue to enroll 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. 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.

**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 and satisfaction in oldest old.

**Proposed One-Year and Long-Term Outcomes:**

We expect to continue clinical phenotyping of participants; collection, characterization and biobanking of additional plasma samples, and refer and co-enroll LCS participants in impactful cognitive aging and biomarker studies, including BBDP; and also to leverage this expanding rich dataset with biosamples for collaborative projects and funding sources for clinico-biomarker correlations discovery and as a basis for growth opportunities as a major AZ-based biorepository, biomarker instrumentation and integrative bioinformatics center.

**Year End Progress Summary:**

The great progress in FY 2022-23, despite Covid-19 restrictions (mostly impacting specimen collection and enrollment of new participants), is summarized in the table below. We expect to add to this progress by further clinical phenotyping of participants; continuing collection, characterization and biobanking of additional plasma samples (added to samples from >533 participants, and 413 participants ApoE-e4 typed) from newly enrolled and returning participants. In the 2022-2023 funding year, there were a total of 186 referrals from the LCS to other ongoing research studies, including 68 to the BBDP.

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Progress made on **Aim 1**: During the 2022-23 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. Montreal Cognitive Assessment, MoCA, scores $\geq 27$ 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. More than 492 CDRs have been performed in the LCS (excluding those of BBDP co-enrolled participants, N=102). 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 **Aim 2**: Response to requesting LCS participants to opt-in to donate $\sim 30$ cc of plasma for aliquoting, banking of plasma and sending the buffy coat to TGen for ApoE4-typing (per collaboration supported by a previous AARC grant to TGen in 2017-2018 which is now ongoing as part of this project) has been outstanding. We had aimed for $\sim 65\%$ of participants opting in to donate plasma, however, to the credit of the participants, >90% of eligible and available participants have donated a plasma sample. In addition to plasma samples from 533 participants banked so far (including for participants co-enrolled with BBDP), 413 participants have been typed for ApoE-e4 status (86 via co-enrollment with BBDP), and samples for an additional 31 participants have been collected and are pending shipment to TGEN (via batch shipment when $\sim 90$ samples are batched and shipped). More than 533 plasma samples have been banked.

Progress made on **Aim 3**: Dr. Atri collaborated with Dr. Chen to preliminarily explore a variety of ML analyses utilizing BBDP longitudinal cohort data. Application and validation of ML methods is an ongoing aim. We are in the final stages of preparation and submission for publication a research manuscript (led by Dr. Malek-Ahmadi) that supports that affective fluctuations in depressive and anxiety symptomatology can predict cognitive decline in older adults. Using data from 817 cognitively unimpaired participants from the LCS (age range 53-102 years) assessed longitudinally, we measured cognition, depressive, and anxiety symptoms. Intrasubject standard deviation (ISD) was used to quantify year-to-year variability of affective measures. Independent mixed-effects models, adjusted for age, education, and sex, showed that greater variability in depression and anxiety symptomatology was associated with cognitive decline. Exploratory analyses, using combined models to assess for additive versus additive and synergistic effects, showed that only depressive symptom variability was significantly associated with cognitive decline. The interaction of depressive and anxiety symptom variability was not a significant predictor of cognitive decline.

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 2024.
Enhancement of Arizona Alzheimer’s Consortium resource sharing and recruitment.
Alireza Atri, MD, PhD, Thomas Beach, MD, PhD, Danielle Cabral, MD, Parichita 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 of AD and ADRD studies.

Background and Significance:
The Arizona Alzheimer’s Consortium is widely recognized as a model of multi-institutional collaboration in biomedical research. It capitalizes on complementary resources and expertise from different disciplines and organizations to address scientific problems in the most impactful way. They continue to provide a world-leading scientific resource of longitudinal and neuropathological data, brain and body tissues for the study of Alzheimer’s disease (AD), Parkinson’s disease, and related disorders in their Brain and Body Donation Program—and they have begun to incorporate ante-mortem biomarkers and new brain tissue resources to help researchers address their goals with even greater impact.

Preliminary Data:
Not applicable – This is a strategic proposal designed to enhance recruitment, increase collaborations, and ensure sufficient infrastructure for rapid enrollment into AD and Related diseases (ADRD) studies.

Experimental Designs and Methods:
This proposal requests complementary support to enhance ongoing efforts for participant recruitment, data, brain and body tissue collection and resource sharing as part of the Arizona Alzheimer’s Consortium, Arizona 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 Uniform Data Set (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 blood-based biomarkers (BBBM) of AD/ADRD.

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 Drs. Parichita Choudhury, Danielle Goldfarb (aka, Cabral), and Beach and team, we performed over 800 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 236 active ADRC participants. In 2022, BSHRI, as part of the newly NIH(NIA)-funded AZ ADRC (P30 expanded NIH funding mechanism that replaced the AZ ADC), expanded its AZ ADRC roles and funding. This NIH-funded AZ Alzheimer’s Disease Research Center (ADRC) provides a $15.8M grant over 5 years, of which ~$4M is to BSHRI. In January 2023, Dr. Atri assumed the roles of AZ ADRC Associate Director, and Leader of the Clinical Core; while also co-leading the newly formed Biomarker Core. Dr. Beach serves as the Leader of the Neuropathology Core. With these changes, the AZ ADRC Clinical Core (CC) leadership team became centered at BSHRI (was previously at Mayo Clinic Scottsdale), and now includes Dr. Christi Belden for CC neuropsychology and Angela Kuramoto for CC operations, and is supported by Dr. Choudhury. This CC leadership team now leads CC diagnostic consensus conferences and directs strategies, coordination and operations across all AZ ADRC CC sites (Banner Alzheimer’s Institute Phoenix, Banner Alzheimer’s Institute Tucson, Barrow Neurologic Institute, and Mayo Clinic Scottsdale). Over 230 of the 450-550 actively annually followed CC participants (are enroled at BSHRI, and >$300K/year of CC funding will be provided to BSHRI for CC activities).

We met the goals of the $1.3M NIA-sponsored grant for an ADCC Brain Imaging and Fluid Biomarkers (BIFB) Core, aimed at acquiring advanced neuroimaging (brain MRI, amyloid and tau PET scans), blood draws and cerebrospinal fluid (CSF) collection for BSHRI participants. Over the three-year funding period, we completed scanning on 190 participants and 112 lumbar punctures for CSF collection. In 2022, the NIA replaced the completed ADCC supplement by expanding the scope of AZ ADRC to include a Biomarker Core, and ~$160K/year of funding is being provided to BSHRI for Biomarker Core activities. Amyloid and Tau PET scans (for detection of AD-related plaques and tangles) and MRI neuroimaging – 270 (188 PET scans, 82 MRI scans) were obtained between in 2022-23.

Under the direction of Dr. Beach, we provided the neuropathologic diagnosis, processed, stored and distributed postmortem brain tissue, and the Neuropathology Core including 1) adding 77
new participant donors; 2) conducting 1,921 annual assessments in 587 living participants; 3) conducting 81 rapid autopsies with an average time of 3 hours from death to autopsy; 4) making 275 tissue disbursements to researchers in AZ (142 disbursements), other US states 119 disbursements to 21 states) and internationally (13 disbursements to 11 countries); 5) Contributing to >60 publications and more than 60 grant-funded research projects and grant proposals.

Progress on Aim 2: We expanded the reach of the Brain Health Check-In (BHCl) program. This free community service, first piloted in December 2018, allows individuals to schedule or drop-in for a 45-60 minute 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 Drs. Atri and Belden, has provided 838 individuals with free brain health concern status assessments (138 in 2022-23) along with feedback, information, education, resources and referrals. Over 450 participants have been reached for follow up and participant evaluations continue to rate it very highly (4.5-4.7 out of 5.0 ratings for Satisfaction and also for Likely to Recommend).

Our BSHRI Research Trials programs, under the direction of Drs. Atri, Dr. Danielle Goldfarb, and Carolyn Liebsack, RN, made referrals for 681 persons in the 2022-23 period.

Our AD/ADRD diversity, equity and inclusion (DEI) efforts, led by Dr. Goldfarb (Cabral), expanded a partnership with First Institutional Baptist Church (FIBC), a predominantly Black/African American church in Phoenix, provided 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 and health fairs we have reached >600 individuals (~87% African-American, Hispanic, Asian or Native American). For example, our June 3, 2023 FIBCO health fair reached 261 individuals and resulted in 11 BHCl’s in one day. Based on these programs we received a $150,000 diversity grant from the ACTC consortium AHEAD AD prevention study (Drs. Goldfarb and Atri) for an Alzheimer’s prevention nurse navigator to promote greater DEI outreach for AD/ADRD clinical care and research.

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 >500 people in 2022-23; our local/regional continuing education (CE) programs/lectures provided 21 programs to ~1000 participants, including over 200 participants via the BSHRI AD/ADRD updates one-day CE symposium in 4/23; and the Dementia Untangled education and support podcasts (26 podcasts in 2022-23) garnered >55,000 downloads; more info is available at: https://podcasts.apple.com/us/podcast/dementia-untangled/id1558126995).

Finally, supported by a track record of successfully conducting the type of programs that received complementary support by this AAC grant, Drs. Atri, Beach and Serrano, multiple-PI, received funding and began work on a 3-plus-year **Foundation for NIH (FNIH) $2.3+ million grant** (with several hundred thousand dollars as add-ons) 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.

Specific Aims:
AIM 1: Design and implement a survey of academic cognitive disorders center specialists to evaluate knowledge, attitudes towards, proficiency, and availability of ultrasound technology to assist in lumbar punctures (LPs).

AIM 2: Design and implement a participant survey in older adults to evaluate willingness to complete LP with and without the use of ultrasound (Us).

AIM 3: Develop and pilot test Us-LP online educational material for academic cognitive disorders center LP clinicians and develop Us-LP competency assessment measures.

AIM 4: (Exploratory) Following LP clinician training in Us-LP and competency assessment, to explore associations between clinical characteristics, and variables and measures of perception, nature, difficulty, utility, and success between randomly assigned, unblinded LPs performed with Us-LP compared to those without ultrasound (conventional LP) in an ADRD clinic and research population.

Background and Significance:
Given the amount of ADRD-related information obtainable in CSF samples, cost, and availability, LP represents the most promising ADRD diagnostic approach to support biomarker development research and to accurately diagnose AD, including in early stages of disease. CSF analysis provides a unique window into brain pathobiology and allows simultaneous testing for multiple biomarkers of disease and injury, including amyloid and tau species, alpha-synuclein, inflammation, and axonal and synaptic injury.

Our study is the first effort, to our knowledge, aimed to advance Us-LP in ADRD research and care. This proposal seeks to build from our proof-of-concept study of Us-LP which demonstrated that Us-LP is feasible in ADRD research, and suggested that LP clinical researchers were more likely to opted to utilize Us-LP in perceived challenging cases including the most obese, and those oldest and moderately overweight-to-obese. Furthermore, our project uses a portable, hand-held ultrasound transducer connected to a tablet (Philips Lumify system), a widely accessible technology accessible. Such innovation is important to increase global capacity for successful ADRD LP programs, particularly as our understanding of AD progresses to link clinical and biological definitions and stages, and knowledge of AD biomarker status becomes a mainstay in clinical as well as research settings. Furthermore, Us-LP bolsters brain health equity in regions where advanced neuroimaging technology, such as amyloid PET and tau PET, are not readily available or accessible. This project is particularly novel as it aims to illuminate the current capability of Us-LP use in ADRD centers, laying the foundations for a future large, multicenter, randomized controlled trial of Us-LP in ADRD, which has the potential to propel a new standard of care for ADRD LP.

Preliminary Data: The proposed study naturally builds from our proof-of-concept study (Goldfarb 2021) which assessed the feasibility, utility, and tolerability of Us-LP in aging and ADRD research described
here. Following didactic and simulation Us-LP training, four LP clinician-researchers from two ADRC centers implemented Us-LP into their practices. Between August 2019-March 2020, 58 research participants underwent LP with enrollment being halted due to COVID. Clinician-researchers used Us-LP on 37/58 (64%) participants. Compared to conventional landmark-based LP, Us-LP choice was associated with higher/highest BMI and older/oldest age categories. Compared to conventional landmark-based-LP, Us-LP choice was associated with higher/highest BMI and older/oldest age categories. A U-shaped relationship between BMI and age in Us-LP choice was noted. Us-LP was the choice in all who were most obese; in most who were moderately overweight-to-obese; and in all who were oldest and moderately overweight-to-obese. There were no differences between those receiving conventional-LP compared to Us-LP with respect to participant history of chronic pain or headache, prior attitudes about LP, success rate, or post-LP complications. These pilot data indicated that LP clinician-researchers were more likely to use Us-LP in perceived challenging cases including the most obese, and those oldest and moderately overweight-to-obese. More studies are needed to determine if using Us-LP in the ADRD population will improve LP success rates, tolerability, and participant willingness to undergo LP. Improving these factors will accelerate CSF biomarker, aging and ADRD research.

Experimental Designs and Methods:
For **Aim 1**, we will design and implement a survey for cognitive center clinicians to collect information on provider specialty and clinic demographics, experience with LP, Us-LP and any ultrasound use. Using a Likert scale (scores 1-5), we will capture attitudes toward Us-LP, willingness to receive US-LP education, willingness to use Us-LP if appropriately trained. We will also solicit comments regarding opinions on ways to improve LP provider comfort with Us-LP. To create this survey and to inform our approach, we will consider other similar ultrasound-assisted procedure knowledge, attitudes, and skills surveys in the literature. We will disseminate this survey to other ADRC sites, Alzheimer’s Clinical Trial Consortium sites, and other academic ADRC/ADCs (n=35).

For **Aim 2**, we will develop and pilot test ultrasound-assisted LP educational materials for cognitive disorders center providers including online educational materials with pre- and post-tests to evaluate change in knowledge and attitudes toward LP and Us-LP along with acceptability of a Us-LP educational intervention. We will develop and implement Us-LP competency measures.

For **Aim 3**, we will design and implement a cognitive disorders clinic patient/study participant survey to collect data on LP perceptions and attitudes toward LP and ultrasound-assisted LP, using a within-subjects study design.

For **Aim 4 (exploratory)**, using a randomized, non-blinded (participants and clinicians will not be blinded to assignment group), parallel group design, we will evaluate conventional landmark-based LP versus Us-LP attitudes, perceived procedure difficulty (before and after LP), procedural characteristics, and outcomes by six LP clinician researchers at Banner Sun Health Research Institute and Banner Alzheimer’s Institute.

**Proposed One-Year and Long-Term Outcomes:**
One-year outcomes are to: 1.) Develop ADRD LP clinician survey to evaluate and, following IRB approval, disseminate survey electronically and analyze results (target n=35). 2.) Develop and pilot ADRD LP clinician online education/training in Us-LP. 3.) Develop and disseminate LP participant survey. 4.) Begin randomized, unblinded, parallel group trial to evaluate conventional landmark-based LP versus Us-LP in ADRD subjects.
Long-term outcomes are to facilitate successful and equitable ADRD biomarker programs via a multi-site, randomized, single blind trial evaluating the safety and effectiveness of pre-puncture ultrasound assistance for presumed challenging lumbar puncture in Alzheimer’s disease and related dementias with the following aims: 1.) To evaluate the effectiveness of pre-lumbar puncture (LP) ultrasound assistance compared to landmark approach, 2.) To evaluate the safety of pre-puncture ultrasound compared to landmark approach with respect to peri- and post-LP complications, 3.) To explore the ability of pre-puncture ultrasound to improve lumbar puncture participant attitudes toward LP.

Year End Progress Summary:

Aim 1: Design and implement a survey for cognitive center clinicians to collect information on provider specialty and clinic demographics, experience with LP, Us-LP and any ultrasound use. We achieved AIM 1 by creating and completing a RedCAP survey for LP clinicians that was disseminated to the Alzheimer’s Clinical Trials Consortium (ACTC) academic sites. Of the twenty-five respondents, nearly all (94%) conduct LP at academic medical centers, 64% were male, and most (72%) were cognitive/behavioral neurologists. Only 8% have access to ultrasound at their centers. The majority (84%) have never had formal training in ultrasound-assisted LP, 60% are extremely uncomfortable or somewhat uncomfortable conducting ultrasound-assisted LP and 64% do not feel qualified to do so. Despite these findings, 88% totally or partly agreed that Us-LP has potential in challenging ADRD LP related to obesity or chronic back deformities. In ranking the barriers to perform Us-LP, nearly all respondents (96%) rated insufficient knowledge or training in the top three biggest barriers.

For Aim 2, we will develop and pilot test ultrasound-assisted LP educational materials for cognitive disorders center providers including online educational materials with pre- and post-tests to evaluate change in knowledge and attitudes toward LP and Us-LP along with acceptability of a Us-LP educational intervention. In partnership with our education team (Matthew Miller and Kaci Lint) and a professional videographer (Philip Walker), we are in the process of developing an online training module on the use of ultrasound-assisted LP in ADRD. The course content is housed in the online learning platform, Canvas, includes pre- and post-tests, and contains education regarding Us-LP preparation, probe positioning, LP spinal anatomy highlighting challenging anatomical variants, identifying the midline and intervertebral space and marking the location. Upon completion, the Us-LP in ADRD learning module will be publicly accessible online. We will consider various approaches to share this training with the ADRD community including with other ADRC sites, Alzheimer’s Clinical Trial Consortium sites, and relevant academic organization listservs (e.g. AAN Cognitive/Palliative Care Neurology Section, ISTAART, Geriatrics and Primary Care) . As well, we anticipate offering continuing medical education credits which may increase participation.

For Aim 3, we will design and implement a cognitive disorders clinic patient/study participant survey to collect data on LP perceptions and attitudes toward LP and ultrasound-assisted LP, using a within-subjects study design. We have designed the patient/study participant survey to collect demographics, clinical characteristics, LP history, and attitudes toward LP from 150 survey participants. Participants will then be provided a brief description of ultrasound-assisted LP and afterwards asked similar questions about attitudes and perceptions about US-LP and willingness to agree to Us-LP. The survey is currently under IRB review. Upon IRB approval, we plan to disseminate the survey to older adults (n=100) who present at BSHRI for research study visits or for clinic visits. Our research assistant (Brett Post) will approach individuals, explain the purposes of the brief survey, and request their participation. All data will be anonymous, entered into a RedCAP database, and analyzed to evaluate for enhanced perception/attitude of Us-LP compared to conventional LP.
For **Aim 4 (exploratory)**, using a randomized, non-blinded (participants and clinicians will not be blinded to assignment group), parallel group design, we will evaluate conventional landmark-based LP versus Us-LP attitudes, perceived procedure difficulty (before and after LP), procedural characteristics, and outcomes by six LP clinician researchers at Banner Sun Health Research Institute and Banner Alzheimer’s Institute. This aim was planned to be accomplished by the originally proposed two-year period, and we were not able to begin working on this aim within the initial 12 months. Efforts were made to carefully consider whether the aim could be achieved next year, however, due to recent personnel changes, it was determined that this aim will not be able to be completed.

**Challenges encountered:**
While we made good overall progress by achieving AIM 1 and making progress towards AIMS 2 and 3, we also faced challenges by encountering delays related to IRB submission and review of survey materials which set our timeline back by about three months. Despite this challenge, we remained on track to complete the majority of our aims based on the original two-year proposed timeline.

**Future grant applications, publications, collaborations:**
Upon completion of the two-year outcomes, we would be poised to apply for a NIA R01 to develop and conduct the Phase 2 multi-site, randomized, single blind trial using Us-LP compared to conventional LP in pre-puncture planning of presumed challenged ADRD LP cases. Two manuscripts would be prepared (within the 2023 calendar year) respectively describing the results of the ADRD LP clinician survey (completed) and the patient/participant survey (pending). Of note, our grant match funds enabled us to purchase two Philips curvilinear ultrasound probes and tablets to be used by BSHRI and BAI LP clinicians. Previously, our Lumify hand-held ultrasound equipment was loaned from Philips under a research agreement. This capital purchase ensures that both sites have uninterrupted access to Us-LP to increase the safety and success of CSF collection. As LP/CSF will be increasingly needed with AD diagnosis to determine patient eligibility for recently approved disease-modifying treatments (e.g. lecanemab), we continue to partner with Philips to determine if there may be a mechanism for other ADRD academic sites to access their Lumify system outside of a traditional purchase agreement. Regarding collaborations, ten ACTC sites have expressed interest in completing the online Us-LP when available.
Assessing EEG as biomarker of cognitive decline in a clinical-pathologic cohort. Alexander Choi, MD, Kewei Chen PhD, John Caviness MD, Nan Zhang, MSc. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: We will assess the prognostic value of qEEG to predict cognitive decline in pathologically confirmed Parkinson’s Disease vs. other pathologies. We hypothesize that qEEG will add the greatest predictive power to cognitive decline in Parkinson’s relative to other pathologic diagnoses. Furthermore, we hypothesize that the predictive power of qEEG on cognitive decline will be mediated by cortical alpha-synuclein.

Background and Significance:
Cognitive decline has been linked in clinical Parkinson’s disease to a “diffuse malignant phenotype.” It is the goal of this application to explore how defined quantitative / qualitative electroencephalogram (qEEG) measures may correlate with various cognitive assessments among individuals with post-mortem neuropathologic diagnosis enrolled in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) / Brain and Body Donation Program (BBDP). Quantitative EEG (qEEG) utilizes digital recording and software for spectral decomposition to define frequency band amplitude (power), phase and connectivity, and network analysis. Specific features of quantitative EEG (qEEG) that have been related to cognitive impairment include diffuse slowing and increased theta : alpha power. These and other qEEG features may facilitate longitudinal cognitive assessment including predicting dementia in MCI with clinically probable Lewy body subtype.

Preliminary Data:
Quantitative EEG and cognitive decline in Parkinson’s disease – processing outline per Stam et al. EEG file (condition eyes closed, resting at least 1 min.) filtered using standard bandpass filter 130 Hz to remove artifact, re-referenced to Common Average Reference, automatically scanned for artifacts via Bad Blocks’ and ‘Threshold’ that detects large amplitude artifacts related to electrode drift, motion, line noise and blink artifact, and visually scanned to derive a visual rating scale as reported previously by van der Zande et al. 2020 (VRS, described below).

Experimental Designs and Methods:
1. We pulled demographic and pathologic features of annually followed AZSAND/BBDP donors with at least one EEG, post-mortem diagnosis and neuropsychological assessment and testing within 2 years of death (n=236, 594 EEG exams). These donors were pooled with a previously analyzed cohort of 248 donors, 606 exams (Dr. Caviness) for MCI subgroup analysis for larger sample size. The following variables were extracted:
   -demographics (age, sex, education, apolipoprotein E4)
   -pathologic features previously correlated with resting state qEEG as in Caviness et al. 2018 (sum of Lewy body density, Braak stage) and/or cognitive status (volume of deep nuclei infarct, Snowdon et al. 1997)

2. The relative spectral power was derived from CURRY 9 Neuroscan. The online data were collected as previously described (Caviness et al. 2007). A minimum of 1-min. eyes closed seated resting state was recorded with linked mastoid online reference. Offline processing involved common average re-referencing, automated amplitude-based and manual removal of artifactual bad blocks /eyeblinks, and bandpass filtering of 1-30 Hz. The EEG was manually
scanned and scored according to a Visual Rating Scale (VRS, Van der Zande et al. 2020). The power frequency spectrum was exported, using the following bands: Delta 1.5-3.9 Hz theta 4-7.9 Hz alpha 8-12.9 Hz alpha2 10-12.9 Hz Beta 13-30 Hz
The following EEG metrics were analyzed:
- Frontal (alpha+beta)/(theta+delta)
- Parietal (alpha+beta)/(theta+delta) Theta:alpha Delta:alpha
- Relative global spectral power (delta%, theta%, alpha%, alpha 2%, beta%)
- Visual Rating Scale (VRS)

3. Visual Rating Scale (VRS) was calculated manually for each scan:
   - 1 = normal EEG [including benign temporal θ of the elderly]
   - 2 = mildly abnormal [occasional θ, rare delta activity]
   - 3 = moderately abnormal [abundant θ/delta activity, lateralized periodic delta discharges (LPDs), Generalized periodic discharges (GPDs)]

4. We explored the relationship between qEEG measures and cognitive worsening outcomes, defined as both consensus categories and through continuous measures, for each of the AZSAND/BBDP donors
   a. Worsening of consensus clinical diagnostic category (CN, MCI, dementia)
   b. MMSE
   c. Worsening of global Clinical Dementia Rating (CDR-SOB)
   d. Trails Making Test A / B (TMTA, TMTB, time s), auditory-verbal learning test (AVLT), (LTM, STM), Judgment of Line Orientation (JLO). These tests were chosen due to adequate representation in the cohort and prior studies showing correlation to qEEG variables.

The analysis included linear mixed effects modeling, which was univariate for independent variable to screen for EEG variables with the largest effect size for cognitive outcome, which were employed along with demographic and pathology covariates in the multivariate model.

With the long-term goal of defining qEEG as a cognitive biomarker for clinical trial therapeutics, a particular focus of this analysis was on qEEG findings in the MCI sub-group of the cohort (n=77). This was defined as a project that is ongoing with mentoring a pre-medical student under the Banner – ASU Neuroscience Scholars Program (Naren Raghu).

**Proposed One-Year and Long-Term Outcomes:**
The Pilot Grant over 12 months provided funding primarily for direct costs of time allocation with salary support for PI and consultant, EEG software training course and software license to perform the analysis, with objective of assessing the prognostic value of EEG on cognitive worsening and providing training in EEG analysis, clinical research and statistics and career development opportunities for PI.

**Year End Progress Summary:**
There were analyzed 484 donors comprising 1187 EEG exams. Of these, initial analysis began with the 236 donor IDs with neuropsych exam <2 years from death, with 594 exams. The cohort of 236 donors were at last evaluation cognitive normal=93 (39%), MCI=46 (20%), dementia=97 (41%), controlled for covariation of the following:

mean: age at death=86 (63.9-103.7 years) education=15 years APOE3/4=61 (26%), APOE4/4=4 (1.7%) sex (91 female, 39%)

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The cohort included final diagnoses PD (n=105) symptom onset age=70.4, AD n=65 (27.5%), Tauopathy NOS n=56 (23.7%), DLB n=8 (3.4%), VaD n=12 (5.1%), idiopathic Lewy Body Disease n=15 (6.4%), PSP n=20 (8.5%), hippocampal sclerosis n=6 (2.5%), argyrophilic granules n=70 (29.7%)

VRS score of 3 (diffuse or frequent generalized slowing) related to increase in consensus diagnosis cognitive worsening (HR 2.02, CI 1.05-3.87).

Cognitive outcome findings, reported multivariate effect size (SE):
Both increase in relative global theta power%, -0.494 ± 0.15, p=0.001 and VRS (-1.338 ± 0.26, p<0.001) were significantly associated with lower MMSE score, and similar associations seen for JLO (theta -0.584 ± 0.173, p <0.001, VRS -1.05 ± 0.32, p<0.001), also elevations in alpha (0.499 ± 0.116, p<0.001) and beta (0.608 ± 0.236, p=0.011) were associated with higher JLO score.

Increase in theta% -0.382 (± 0.12, p=0.002) and reduction in beta% 0.459 (± 0.16, p=0.005) were significantly associated with lower AVLT STM and LTM scores.

Increase in theta% 4.91(± 1.18, p<0.001) and VRS 9.46 (± 1.96, p<0.001) were significantly associated with longer TMT-A while increase in beta -3.35 (± 1.55, p=0.03) was significantly for shorter TMT-A. Similarly, increasing EEG theta 11.92 (± 2.97, p<0.001) and VRS 24.90 (± 4.99, p<0.001) were significantly associated with longer TMT-B while increasing EEG beta 11.93 (± 3.82, p=0.002) was significantly associated with shorter TMT-B.

CDR-SOB showed significant association for VRS 0.995 (± 0.232, p<0.001), alpha (-2.14 .083 p=0.011) and theta 0.354 (± 0.121 p=0.004).

Delta spectral power showed similar, significant inverse associations with cognitive performance as theta, however with lesser effect sizes. Alpha also showed similar associations across measures as beta, generally with similar effect sizes. Theta:alpha and delta:alpha effect sizes were smaller, and frontal spectral power ratio was not associated with cognitive measures. Parietal spectral power ratio showed high correlation (>0.7) to alpha power and so was excluded from the analysis.

Age showed significant inverse associations with cognitive performance of variable effect size (larger: TMTB 3.5, TMTA, 1.29; smaller: MMSE, AVLT and JLO, –0.1-0.16). Sex showed significant associations with cognitive performance (MMSE 0.78, AVLT 2.25, TMTA -7.8, TMTB - 16.1, CDR-SOB -1.32). Education related to MMSE (0.257 ± 0.095, p=0.007), faster TMT B-A time (-3.37 ± 1.47 p=0.02) and modest association with AVLT 0.176, JLO 0.191, CDR-SOB - 0.078. ApoE4 allele was not significantly associated with any cognitive measure.

Braak stage was inversely significant for cognitive variables (MMSE, AVLT STM and LTM, effect sizes -0.4-0.7), and sum of Lewy Body density score was significantly associated with TMT-A time (0.784 ± 0.164, p<0.001) and TMT-B time (2.29 ± 0.415 p<0.001) and had small inverse effect sizes for MMSE, AVLT, JLO, CDR-SOB -0.06-0.08. Infarct volume of deep nuclei was not significantly related to cognitive measures.

In summary, elevation in spectral theta power and reduction in beta and alpha power were consistently linked to worse cognitive performance across cognitive tests related to executive, memory and visuospatial functioning. The manually performed visual rating scale showed similar associations to cognition as the binned relative spectral power.
**Conclusion:**
Resting stage EEG analysis through simple, semi-automated spectral power output and through a rapid manual visual rating scale each were meaningfully related to cognitive performances measures. EEG shows promise as a cognitive biomarker to avoid bias from learning or ceiling effects for cognitive measures. The Visual Rating Scale also appears to offer real-world clinical utility, as a simple and easy to use measure requiring only the standard EEG presentation software already available in clinical testing centers.

**Subgroup analysis – MCI (N=77):**
A subgroup analysis of donors was performed with consensus diagnosis MCI cross-sectionally, most proximal to death. The following pathologic groups were analyzed: MCI-ADPD (n=9), MCI-PD (n=24), MCI-AD (n=19), MCI-Tau (N=10), MCI-Control (N=15). EEG exam at that time, or closest timepoint were analyzed. The results were consistent with previous findings, viz. that clinically probable MCI-LB showed more diffuse slowing and higher theta:alpha ratio than clinically probable MCI-AD. In this MCI cohort with pathologic confirmation of diagnosis, ADPD and PD groups showed more diffuse slowing and higher theta:alpha ratio than AD, tau and Control MCI. MCI-ADPD > MCI-PD and MCI-AD showed faster progression to dementia than MCI-Tau NOS and MCI-Control.

**Challenges encountered:**
Delays related to software purchase, Banner IT firewall for installing software (also data transfer agreement for EEG data from Mayo Clinic – Scottsdale, but the software ultimately took longest, July – Dec 2022). Technical difficulty using software to export csv / text file to allow for other software analysis, such as mean frequency or graph theory connectivity metrics – this prevented inclusion of additional EEG measures in the analysis, but the core measures based on the rsEEG cognition literature were included.

**Collaboration:**
Aims / preliminary data presented at AAC Annual Meeting 2023 and shared with mentor, Dr. Caviness. Data presented to Clinical Core Meeting June 2023.

**Publication:**
Pending. Draft started, and plan for abstract/poster submission to scientific meetings such as AAC/PSG 2023, AAN/MDS 2024.
Clinical trajectories in Lewy Body Dementia and development of a composite score to predict pathological burden of Lewy bodies. Parichita Choudhury, MD, Nan Zhang, MSc, Kewei Chen, PhD, Geidy Serrano, PhD, Cecilia Tremblay, PhD, Thomas Beach, MD, PhD, Alireza Atri, MD, PhD. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: To clearly define and characterize longitudinal neuropsychological profiles in patients with clinicopathologically confirmed diagnosis of Dementia with Lewy bodies, Parkinson’s Disease Dementia and Alzheimer’s Disease.

Aim 2: To develop a readily interpretable composite score to predict disease burden (as manifest by Unified Lewy body staging system or Lewy body density) based on validated, brief and standardized measures of cognitive function, motor severity, dementia severity, neuropsychiatric severity, and daily function via comparisons of a simple weighted sum and machine learning/artificial neural network (ANN) approaches.

Background and Significance:
Lewy body dementias (LBD), comprised of Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD), share pathophysiological substrates and clinical features, with current diagnostic criteria differentiating the two based on relative timelines of emergence of symptoms.

DLB is characterized by deficits in semantic fluency, attention, and visuospatial construction deficit, whereas AD markers include episodic and recognition memory deficits. However, the affected cognitive domains overlap between both clinically and pathologically defined dementia subtypes and lack diagnostic accuracy. Among Lewy body dementias, there is a dearth of research defining longitudinal evolution of cognition beyond 2 years in patients with autopsy confirmed DLB.

LBDs can present with overlapping prodromal, cognitive dysfunction, motor, autonomic or neuropsychiatric symptoms leading to challenges in diagnosis, management and clinical trial design. Corollary to that, presence of pathological Lewy bodies may not manifest clinical symptoms (such as in incidental LBD or ILBD), indicating latent or preclinical disease stage, or variability in individual response to injury and reserve. Impairment in each domain in LBDs may be inter-dependent, be mediated or moderated by other domains and may not represent direct manifestations of underlying pathology. Some studies suggest that increasing cognitive impairment, neuropsychiatric symptoms and motor impairment correlate with higher stages of Lewy body pathology. A more comprehensive characterization of the clinical trajectories, symptom interaction and associated pathological severity would allow for identification of clinical trial end points and monitoring.

Preliminary Data:
Preliminary data for each group shows a baseline MMSE of 26.3 (PDD), 22.6 (DLB), 22.6 (AD with Lewy bodies) and 25.3 (AD). Except for the PDD group, most participants at baseline visit did not have evidence of parkinsonism. Preliminary linear modelling shows faster decline in AD with Lewy bodies group compared to other groups in domains of memory.
Experimental Design and Methods:

Subject Inclusion/Exclusion Criteria: Cases included in this analysis will span the entire spectrum of Lewy body pathologies in the AZSAND database: Parkinson’s Disease with and without dementia (n=277), Dementia with Lewy Bodies (n=189), Alzheimer’s Disease with Lewy-type synucleinopathy (n=291) and Incidental Lewy body disease (ILBD) (n=134). For Aim 1, cases will be excluded if they have only one neuropsychological evaluation.

Measures of clinical characteristics: In addition to demographic information, we will utilize several scales to explore a unified composite risk score. The following scales will be considered as components of Lewy body score: Mini Mental Status Exam (MMSE), Montreal Cog Assessment (MoCA), Clin Dementia Rating Scale (CDR) glob, CDR-Sum of Boxes (CDR-SB), Neuropsychiatric Inventory quest (NPI-Q), Unified Parkinsons Disease Rating Scale (UPDRS-part 1), Geriatric Depression Scale (GDS), Functional Assessment Screening tool (FAST), Unified Data Set (UDS) Cognitive tests.

Statistical Analysis for cognitive trajectories: Neuropsychological data will be extracted for each group and each test will be grouped according to cognitive domains. Trajectories will be explored by scattered plots initially. We will use mixed models (linear and non-linear) methods to study between group differences, drawing on our previous experience with longitudinal motor trajectories in this cohort. We will co-vary for baseline age, education and baseline MMSE.

Composite score determination
We introduced, validated, and used the composite score approach for our Alzheimer’s Prevention Initiative (API) trials such as the Colombian Autosomal Dominant Alzheimer's Disease (ADAD) trial, and the Generations trials. Using the same composite score construction approach, a composite score will be developed for this project. The sub-set of these tests and the best combination of this test sub-set, in the form of unequal weights, will be determined via exhaustive search optimization numerical procedure (after each measure is converted to the corresponding Z-score to standardize the scales) with higher scores indicating higher symptom intensity. The optimization is to minimize the mean square error (MSE) between the actual and the predicted Lewy body staging or Lewy body density. This procedure combines the feature selection (tests with zero weights are filtered out) and optimization together.

To examine the generalizability of the constructed composite score, we will randomly divide the data as 70% training, 15% validation and 15% for separate testing datasets (with group membership balanced in each). The same cross-validation scheme will also be used for the machine learning approach below. Taking advantage that we have a very complete arsenal of well-established machine learning pipelines in place to explore, we will explore to use relevant vector regression (RVR), and especially the shallow artificial neural network (ANN) with only one or two hidden layers balancing the capacity of adequate, accurate prediction and the interpretability of the results (such as the relative importance of a given individual test score or demographic info). The use of such ANN and RVR is supported by the results we obtained from our own studies, previously. With the appropriate use of shallow ANN (which is contrast to the deep learning neural network such as CNN), we will be able to select important scales/components of scales that either cluster or appear to be most predictive of Lewy body staging or density. In the same cross-validation scheme as described above, the ANN will be trained to minimize the MSE as the loss function.

Proposed One-Year and Long-Term Outcomes:
By July 2023 we expect to have accomplished the following:
1. Create defined clinical data sets including cognitive scales, movement exams and pathological confirmation for different cognitive behavioral syndromes and underlying pathological entities.
2. Delineate predicted cognitive trajectories
3. Submitted at least 2 Abstracts and one peer-reviewed manuscript.
4. Developed preliminary composite risk score

Our Long-term goals are as follows:
1. Further our understanding of composite risk score and its relationship to pathological burden and interaction with co-pathologies.
2. Pilot the utility of a composite score in clinical trial cohort.

Year End Progress Summary:
Aim 1: We have created clinical data sets for Lewy body disorders, that specifically look at motor trajectories, cognitive trajectories, and neuropsychiatric symptoms. Cases from the AZSAND with a cognitive diagnosis of dementia at death and who had at minimum, two neuropsychological evaluations were included. Final neuropathological diagnosis was determined as LBD (neocortical or limbic LB ± AD), ADLB (not meeting distribution and density threshold for neuropathological LBD) and AD pathology only. Using linear mixed modelling we have evaluated predicted cognitive trajectories for these pathological entities for a given baseline MMSE. Baseline MMSE was similar across all pathologic groups. Linear mixed modelling methods showed faster decrease in memory domain scores (decreasing 0.22 units/year – 0.42 units/year faster, p=0.01) in ADLB group compared to other groups. Significantly faster decline was noted in LBD and ADLB group in clock drawing (p<0.001), fluency scores (declining 1.02 unit/year faster p<0.001) compared to AD group. In autopsy confirmed cases, ADLB had an accelerated trajectory of decline in memory tasks, while AD and LBD appeared to have similar trajectories.

These results have been accepted as a poster presentation at Alzheimer’s Association International Conference (AAIC 2023). Further, a manuscript is in preparation.

Concomitantly, the manuscript describing results for Longitudinal motor trajectories in Lewy body disorders (previously described) was accepted to Alzheimer’s and Dementia Journal and is in press.

Neuropsychiatric symptoms (NPS) in Lewy body spectrum were also analyzed for preliminary results and furthering Aim 1. We investigated changes in NPS severity over time using the Neuropsychiatric Inventory-Questionnaire (NPI-Q), comparing neuropathologically defined cohorts of AD (without LB), ADLB, DLB and controls. NPI-Q scores at enrollment were highest in ADLB (7.33 ± 4.85), and higher (p<0.001) than DLB (5.10 ± 3.37), AD (4.54 ± 3.63) and controls (1.78 ± 1.70). At final evaluation, NPI-Q scores were highest in DLB (10.04 ± 6.28), followed by ADLB (8.0 ± 4.68), and ADD (7.61 ± 5.05) when compared to controls (2.78 ± 3.97) (all p<0.001). DLB and AD demonstrated significant increases in NPI-Q severity during follow up (p < 0.001).

These preliminary results were also presented as an oral presentation at the American Academy of Neurology (AAN 2023) and will be presented in poster form at AAIC 2023 and will be submitted to Arizona Alzheimer’s Consortium scientific conference. A manuscript is being prepared.

Aim 2: We have obtained preliminary results on constructing a composite score using several different methods. A total of 234 subjects from AZSAND with pathological presence of Lewy bodies were identified who had their first evaluation when cognitively unimpaired or mild cognitive impairment stages. None of the subjects had all clinical, behavioral or cognitive measures...
completed. To use the available data most efficiently for our preliminary cross-sectional analysis for this project, we adapted the following strategy:

1. Identified subjects whose first and second visits were within 1.5 years from each other. For each measure, we either averaged the two-visit scores for those subjects whose had the tests for both visits, utilized just the not-missing one, or keep as missing if both visits had no value. The 1.5-year cut-off is optimal for current dataset for sample size adequacy and measure stability. It can be adjusted in different datasets.
2. Used only the baseline visit measures for the remaining subjects.
3. Identified those subjects who had missing values for more than 10 tests (also can be adjusted for the same reason as above) and excluded them for subsequent analysis. This is subject-wise cleaning.
4. Eliminated tests which had missing measures for 10 or more subjects. This is test-wise cleaning.

After the data cleaning procedure above, we had 172 subjects with complete scores for 32 out of 46 measures. We used leave-one-out cross-validation (LOOCV) strategy instead of the originally planned random partition (70% training, 15% validation and 15% testing). The LOOCV allows for accurate performance estimation of the model which reduces bias by random selected subset (due to the small sample size).

We first explored composite score construction using the exhaustive search strategy we developed and utilized in our API-ADAD and Generation trials. We varied the number of measures for the composite score (with non-zero coefficients in the weighted linear combination) from 3 to 30. Such constructed composite scores, however, were suboptimal at predicting the unified Lewy body staging or the sum of LB density satisfactorily (the correlation coefficients, R between the constructed scores and each one of the two neuropathological measures were all less than 0.2). We then examined the two ML algorithms as planned and mentioned above. We view these ML algorithms as nonlinear alternatives to the exhaustive search for the construction of the composite score (which is the outputted values of the ML algorithms). The Relevant Vector Regression (RVR) very adequately predicted aggregate Lewy body density pathology using clinical and cognitive measures available (R=0.83 and R squared $R^2 =0.691$, $p<0.00001$). Given the relatively high demand for computational power, we only have preliminary results for the use of Artificial Neural Network (ANN). It also showed a promising prediction with a goodness of fit of the composite score as measures by the correlation coefficient $R=0.723$ and $R^2 =0.527$ ($p=0.00002$).

We hope to submit an Abstract with these results to the Arizona Alzheimer’s Consortium conference, 2023 and AAIC 2024.

Overall progress in LBD research: Ongoing work in Lewy body disease spectrum has led to appointment in Lewy Body Dementia Association’s (LBDA) Clinical Trial Working Group (CTWG) and Professional Education Working Group (PEWG) as early career representative. Additional collaborations with LBDA to disseminate information about DIAMOND Lewy toolkit are underway (symposium abstract submission to American Association of Geriatric Psychiatry Annual Meeting). Finally, we will be applying to join the LBDA Research Centers of Excellence (RCOE) sites, responding to their most recent RFA.
A human brain single-cell suspension resource. Geidy Serrano, PhD, Thomas G. Beach, MD, PhD, Ignazio Piras, PhD, Matthew Huentelman, PhD, Ben Readhead, PhD, John Fryer, PhD. Banner Sun Health Research Institute; Mayo Clinic Arizona; Translational Genomics Research Institute; Arizona State University, Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: To provide the foundation of a shared resource of separated cells to researchers within and outside Arizona.

Aim 2: Phenotypically and biochemically characterize single cells and phenotypically-specified populations of cells from single-cell suspensions created with an optimized standardized method (from Specific Aim 1).

Background and Significance:
Biochemical analysis of human neurodegenerative brain tissue, especially from Alzheimer’s disease (AD) and Parkinson’s disease (PD) patients, has produced much of what is known about these conditions, and has led to the major FDA-approved therapies. The typical approach has been to homogenize whole pieces of brain tissue and separately characterize the proteins, RNA, DNA and other macromolecules within. While this has been sufficient to identify large changes, there is very little ability to identify small changes, or changes in small subsets of cells. Furthermore, neurodegenerative disease often leads to massive losses of the targeted and disease-relevant cells, for example the entorhinal cortex layer II stellate neurons or substantia nigra pigmented neurons. Whole-homogenate analysis of such brain regions can give completely misleading results, as any biochemical constituent that is selectively localized to the depleted cells will appear to be “down-regulated”, whereas in fact it has most likely been lost only as an “innocent bystander.” Also, a relevant loss or increase might be completely missed, if the biochemical entity is found in many cell types, diluting the ‘lost’ signal from the cell of interest, especially if that cell type is uncommon or rare. To effectively investigate the biochemistry of neurodegenerative disease in the brain, with its thousands of different cell types, we must first separate the cells, and study them as phenotypically-defined populations and even as individuals. In recent years, methods have been developed that allow an initial creation of single-cell suspensions from solid tissue followed by analysis of phenotypically-defined cells sorted on the basis of cell-type identifying proteins or RNA expression.

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, 444 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 158 subjects has been used to generate WSDS. On average we are now collecting 10.0 million cells/gram of tissue. Final suspensions are aliquoted for tissue banking in cryopreservative solution and stored at -80°C and for quality control (QC) assessments. We also developed a new protocol that allow us to generate suspension from frozen tissue and performed single nuclei prep
that allowed us to compare whole cell preparation vs nuclei preps. We also gather preliminary data supporting the hypothesis that whole cell provides more complete sequencing information than just single nuclei (Figure 1).

In addition, 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. This past year we promoted the cell core in four different conference and virtual meetings. From those we were able to create collaboration with Dr. Lee’s group in Harvard and Dr. Ishihara from Eisai, both interested in testing their single cell sequencing protocol on our suspensions.

In addition, during this year we concluded the work of three high-profile projects that further established the importance of the general approach and to further awareness of the resource among the neurodegenerative disease scientific community. We have enough primary data that will allow us to publish additional manuscripts before the end of the summer, we will publish on astrocyte on the changes of astrocyte populations in Alzheimer’s Disease (AD), Parkinson’s Disease (PD), progressive supranuclear palsy (PSP) and controls using new approaches to analyze complex data set generated from subjects with multiple pathological diagnosis. In short, to find the correlation between pathology and the differentially expressed genes (DEGs). We chose the higher upregulated/downregulated DEGs obtained from the comparison between PD and control, PSP vs control and AD vs control and independently correlated to pathologies scores common in each disease group. We created composite scores combining plaque and tangle scores. Raw scores of both AD pathologies were converted to Z scores by using the mean and standard deviation, and then z-scores were averaged to form the composite measures. PSP tangle scores, and total Lewy body summation scores were also used to see how PSP and LB
pathology affected the gene dysregulation. Spearman’s correlation method was used to find the correlation between the gene count of DEGs and pathology score.

**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.
2. We are now actively promoting this resource in our website and meetings and have been able to establish collaborations with other scientists from local, national, and international institutions.
3. A new manuscript will be published in the summer, using sorted astrocyte populations.
4. Single nuclei data collected from PSP, AD and controls still need to be further analyze.
5. A grant was submitted to the AD associations aiming to use our cells suspensions to study synapses.
6. Further analysis of cell suspensions using next generation RNA sequencing (RNA-Seq) should be implemented in order to approach how mix pathologies might be influencing dysregulation of genes.
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; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:
Aim 1: To build on what we have already established in the last three 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's 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 cells 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 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 assessments yearly. The validation of their clinical diagnosis was made by neuropathological examination of the postmortem brain tissues. Taken together, these could provide valuable information for understanding cases with sporadic AD, whose phenotypes might be affected by the co-presence of other neurodegenerative diseases.

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 52 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 was 57.3 ± 24.3 days. The culture was started from dermal explants. The average number of days for skin cells to grow out was 12.7 ± 7.0 days. Cultures were maintained in FibroLife media with supplements twice a week. The expansion of proliferating fibroblasts was passaged three times. At the 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.
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. This is 3-4 cases each month for 10 months as each case takes approximately 2 months to maintain and an additional months to characterize batches of cultures. We will also bank cryoprotected scalp tissues. The tissue banking will be assessed for storage duration so that viable cells could be produced. We will keep 1/3 of the tissues from each case in cryoprotectant and store 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 point 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. 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. During this funding period, we successfully banked fibroblasts from 24 scalp tissues out of 32 donor cases processed. A total of 592 million P2 and P3 fibroblasts have been collected and cryopreserved. The success rate for scalp explant culture was 75%. In the upcoming fiscal year, we anticipate processing 27-36 scalp tissue samples, averaging 3-4 cases per month over 9 months. Each case requires 2-3 months for maintenance. Assuming a 70% success rate, we expect to bank an additional 19-25 samples, expanding our biorepository with fibroblasts from individuals with diverse neurodegenerative diseases and control groups.
2. As part of our quality control procedures, we conducted the following assessments:
   a) Cryopreserved P2 and P3 fibroblast aliquots were thawed, and their viability rates exceeded 90%. Regular mycoplasma tests confirmed the absence of contamination.
   b) Characterization of banked fibroblasts included qPCR analysis of fibroblast markers (FAP, FN1, THY1, VIM, KRT14) and immunostaining. Positive expression of FAP, FN1, THY1, and VIM was observed. Fifteen fibroblast lines have passed quality control, while nine lines are pending evaluation.
3. In the past two years, we have provided a total of 42 fibroblast lines to research groups and biotech companies. Three groups requested fibroblasts for reprogramming, while one group is employing them for a model system to map lysosomal ions. Collaborating with Dr. David Brafman, Dr. Rita Sattler, Diego Mastroeni, and Dr. Aleksandar Bajic, we have successfully generated induced pluripotent stem cells (iPSCs) from the provided fibroblasts. Positive feedback was received for the reprogramming, with two lines successfully reprogrammed into iPSCs, while three lines did not achieve reprogramming success. The remaining lines are awaiting results. The group using the fibroblasts for the ion mapping model system is satisfied with the fibroblast quality and plans to expand their study with additional samples. Additionally, we have 16 fibroblast lines prepared for delivery to a biotech company in the upcoming summer for their study on identifying a morphometric imaging biomarker for Alzheimer's disease (AD).
4. During this grant period, we performed RNA sequencing analysis on scalp and fibroblast samples obtained from both control subjects and individuals with AD. The analysis is currently in progress, and we anticipate completing it and publishing the results before the conclusion of this autumn. Preliminary results showed over 11,000 genes dysregulated in the scalp of AD subjects when compared to AD and 375 in AD fibroblast when compared to controls.
5. As the demand for reprogramming cells derived from our fibroblasts increases, we have successfully developed a protocol for directly reprogramming human fibroblasts into hSKPs (human skin-derived precursor) cells and neurons. We believe this technique has advantages
over IPSCs because the reprogramed cells genetic phenotype will be closer to the donor genetic profile than IPSCs reprogrammed cells.

a) We generated hSKPs from a selected subset of 9 banked fibroblasts through direct reprogramming using specific transcription factors. Morphological analysis, immunofluorescence staining, and RT-qPCR were employed to evaluate the differentiation potential of these somatic stem cells (hSKPs) into adipogenic, chondrogenic, and osteogenic lineages. Our findings demonstrate the successful isolation of hSKPs from aged human scalp fibroblasts obtained from autopsies. Characterization of hSKPs was confirmed by immunofluorescence staining, which showed the expression of SOX2 and nestin, as well as qPCR analysis of stem cell-specific markers including SOX2, NES, POU5F1, and NANOG. Furthermore, hSKPs exhibited the capability to differentiate into adipocytes, chondrocytes, and osteocytes.

b) We also successfully generated a batch of neurons through direct reprogramming of control fibroblasts. Morphological analysis revealed bipolar neuronal morphologies and the expression of MAP2, indicating successful neuronal generation. Further characterization tests for these neurons are currently pending. However, we acknowledge challenges resulting from low conversion efficiency and poor survival of reprogrammed neurons in vivo direct reprogramming. To address this, our plan for the coming fiscal year involves collaborating with the Human Stem Cell and Neuronal Differentiation Core at the Dan Duncan Neurological Research Institute. Together, we aim to develop an optimized direct reprogramming approach designed specifically for aged and diseased fibroblasts.

6. Our primary goal during this grant year is to enhance the visibility and recognition of our biorepository by strategic approaches, including scientific manuscript submission and active engagement in conferences:

a) Scientific manuscript submission: We aim to publish the results of our RNA sequencing analysis before conclusion of this autumn, to promote the utilization of our cell lines in scientific research.

b) Conference participation: This year we participated in The Brain Conferences, which focus on the utilization of brain cells for disease modeling, and the ISSCR annual meeting, that emphasizes stem cells and cellular reprogramming studies. Both conferences offer exceptional opportunities for collaboration with scientists utilizing brain cells and reprogramming techniques for disease modeling. These conferences provide networking opportunities with researchers worldwide and the potential for collaborations with professionals from the biotech and pharmaceutical areas. We aim to increase awareness of our biorepository, foster collaborations, and establish partnerships with experts from academia and industry.
BARROW NEUROLOGICAL INSTITUTE
PROJECT PROGRESS REPORTS
Imaging and molecular biomarkers of blood-brain and blood-CSF barrier cerebrovascular health in dementias. Nadine Bakkar, PhD, Ashley M. Stokes, PhD, Maurizio Bergamino, PhD. Barrow Neurological Institute, Arizona Alzheimer’s Consortium.

Specific Aims:
1) Specific Aim 1: Assessment of neuroimaging biomarkers of cerebrovascular health in dementia with Lewy bodies (DLB), mild Alzheimer’s disease (AD), and vascular dementia (VaD)
2) Specific Aim 2: Assessment of serum biomarkers of cerebrovascular health in DLB, mild AD, and VaD

Background and Significance:
Cerebrovascular changes are common neuropathologic findings in dementia [8]. Neuroimaging studies have shown white matter hyperintensities and altered cerebral blood flow, while ultrastructural microvasculature analyses highlight vessel wall basement membrane thickening [9] and pericyte degeneration [10], resulting in BBB and BCSFB permeability. Damage to the brain barrier enables plasma proteins such as albumin, fibrin, thrombin, as well as immune cells, to enter the CNS. This in turn exacerbates neuroinflammatory pathways, further damaging the BBB/BCSFB. Since brain barrier alterations occur prior to dementia onset and cognitive decline [11], its early detection could be key to deliver treatments prior to permanent tissue damage. However, the lack of quantitative, robust neurovascular biomarkers limits our ability to dynamically measure vascular health and dysfunction. To overcome this limitation, we propose to combine fluid-based biomarkers with neuroimaging biomarkers.

Advanced magnetic resonance imaging (MRI) methods that are sensitive to neurovascular characteristics include functional MRI (fMRI) to reveal brain connectivity [12] and cerebrovascular reactivity (CVR) to assess the response of cerebral blood vessels to vascular stimuli [13]. Numerous studies of functional connectivity have shown impaired networks in dementia [14], particularly in the default mode network (DMN), salience network (SN), and frontoparietal network (FPN). Furthermore, CVR has been shown to reveal changes in regions where perfusion did not change [15], providing unique information that may be more sensitive to early cognitive decline. Biofluids-based biomarkers have been investigated for dementia diagnosis and disease classification with varying efficiencies and sensitivities [16]. These include neurofilament light chain, phosphoTau and Aβ42/40 for AD and DLB [17], various forms of α-synuclein for DLB [7], and c-reactive protein (CRP) and homocysteine for VaD, as well as glial fibrillar acidic protein (GFAP). These biomarkers however have not been tested in combination with neuroimaging data, and neither have vascular injury biomarkers been assessed in mild AD, DLB, and VaD. Completion of this proposal will provide new insight into disease-specific changes in the BBB and BCSFB vasculature, highlighting commonalities and differences between these dementias at the level of those critical neuro-immunological interfaces into the CNS.

Experimental Designs and Methods:
Specific Aim 1: Neuroimaging biomarkers of cerebrovascular health in DLB, mild AD and VaD. Participants will be recruited to each cohort (AD, DLB, and VaD, n = 12 each) based on current diagnostic criteria by a practicing neurologist; healthy age-matched controls will also be recruited (n = 12). Fluid biomarkers will be obtained from blood samples. An abbreviated neuropsychological battery will be performed on all participants, including the Montreal Cognitive Assessment, Hopkins Verbal Learning Test, and Trail Making Test Parts A & B. Following neuropsychological assessment, MRI will be performed at 3T (Philips) using our advanced vascular imaging protocol. This MRI protocol includes standard structural imaging (to assess
Regional atrophy patterns), perfusion MRI (to assess cerebrovascular function and blood flow), and functional MRI (to assess whole-brain network connectivity). Neuroimaging data will be analyzed using standard processing pipelines on a voxel-wise level with validated atlases.

**Specific Aim 2:** Serum biomarkers of vascular health in DLB, mild AD and VaD

Blood collected from participants will be analyzed using ELISA-based Mesoscale discovery (MSD) to obtain various biomarkers of neuroinflammation and vascular injury. Specifically, neurofilaments will be measured in plasma to assess neuronal axonal injury, while metalloproteinases (MMP1, 3, and 9) and Selectins (E-Selectin, ICAM-3, P-Selectin, and Thrombomodulin) will measure vascular injury and endothelial dysfunction, respectively. Additional markers of acute neuroinflammation implicated in dementias (SAA, CRP, VCAM-1, and ICAM-1), and chitinases (Chit-1 and Chi3L1) will be assessed. Cognitive, biofluid, and neuroimaging metrics will be compared among the four groups. Additionally, correlations between biofluids and corresponding neuroimaging data will be assessed on a voxel-wise level, as well as with collected cognitive measurements.

**Proposed One-Year and Long-Term Outcomes:**

Data generated from this project will shed the light onto early cerebrovascular changes occurring in each of mild AD, DLB, and VaD, and correlate them with biofluid biomarkers of BBB/BCSFB dysfunction. This information will help highlight commonalities and differences in the microvasculature across these three clinically different dementias.

This grant will help generate preliminary data to apply for larger national multi-year funding, increasing sample size for improved statistics, as well as adding further molecular biomarkers of BBB and BCSFB structure and function including CSF biomarkers and CSF cellular profiling. Given the unique role of the cerebrovasculature of the BCSFB and BBB as a gate into the CNS, this will in turn help to prevent or delay onset of dementia, as well as provide insight into development of better drug delivery routes for neurodegenerative diseases.

**Year End Progress Summary (as of 6/13/2023):**

Four subject groups are being recruited for this study, including healthy control (HC), vascular dementia (VaD), dementia with Lewy bodies (DLB), and Alzheimer’s disease (AD). As part of the study, each subject has one visit of 2 hours that includes imaging, cognitive testing, and collection of a blood sample. Neuropsychological data was collected for all subjects who then underwent MRI scanning. At present, HC, VaD, and AD cohorts have been enrolled. The mean age is similar across cohorts (mean age ± standard deviation: 76.3 ± 6.7 for VaD, and 76 for HC). All subjects are right-handed.

Baseline and follow-up neuropsychological data was entered into a REDCap database for each participant and assessment. Preliminary analysis shows a trend for the MoCA across cohorts, where the HC and VaD groups show scores of 27 and 22 (SD 6.5), respectively. Similar trends were observed for scores on the Trail Making Test Parts A and B, with more subtle trends in scores on the HVLT, the COWAT, and the Complex Figure Test. For the Trail Making Test, we observed a mean completion time of 58.2 seconds (SD 39.7) and 231.2 seconds (SD 182.8) in the VaD group for parts A and B, respectively, and 28.6 seconds and 54.76 seconds in the HC for parts A and B, respectively. For the HVLT, we observed a mean total recall score of 18 (SD 8.2) and 20 for the VaD and HC groups, respectively. Average COWAT score was 11.6 (SD 2.2) and 14.3 for the VaD and HC groups, respectively. Finally, scores on the Complex Figure Test copy trial, 3-minute delay trial, and 30-minute delay trial was 25.6 (SD 7.9), 11.4 (SD 7.9), and 12.8 (8.4), respectively for the VaD group, and 28, 13.5, and 16.5, respectively, for the HC. Further analysis of scores for the remaining cognitive assessments is currently underway across groups.

Serum and plasma samples for all subjects were collected and are frozen to be processed. All ELISA-based biomarkers assays have been optimized in the laboratory and are ready to be performed.
The MRI scanner was down for over three months due to a planned upgrade, thus severely delaying subject recruitment and imaging. For the MRI data, segmentation and parcellation is performed on the structural T₁-weighted images using standard FreeSurfer (http://www.freesurfer.net) pipelines. Diffusion MRI data is analyzed using our standard pipeline, including denoising, distortions, motion and eddy current correction, bias field correction, and brain extraction. Standard diffusion tensor imaging (DTI) parameters can be obtained using dtifit (FSL, https://fsl.fmrib.ox.ac.uk/fsl/). An in-house Matlab script is used to correct the DTI metrics for free-water (isotropic motion) components, and anatomically-constrained tractography is used 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 functional connectivity, using our advanced echo-time dependent analysis with multi-echo independent component analysis (MEICA). Correlations between neuropsychological assessments and neuroimaging data will be performed using Spearman’s correlations. Perfusion imaging is performed using our standard analysis pipelines, including distortion correction, motion correction, and brain extraction, followed by determination of dynamic time-points, automated selection of the arterial input function, and calculation of both macro- and microvascular perfusion metrics (cerebral blood volume and flow). As capillary changes are expected, these metrics are combined to generate maps of vessel size and function. Further data analysis for MRI is ongoing.
Preclinical assessment of retinoic acid metabolism inhibition in Alzheimer’s via AAV delivery. David Medina, PhD, Fredric Manfredsson, PhD. Barrow Neurological Institute, Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1) Identify optimal dosing regimen of shRNA AAVs to reduce CYP26 isoforms individually and increase RA signaling in vivo.

Aim 2) Measure the effects of CYP26 knockdown on cognitive and pathological markers of AD in 3xTg-AD mice.

Background and Significance:
This project aimed to develop a novel gene based therapy for the treatment of Alzheimer’s disease. Here, we will target the retinoic acid (RA) signaling pathway as a means of neuroprotection. RA is an important signaling molecule involved in a host of vital functions in the central nervous system (CNS). Vitamin A is converted into RA which then acts on retinoic acid receptors to control the transcription of numerous genes. RA levels are controlled mainly by degradation via cytochrome p450 family 26 (CYP26) enzymes (isoforms include CYP26a1, CYP26b1, and CYP26c1). Genetic and proteomic studies have shown that members of the retinoid signaling pathway are alternatively expressed in neurodegenerative conditions including in Alzheimer’s disease and neurodegenerative disorders. This proposal is an expansion of work we have previously done exploring the role of retinoic acid signaling in another neurodegenerative disease-amyotrophic lateral sclerosis (ALS). Our work, and work from other groups, have demonstrated links between RA signaling and neurodegeneration, thus we are motivated to adapt our approaches for AD. We seek to build on previous work to address our overarching hypothesis: Increased retinoid signaling activity in the central nervous system is neuroprotective, and can be used to curb the Alzheimer’s disease progression.

Pharmaceuticals targeting the retinoic acid pathway have been proposed for a variety of neurodegenerative disorders, but their pharmacological properties, such as poor solubility and rapid clearance from the body, have prevented the accurate assessment of their therapeutic potential. Furthermore, long-term use of retinoid analogues can produce resistance by increasing metabolism of endogenous RA via increased CYP26 expression. Previously, to solve the delivery problem we developed a novel polymer based nanoparticle formulation that allowed us to deliver an FDA approved synthetic retinoid, into the CNS which activated retinoid signaling. Our study demonstrated that increasing RA signaling increases lifespan, reduces motor impairments, and is neuroprotective in a transgenic mouse model ALS. Taken together, our data demonstrate that increased RA signaling can produce neuroprotective effects in the ALS mouse model. Moreover, previous work from various groups have used all-trans RA (ATRA), or other retinoid to determine the effects of RA signaling on AD disease progression. For example, ATRA administration has been shown to reduce Aβ deposition, rescue memory deficits, and reduce neuroinflammation in APP/PS1 transgenic mouse models (Ding et al., 2008). Many other studies have demonstrated similar effects in other mouse models such as the 3xTg-AD mouse model, as well as using other retinoid, and have also demonstrated reduced tau phosphorylation and increases in cholinergic signaling. While we previously developed a novel retinoid formulation, it still suffered from the same pitfalls of other retinoid such as unspecific delivery of drug to peripheral tissues, frequency of administrations required, and inability to activate different RA receptors.

To generate a more tissue-specific, long-lasting, and robust therapeutic we will generate adeno-associated viral vectors (AAV) (in collaboration with Dr. Fredric Manfredsson) to increase
RA signaling by reducing the RA-degrading enzymes CYP26 via delivery of shRNA containing AAVs.

**Preliminary Data, Experimental Design and Methods:**
Specific Aim 1: AAV expressing shRNA towards CYP26B1 were generated. Likewise, control AAV expressing scrambled shRNA (AAV-shCTL) are being produced. shRNAs against mouse CYP26B1 and CYP26C1 were designed using established algorithms (PMID: 33249031, PMID: 31002755) and blasted against the mouse genome to ensure no off-target activity. In the pre-funding period candidates will be validated *in vitro*. Using this workflow, my collaborator on this proposal (Dr. Manfredsson) has successfully engineered numerous shRNAs for *in vivo* use. The viral genome also contains a separate GFP reporter cassette as a marker of transduction.

These experiments are designed to select a viral dosing paradigm that will provide the greatest opportunity to sustain retinoid activation without producing adverse or toxic events.

**Approach:** We will utilize the RARE-reporter mice, of which we have a breeding colony established at the Barrow Neurological Institute. These mice express the LacZ gene under the control of the Retinoic Acid Response Element. Our previous work demonstrates RA activation after the administration of an exogenous retinoid. Thus, these mice are an appropriate tool for assessing RA activity after administration of AAV-shCYP26B1, AAV-shCYP26C1, or AAV-shCTL. These experiments are designed to test between 3 doses: a low dose, mid dose, and high dose. Optimal dose will be identified as one that elicit high and prolonged retinoid activation without producing toxicity. Should more than one dosing scheme meet the criteria in absence of overt toxicity, we will select the dosing scheme that achieves highest total activation at lowest viral dose in the brain.

Specific Aim 2: Measure the effects of CYP26B1 knockdown on cognitive and pathological markers of AD in 3xTg-AD mice. Completion of aim 1 will allow us to define the dose to achieve the highest retinoid activation without causing toxicity. Aim 2 will test the efficacy of the optimal dose to curb AD pathology in the 3xTg-AD mouse model. The 3xTg-AD mouse model is appropriate as it displays many of the hallmarks of AD including accumulation of Aβ, Tau phosphorylation, and progressive cognitive impairment [27].

**Approach:** We will administer AAVs via the dosing paradigm finalized in Aim 1 into 3xTg-AD mice. Bilateral intrahippocampal injections will be performed at 6 months of age (10/group, balanced for sex). This age is prior to Aβ plaque deposition, tangle formation, but the beginning of cognitive impairments, mimicking intervention at an early phase of the disease. Mice will be monitored for health for the remainder of the study. We will measure the effects of CYP26B1 knockdown on cognitive and pathological markers of AD in 3xTg-AD mice.

**Proposed One-Year and Long-Term Outcomes:**
The development of therapeutics for Alzheimer’s and other neurodegenerative diseases has been drastically limited by the inability to effectively deliver candidate drug compounds into the CNS. Completion will demonstrate proof-of-concept data for a genetic therapy approach in Alzheimer’s. However, this work has potential to produce significant and long-lasting impact on the field by creating a new therapeutic approach targeting the RA signaling pathway. To our knowledge, this would be the first attempt at manipulating RA signaling for a neurodegenerative disease using AAV technology. Successful demonstration of any or all of these aims would warrant further studies to refine our approach for clinical development. Further, based on our work and the work from other groups, we reason that our approach of targeting the RA pathway could have wide ranging applicability to other neurological and neurodegenerative diseases.
Year End Progress Summary:
The team has been able to develop the AAV9 vector that was proposed in order to knockdown CYP26B1. This virus was tested in an in vitro system to confirm that knockdown can be achieved using this system. Importantly we have performed in vivo studies in order to confirm viral activity. Following direct injections into the hippocampus of mice, we have not observed any overt toxicity in the mice. We are seeking to validate the activity of virus by showing expression of the GFP reporter, reductions in levels of CYP26B1 in transduced cells, and increased activity in areas around transduced cells using LacZ detection. Our initial data clearly shows that we are able to directly administer our virus, as demonstrated by robust GFP expression, 3 weeks post injections. However, we have failed to definitively demonstrate the CYP26B1 levels are reduced using western blot analysis or immunohistochemistry. We attribute this to the lack of sensitivity with these two approaches. We will continue to validate reduced CYP26B1 levels using other approaches such as RNAscope or qPCR. We have also performed LacZ detection via direct (immunofluorescence) or indirect methods (Xgal staining). Using the latter approach, we have detected small changes in LacZ staining, indicating an increase in retinoid activity following AAV injection, indicating proof-of-concept that our approach is viable, yet has to be optimized.

Unfortunately, our study was hindered by the time it took to develop the AAV vector. This was mainly due to the poor efficiency of viral production. We posit that the construct that is used to produce the siRNA which gets packaged into the viral vectors is somewhat toxic to the viral producing cells. Thus less virus is produced per round, and still has to be concentrated to achieve somewhat low viral titers. We plan to overcome this challenge by producing larger batches of virus followed by concentration to achieve the higher doses that we hypothesize will be needed to optimize the response.

The goal is to validate the activity of the virus in the reporter mice and then the focus will be to inject these virus into a mouse model of Alzheimer’s to test for efficacy. We have increased our surgical schedule to rapidly increase ability to quantify our results. Once we feel confident that our virus is producing the activity we seek, we will apply our virus into a cohort of Alzheimer’s mice, to perform intrahippocampal injections of virus and test efficacy.

The findings we have obtained from this project will be used to be part of a bigger NIH (RO1 or R21) application to refine this approach in AD. This work has also allowed us to develop a greater understanding our AAV work flow, which will be important as we continue the work with other funding mechanisms, including a DOD grant that is funding production of AAVs for amyotrophic lateral sclerosis. We hope to optimize our AAV administration protocols and apply them to neurodegenerative models within the calendar year.
Brain cell-derived extracellular vesicles as biomarkers for FTD. Rita Sattler, PhD, Anna Burke, MD, Marwan Sabbagh, MD, Kendall Van Keuren-Jensen, PhD. Barrow Neurological Institute, Translational Genomics Research Institute, Arizona Alzheimer’s Consortium.

Specific Aims:
Specific Aim 1. Isolation and transcriptomic characterization of cell type specific EVs from FTD patient-derived iPSC-differentiated brain cells. Using established techniques, excitatory cortical neurons, astrocytes and microglia will be differentiated from healthy control and FTD patient induced pluripotent stem cells (iPSCs). Cell culture supernatants will be collected and used for cell-type specific EV isolation using recently published specific protein markers: ATP1A3 and NCAM1 for excitatory neurons; LRP1 and ITGA6 for astrocytes; ITGAM and LCP1 for microglia. Transcriptomic characterization will be done with RNA sequencing analyses. Remaining supernatants will be stored at -80C for future EV analyses on proteomics, lipidomics and metabolomics.

Specific Aim 2. Isolation and transcriptomic characterization of cell type specific EVs from FTD patient plasma samples. Using the same protein markers as described in SA1, we will isolate brain cell specific EVs from FTD patient plasma samples. RNA sequencing analyses will be performed for transcriptomic analyses, and aberrant transcriptomic changes will be compared to those obtained from iPSC brain cell derived EVs from SA1. Similar to above, remaining plasma samples will be stored at -80C for future expanded EV analyses.

Background and Significance:
EVs have gained significant interest regarding their role in inter-cellular communication during both physiological and pathological conditions. To date, every brain cell type has been shown to secrete EVs, which can be detected in biofluids, including plasma. In the brain, released EVs from one cell type can be taken up and emptied by a neighboring cell, suggesting regulatory activities that contribute to cellular dysfunction during disease progression. For example, microglia-derived EVs have been shown to contain interleukin-1β and thereby regulate inflammatory responses, while others showed microglia EV-mediated synaptic activity. Finally, EVs are also considered to be responsible to the spread of disease-specific proteinopathies. For example, microglial-derived EVs were shown to spread tau in vitro and in vivo.

In addition to the role of cell type-specific EVs in disease pathogenesis, the fact that the cargo of brain cell-derived EVs reflects disease-specific molecular signatures of the neurodegenerative disease of the individual patient allows to distinguish neurodegenerative disease patients from healthy controls. Therefore, EVs may serve multiple roles during our quest to better understand disease pathogenesis, diagnose patients, but also to develop and monitor new therapeutic treatments.

Preliminary Data, Experimental Design and Methods:
The Sattler laboratory has extensive expertise in iPSC culture modeling and has established and validated the generation of patient-derived iPSC differentiated neurons, astrocytes and microglia. Dr. Kendall Van Keuren-Jensen has extensive expertise in the isolation and transcriptomic characterization of EVs from varying biofluids, including plasma. Drs. Burke and Sabbagh treat large numbers of FTD patients at the BNI Alzheimer’s and Memory Disorders Clinic and can therefore provide FTD patient plasma to be used for the proposed studies.

Preliminary data to support these studies:
(1) Oligodendroglial-specific EV isolation from patient plasma
Dr. Van Keuren-Jensen’s laboratory used well characterized RNA and protein databases to mine and identify candidate membrane proteins for enrichment of tissue-specific EVs. Using this
approach, myelin oligodendrocyte glycoprotein (MOG) was identified and validated as a protein to target oligodendrocyte-specific EVs.

(2) RNA composition of iPSC microglial-derived EVs

Over the last year, the Sattler laboratory has established a large bank of iPSC-patient derived cell type specific EV-containing cell culture supernatants (microglia, astrocytes, neurons) from varying patient subgroups (ALS, ALS/FTD, FTD and healthy controls). Preliminary analyses of these samples confirmed the presence of varying RNA subtypes.

Experimental Design and Methods

Specific Aim 1

Patient iPSC cell line source/acquisition. For these exploratory studies, we will use 4 familial FTD patient iPSC lines (3x C9orf72, 1x GRN) and 4 age and sex-matched healthy controls. All of these iPSC lines are already present in the laboratory and have been successfully differentiated into varying brain cell types.

(1A) Differentiation of brain cells. iPSCs will be differentiated into cortical neurons, microglia and cortical astrocytes using established and validated protocols. Upon maturation of each cell type, supernatants will be collected at each media change for 2 weeks. After the final supernatant collection, cells will be pelleted and used for cellular EV isolation. We will include collection of EVs from iPSC cell supernatants after stressing the varying cell types with cellular stressors that resemble known disease conditions, such as oxidative stress and glutamate excitotoxicity.

(1B) Isolation of EVs

(1C) RNA sequencing of EV cargo.

Specific Aim 2

Patient blood source/acquisition. In collaboration with Drs. Burke and Sabbagh, we will 15 FTD patient samples and 15 non-neurological control samples.

(2A) Collection of patient blood. 42 mL of blood will be collected during a regularly scheduled outpatient visit or a study visit for a research trial that the subject is participating in at BNI/SJHMC. Blood plasma will be isolated from the collection tube and stored at -80C or immediately used for EV isolation.

(2B) Isolation of plasma EVs. Plasma samples will undergo EV isolation and characterization similar to the iPSC cell culture supernatant analyses.

(2C) RNA sequencing of EV cargo.

Proposed One-Year and Long-Term Outcomes:

These exploratory studies will enable us to fully establish and validate the use of FTD patient plasma for the isolation of brain cell type specific EVs and the characterization of its cargo. The results of these studies will serve as preliminary data for a larger federal grant application to either the NIH or the DOD in which we will propose to fully characterize brain cell EVs for RNA, protein, lipids and metabolites from matching patient samples: plasma, iPSCs and whenever available, postmortem brain tissues.

Year End Progress Summary:

Completed aspects of our studies:

Specific Aim 1

(1A) Differentiation of brain cells.

We successfully differentiated FTD patient-iPSCs into cortical neurons, microglia and cortical astrocytes from each of our patient iPSC lines. As proposed, each cell type differentiation was performed three times to account for potential differentiation variability. Supernatants containing EVs from each cell type were collected and stored at -80C once maturation was reached.
Specific Aim 2
(2A) Collection of patient blood.
After delayed IRB approval, we are actively enrolling study participants and as of today, have collected 6 plasma samples (3 disease and 3 controls). Plasma was isolated within 1 hr after each blood draw and is stored at -80C. Enrollment and plasma collection is ongoing until completed.

To be completed:
Specific Aim 1
(1B) Isolation of EVs.
Supernatants from iPSC cultures were stored at -80C for EV isolation. We will process these supernatants after we collected all patient plasma samples from SA2 (see below) to avoid variabilities and batch effects regarding the EV isolation process.
(1C) RNA sequencing of EV cargo.
Once successfully isolated, we will proceed with RNA isolation of the cell-type specific EVs and perform RNA sequencing analyses. All reagents have been acquired to proceed with these analyses beyond the award deadline.

Specific Aim 2
Patient blood source/acquisition. In collaboration with Drs. Burke and Sabbagh, we will continue enrollment to reach 15 FTD patient samples and 15 non-neurological control samples in total.
(2A) Collection of patient blood. We will continue participant enrollment and plasma collection until we reached our proposed sample number of 30.
(2B) Isolation of plasma EVs. Plasma samples will undergo EV isolation and characterization similar to the iPSC cell culture supernatant analyses.
(2C) RNA sequencing of EV cargo. RNA isolation and analyses will be done together with the cell culture EV RNA analyses (SA1C).

Challenges
Our biggest challenges lied in timely IRB protocol writing and submission. We have learned a lot through this process and are excited that we now actively enrolling participants. Despite this delay, we were able to collect all of the iPSC cell culture supernatants and are ready to EV isolation and transcriptomic analyses.

Future grant applications
We are preparing for a multi-omics single-cell (including spatial resolution) NIH grant application to study mechanisms of neurodegeneration in C9orf72 FTD in patient tissue and iPSC cell culture models. The EV information we obtain from this proposal will allow us to bring forward candidate genes/pathways which we can then correlate with single cell omics data sets to be generated for this future application.
Defining neurocircuitry in Parkinson’s disease dementia using a multi-species approach.
Fredric P. Manfredsson, PhD, Sana Aslam, MD. Barrow Neurological Institute, Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1. Clinical-pathological assessments of cognitive decline in human PD.
Aim 2. Neurocircuitry of cognitive decline in the rodent

Background and Significance:
Resolution or prevention of the cognitive impairment and dementia seen in Parkinson’s disease (PD) patients is the single greatest challenge facing the PD scientific community. Ten to 15 percent of individuals display mild cognitive impairment at the time of diagnosis and up to 80% of PD patients ultimately suffer significant cognitive decline and dementia. Despite the high prevalence, the etiopathology underlying PD dementia is unknown. There is growing evidence that there are common pathologies shared between PD and other disorders involving dementia such as dementia with Lewy bodies (DLB) and Alzheimer’s disease (AD). For instance, in PD, amyloid-β (Aβ) and tau deposition are comorbid associations and especially Aβ deposition is associated with cognitive decline in PD. Conversely, widespread PD-like Lewy pathology is seen in sporadic AD cases without parkinsonian symptoms. Thus, efforts are currently ongoing to model the etiopathology of PD dementia using a combination of proteins associated with these pathologies such as alpha-synuclein (αSyn) and tau. Herein we propose to take a parallel approach to assess the neurocircuitry relevant to co-pathology induced dementia in both human disease and in the rodent.

Preliminary Data, Experimental Design and Methods:
N/A

Proposed One-Year and Long-Term Outcomes:
Taken together, with this proposal we aim to lay the foundation for a research program aimed at better understanding the molecular and anatomical underpinnings of dementia in PD. The generation of a rodent model will be a crucial step towards this goal. Moreover, PD dementia is a feature of advanced PD-a programmatic focus being developed for a Udall center application by clinicians and basic scientists at BNI. Thus, this proposal will help to further the overall goals and research missions of the BNI. Finally, the execution of (parts) of this proposal will facilitate additional collaborations at BNI and beyond.

Year End Progress Summary:
Should be 1-2 pages detailing progress made from 07/01/21 to 06/30/22. Explain progress made towards the proposed one-year outcomes. Describe findings and provide explanation for any challenges encountered. Describe progress made on the proposed long-term outcomes. Include future grant applications, publications and collaborations that arose from the research.

The original proposal set out to assess whether the combination of Lewy pathologies (LP), tau, and amyloid observed in distinct anatomical regions of the PD brain is a key substrate for the development of affective symptoms such as dementia. The overarching goal is to develop preclinical models that better model non-motor symptoms (NMS), such as cognitive dysfunction, in PD.
In prior work in rodent models of PD we found that dopamine denervation and subsequent DA agonist administration (a key model resulting in aberrant motor learning and the formation of levodopa-induced dyskinesia (LID)) also result in changes in affective nuclei/circuits and produces non-motor phenotypes. For instance, the same manipulations also give rise to a reduction in impulse control and changes in plasticity in cortical inputs. However, one significant shortcoming of our earlier work is that it relied upon toxin-based models of nigrostriatal denervation while ignoring a key component of Lewy pathology- the protein alpha-synuclein (α-syn). This protein is found throughout the brain, including areas important to cognitive function, and is a key modulator of synaptic function. In the absence of overt neurodegeneration, pathological accumulation of this protein results in altered synaptic function. In rodents, overexpression of aSyn in nigrostriatal neurons results in neuronal dysfunction followed by degeneration. However, few studies, if any have evaluated functional consequences of aSyn pathology in affective areas. To that end, the foundation for the overarching hypothesis that we are investigating in the current proposal; asks the question: how does nigrostriatal denervation together with aSyn pathology in other areas such as frontal cortex, amygdala, etc. contribute to cognitive decline in PD.

Towards our goal we have taken a parallel approach in the human post-mortem brain and in the rodent.

1) Human studies
In the current study we decided to capitalize on the local BBDP resource; however, a significant caveat was the stratification of selected cases. Most patients will exhibit dementia throughout the disease course, moreover, LP as assessed by gross pathology, is a common feature. We thus took the following strategy: Initial stratification of cases was based on the clinical onset and presentation of dementia: PD no dementia, PD Dementia. Finally, we selected brain areas presumed important to cognitive function: Frontal cortex, Occipital cortex, Cingulate cortex, Amygdala, SN, LC and Dorsal raphe. In selecting cases we ignored conventional pathological staging already performed. Ongoing work is now 1) Assessing LP, tau, and amyloid pathology using an Al based algorithm, 2) Assessing inflammatory markers in relation to pathological markers using a modified Al-based Scholl analysis, 3) Assessing functional connectivity in affective areas using histological synaptic reconstruction and its relation to pathological markers. Once completed, histological outputs will be analyzed in the context of dementia as well as secondary parameters such as psychosis. Finally, we will also analyze our automated histological data in the context of existing pathological analyses performed at the BBDP.

2) Rodent studies.
Although prior rodent studies have been valuable in understanding how circuits important for affective function may change in the PD brain, these studies have had several shortcomings: 1) An acute lesion does not facilitate long-term adaptation and plasticity changes, 2) Studies have not incorporated pathological α-syn which can alter neuronal function. 3) Due to the acute nature of the neurodegeneration, the lesion has to be unilateral, possible negating any behavioral phenotype that requires bilateral changes. To that end, we have established a novel, bilateral and progressive model of PD that incorporated relevant aSyn pathology; not only in the midbrain but also in distinct nuclei throughout the brain. Although studies are ongoing, important findings are: 1) Bilateral nigral aSyn overexpression leads to nigrostriatal dysfunction and protracted neurodegeneration and exhibits a progressive motor phenotype, 2) Administration of levodopa in this model rescues motor function but also results in the presentation of altered pre-pulse inhibition (behavior thought to be analogous to human psychosis), 3) Altered plasticity in the orbitofrontal cortex, 4) Presence of Lewy-like pathology in targeted areas such as the PFC and the BLA.
Several collaborators are now utilizing this model in pharmacological, behavioral, and electrophysiological studies and the initial findings from this model was presented at the International Basal Ganglia Society Annual Meeting (June 2023). Together with this group of collaborators we are planning to submit an MPI application to the DOD in Aug. 2023. Moreover, long-term goals have not changed; we will continue to generate data as outlined above and submit relevant grant applications supported by this data. Finally, we remain poised to submit an application for a Udall Center of Excellence, and all the data generated through this award will be an important component of the basic science component of that application.

Specific Aims:
Specific Aim 1. Reducing astrocytic CHI3L1 expression will improve behavioral outcomes and ameliorate pathology in the 5XFAD mouse.

Background and Significance:
Despite preclinical and clinical advances, with FDA-approved treatments of AD aimed at slowing disease progression now available, disease modifying treatments to halt the disease in the entire patient population is lacking. Accordingly, AD remains one of the largest health crises in the US and beyond. One critical barrier to successfully defining disease etiology and developing successful treatments may lie in the fact that AD is a heterogenous disease that converges on common clinical endpoints late in the disease. Thus, in order to develop treatment modalities to target all of AD it may be necessary to move away from targeting molecular pathways that potentially differ between patients and focus on processes that are shared in disease. We propose that inflammation represents a common target throughout all forms and stages of disease. Although this concept in and of itself is not novel, this proposal is significant in that we propose that inflammation has to be differentially modulated in different subtypes of glia, and that defining the contribution of subsets of glia to disease progression will lay the foundation for a new line of AD research in our group and beyond.

Preliminary Data, Experimental Design and Methods:
1) Novel AAVs designed to target astrocytes, 2) miRNAs designed against BRP-39

Proposed One-Year and Long-Term Outcomes:
The limitations of the current study are obvious. First, we are focusing on a single target, CHI3L1, whereas literature suggests that multiple members of this family are important pro-inflammatory mediators. Second, we are limiting our study to single model of AD. Finally, we are only investigating a single glial subtype. Nonetheless, this proposal falls within the scope of the current RFA as the successful demonstration of BRP-39 as an important mediator of neurotoxic inflammation will generate technical and conceptual feasibility and thus lay a strong foundation for larger research program/grant applications where all members of this family of proteins would be assessed, in multiple cell-types and in multiple models of AD. Finally, this proposal represents the first joint effort by Drs. Manfredsson and Velazquez and with the successful execution of the work proposed herein we envision the submission of numerous collaborative proposals. Finally, in ongoing work we are developing and assessing techniques that will allow us to further assess the distribution of C/CLPs in even more refined subsets of glia (e.g. “A1” versus “A2” astrocytes; also see) and we expect that future applications will focus on such analyses in human postmortem material (e.g. from the ADRC Neuropathology Core) to further inform gene therapy approaches.

Year End Progress Summary:
1) Validation of miRNA in vivo: We generated AAVs carrying several different miRNAs against Brp-39. In the first round of validation we observed significant reduction in astrocytic Brp-39. However, we also observed off-target expression of our GFP reporter in neurons. We attributed this to the high dose utilized in the initial experiment. However, during this time we also identified additional novel AAVs capsids from our library screen with high astrocyte tropism.
We repeated the experiment with the new capsids using the same titer as in the initial screen, this time we achieved a similar degree of knockdown with no detectable off-target infectivity.

2) Once we validated the vector we ordered 5XFAD animals and initiated the establishment of a colony. Roughly 60% of animals have been dosed and we are planning to run the behavioral testing as outlined in the original proposal.

There are no changes to our long-term goals and we plan to submit a R21 once we obtain preliminary in vivo data.
Specific Aims:
1. Implementation of the HEART Program includes a formal development plan outlining internal and external outreach strategies to increase recruitment and the establishment of organizational infrastructure, resources, and written translational materials to promote trial retention while recognizing the unmet needs of a large Spanish-speaking community seeking care within Maricopa County.
2. To forge a close working relationship with members of our Hispanic community to formalize the HEART outreach program to increase Alzheimer's disease awareness while addressing clinical research opportunities and family/caregiver support needs to increase trial retention through novel service-related solutions.
3. To identify and mitigate against cultural barriers limiting access for Hispanic patients to enroll into Alzheimer's disease clinical trials.

Background and Significance:
Hispanics facing the problem of Alzheimer's disease (AD) constitute an underserved and understudied population in the United States. BNI has partnered with various organizations in the community to help address the educational and clinical needs of patients and families and to demonstrate to this underserved community our strong interest in understanding the unique factors affecting their cognitive health.

Preliminary Data, Experimental Design and Methods:
The HEART Program's outreach objective is designed around an internal (within BNI and Dignity Health opportunities) and an external outreach plan (community) for recruitment, with an established recruiter training program, metrics, and goals to maximize engagement among the Hispanic community. Our retention plan includes focused translational tools (such as Spanish translated rating scales and educational materials) and expanded training among research team personnel offered by Promotores and Hispanic Community Stakeholders to address unique cultural needs. The HEART Program plans to recruit participants from the community through education, outreach, and various events such as memory screenings.

To support the core in recruiting, enrolling, and retaining 100 participants in the newly opened Arizona Alzheimer’s Disease Research Center (ADRC) study, we will attend community events celebrating Hispanic culture, develop written culturally sensitive educational materials, in both English and Spanish to expand our reach, and partner with various agencies serving both English and Spanish speaking Latino seniors.

Proposed One-Year and Long-Term Outcomes:
The HEART Program plans to recruit participants from the community through education, outreach, and various events such as memory screenings. To support the core in recruiting, enrolling, and retaining Hispanic participants, we will attend community events celebrating Hispanic culture, develop written materials, including a caregiver dementia handbook, in both English and Spanish to expand our reach, and partner with various agencies serving both English and Spanish speaking Latino seniors. As of March 2023, in response to evolving circumstances
at the site level and in collaboration with Banner Alzheimer’s Institute, BNI’s enrollment goal for the year was updated to 25 Hispanic participants enrolled by the end of September 2023.

An outline of BNI’s specific aims to achieve the above-stated enrollment and retention goals includes:

1. Recruitment of an additional 25 new Hispanic enrollees in the next year.
2. Retention of existing Hispanic enrollees.
3. Development of culturally sensitive dementia related educational materials including tip sheets for various dementia related symptoms.
4. Quarterly memory screens targeted for Spanish and English speaking Hispanic populations.
5. Outreach events dedicated to the Hispanic population, such as Spanish speaking memory cafes.
6. Continue to push for further growth in the number of bilingual staff members within the Cognitive Research Program at BNI and support the cost of those staff members becoming certified medical translators.

**Year End Progress Summary:**
The HEART Program within the Alzheimer’s Disease and Memory Disorders Division of Barrow Neurological Institute under the direction of Marwan Sabbagh, MD and Anna Burke, MD is designed to increase recruitment and retention of Hispanic subjects in the Arizona Alzheimer's Disease Research Center (ADRC) and other research protocols by removing unique cultural barriers and increasing awareness and access to meet the defined program goals.

1. Over the course of the 2022-2023 project period, Barrow Neurological Institute successfully retained all existing bilingual team members, including the full-time bilingual research psychometrist, despite the uncharacteristically high staff turnover rates that were experienced throughout the field of research as a whole. The retention of our entire pool of Spanish speaking staff members continues to significantly enhance our ability to reach community members, retain existing participants and gather more accurate data.

2. Following an in-depth review of BNI’s 1st quarter enrollment numbers, we determined that a significant increase in the number of staff members assigned to work on the ADRC and HEART projects would be required in order to meet enrollment goals for the current grant year. Given the historically tight labor market being experienced within the field, we opted to utilize contract labor in order to more quickly meet our staffing needs. As a result, BNI requested and received approval from AAC leadership to reallocate funds in order to accommodate the increased staffing costs, which were significantly higher than was anticipated in the original FY23 budget. The approval of this request allowed BNI to considerably increase recruitment, retention and enrollment activity at our site.

3. In addition to retaining all existing bilingual team members, BNI also hired two additional full-time Research Assistants — one of whom is also bilingual in English and Spanish. Both of these Research Assistants have dedicated 100% of their time and effort to enrollment of subjects into the ADRC project at the BNI site, which included the enrollment of Hispanic participants as part of this HEART Program.

4. Barrow staff worked relentlessly to maintain existing relationships with Hispanic study participants while also enhancing the site’s ability to communicate meaningfully with the Hispanic community. As part of this effort, we have provided all five bilingual staff members with the necessary resources to become certified to perform the Clinical Dementia Rating (CDR) scale assessment in both English and Spanish. The ability of the BNI study team to effectively and efficiently connect with Hispanic participants in both English and Spanish allows for assessments to be performed in a participant’s preferred language. 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.

5. Angelica Garcia, a BNI Project Manager, attended the 2023 AAIC Satellite Symposium which focused almost exclusively on the impacts of dementia in Latin America. Attending this symposium provided important insight into how caregiver understanding of dementia in Mexico may differ from what’s seen in the US and elsewhere. The symposium provided unique viewpoints on the national experience of dementia in Mexico and was incredibly relevant to understanding the lived experiences of Hispanic persons who have been touched by dementia and helps inform the Barrow team on how they can deepen their empathy by learning how the experiences of Hispanic persons may differ from those of Caucasians who have been traditionally overrepresented in research cohorts.

6. Barrow 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.

7. Barrow’s partnership with the Promotores program remains strong and with their help, Barrow continues to expand its reach within the Hispanic/Latino community by fostering collaboration among organizations with similar goals for the Hispanic population. The “2023 Dia Del Promotor” conference, held in conjunction with the Promotores HOPE Network on March 23, 2023 was one of our most well attended events to date with over 150 people in attendance.

8. The Mohammed Ali Parkinson Center (MAPC) Hispanic Outreach team at Barrow gave a presentation to the “Comadres y Compadres” Spanish language support group where they discussed the impacts of dementia and what barriers to care have been encountered. At this event the outreach team also provided information about BNI’s current research opportunities, including Spanish language fliers for the ADRC study. The importance of having bilingual staff representing the institution and providing fliers in both English and Spanish cannot be overstated. In fact, Barrow’s Cognitive Research team constitutes an exceptionally diverse group of people whose unique experiences and perspectives are shared and respected. The diversity of BNI’s staff, a substantial number of whom identify as Hispanic or Latino, is one of its biggest strengths especially as the field of scientific research continues to focus on the profound importance of including underrepresented groups (URGs) in clinical research.

9. Barrow continues to translate consent forms for actively enrolling trials. Additionally, this year BNI has pushed for sponsors to provide Spanish language study materials prior to the start of enrollment for all new studies whenever feasible. This initiative to obtain Spanish language materials from as many new study sponsors as possible is intended to enhance our portfolio of study options for those whose primary or preferred language is Spanish. This will also ensure that potential participants who may benefit from participating in clinical research are not being lost simply due to a lack of information available for them to read.

10. This year, approximately 25% of all participants enrolled in the ADRC study at Barrow identify as being of Hispanic or Latino ethnicity. Of the 41 participants enrolled at the BNI site this funding period, 10 have indicated that they identify as Hispanic/Latino with 2 having completed PET scans. BNI has also identified 6 Hispanic participants who have consented to the optional LP/CSF collection and are in the process of scheduling those procedures. We have not yet reached the site goal of 25 Hispanic participants enrolled this year however, in light of the slow start in Q1 and subsequent course correction, Barrow has been gaining momentum with our enrollments and is on track to meet this goal within the updated target date of September 30, 2023.

As Barrow Neurological Institute looks ahead to what lies in store for next year there is no doubt that the diligent and consistent efforts put forth by the staff, who strive to improve the lives of our Hispanic patients and community members, will remain invaluable. Barrow’s dedication to enhancing not only the number of Hispanic patients interacted with but, perhaps more importantly, the quality of those interactions will prove crucial in reaching its goal of establishing and maintaining deep community ties.
CRITICAL PATH INSTITUTE
PROJECT PROGRESS REPORT
Development of a data interrogator to enhance accessibility of the CPAD database, thereby accelerating model-informed drug development in AD. Sudhir Sivakumaran, PhD, Mike Pauley, Nicholas Cullen, PhD. Critical Path Institute, Arizona Alzheimer’s Consortium.

**Specific Aims:**
Development of a web-based graphical user interface (the "actionable data model" (ADM) tool) to facilitate data exploration and analysis subset creation from the Critical Path for Alzheimer's Disease (CPAD) Consortium database. Additionally, demonstration of the value of analysis subset creation from the ADM tool through modelling of cognitive decline from baseline characteristics for the purpose of clinical trial enrichment in Alzheimer's disease.

**Background and Significance:**
The primary goal of CPAD is to develop quantitative models of Alzheimer's disease (AD) progression to improve clinical trial design and execution. CPAD curates a unique database with subject-level data across the AD continuum from various sources. These diverse datasets include various biomarker modalities (e.g., MRI, PET, CSF, blood) and longitudinal clinical endpoints, offering great potential for answering key questions in AD trial design related to screening, enrichment, and tracking disease progression. However, the complexity and diversity of CPAD’s data pose a challenge for researchers more skilled in modeling than data processing. To address this, a user-friendly web-based interface called the "actionable data model" (ADM) tool was proposed. This tool will allow users to generate analysis-ready data subsets based on participant characteristics filters in a simple, web-based user interface. The ADM tool captures relationships between data domains for fast querying and enables easy integration with statistical analysis programs. The expected outcome includes a user-friendly interface and a statistical model for clinical trial enrichment in pre-dementia patients, derived from analysis subsets generated with the ADM tool. This statistical model will demonstrate a canonical example of how to leverage the ADM tool. Successful completion will provide invaluable tools to industry sponsors, regulators, and researchers, optimizing clinical trial design and execution, reducing costs and patient burden, and accelerating scientific understanding of AD.

**Preliminary Data, Experimental Design and Methods:**
The initial version of the ADM tool was created using Shiny software and sample data from the CODR database. The ADM Graphical User Interface (GUI) includes a dashboard with variable lists, summary statistics, and visualization. Users can perform data exploration and visualization using the current version of the ADM GUI. Internal colleagues have tested the tool end-to-end, from navigating the web tool to creating relevant analysis subsets and using them to build statistical models for disease progression and clinical trial enrichment. Logistic regression models were initially used to predict the risk of developing AD dementia in patients with mild cognitive impairment (MCI) and positive amyloid status. The analysis utilized data downloaded from the ADM tool based on user-defined characteristics, such as MCI diagnosis, positive amyloid status, baseline cognition, MRI and plasma biomarkers, and longitudinal clinical data.

The capabilities of the tool will be expanded to include tabs for data exploration and analysis subsets. The "Data Exploration" tab enables users to explore available variables, view data
structure, and generate plots and summary statistics. The "Create Subset" tab allows users to build custom datasets by selecting variables of interest and applying filters, with the ability to download the customized data frame. The long-term goal is to create a user-friendly environment for researchers to efficiently explore datasets and identify interpretable baseline characteristics of subjects across the AD continuum, aiding in disease progression prediction. The ADM will be used to develop a quantitative disease and biomarker dynamic model for amyloid-positive pre-dementia participants from the CPAD database. Clinical outcome assessments and longitudinal biomarker dynamics will be modeled using a mixed effects approach, incorporating relevant covariates. Baseline age, sex, APOE4 genotype, baseline Mini-Mental State Exam, and biomarker covariates will be tested. The models aim to support disease progression simulations for defining trial-specific biomarker enrichment thresholds.

**Proposed One-Year and Long-Term Outcomes:**

One-Year Outcome: Finish the first version of the ADM GUI using the Shiny software and launch the web software application to researcher to use. Create a mechanism to receive feedback from the users. Demonstrate and document a relevant end-to-end use case where the ADM GUI adds value - namely, creating a clinical trial enrichment model to predict longitudinal cognitive decline from baseline patient information using data downloaded from the ADM GUI tool.

Long-term Outcome: Add additional data and features based on the feedback received from the users. Integrate the ADM GUI tool as a standard tool for creating analysis subsets from the CPAD database. Observe increased use of the ADM GUI tool in relation to other forms of analysis subset creation (e.g., custom processing scripts) according to user feedback surveys.

**Year End Progress Summary:**

This progress summary provides an overview of the advancements made in the development of the ADM (Actionable Data Model) GUI tool and its impact on clinical trial enrichment. The summary highlights the progress achieved towards the proposed one-year outcomes and outlines the findings, challenges encountered, and progress made towards the long-term outcomes. Additionally, future grant applications, potential publications, and collaborations resulting from this project are discussed.

Progress towards One-Year Outcomes:

Significant progress has been made in achieving the one-year outcome. We have successfully completed the initial version of the ADM GUI, which includes a user-friendly interface with a comprehensive set of features. The GUI allows researchers to explore data, visualize variables, and generate analysis subsets based on user-defined characteristics. The launch of the web application has been successful, and initial feedback from users has been encouraging.

Feedback was collected from four different sources – internal colleagues, industry colleagues, researchers, and regulatory agency colleagues. Feedback from these different sources is important because each user has different needs and perspectives.

To demonstrate the value of the ADM GUI, we focused on a relevant end-to-end use case: creating a clinical trial enrichment model to predict longitudinal cognitive decline using data downloaded from the ADM GUI tool. Through this use case, we have documented the process and established a robust model that shows promising results in predicting cognitive decline based
on baseline patient information. This model has since been included in a platform to simulate clinical trials based on patient inclusion criteria. The findings indicate the potential of the ADM GUI in improving clinical trial design and execution.

Challenges Encountered:
One significant challenge was integrating diverse data sources into the ADM GUI tool. The CPAD database, which serves as the primary data source, presented complexities in data structure, quality, and interoperability. Extensive effort was invested in data preprocessing and harmonization to ensure accurate and reliable results. Additionally, incorporating user feedback and accommodating diverse user requirements posed challenges. The different needs of users often conflicted with each other; for instance, some users preferred less customizability in favor of ease-of-use, while others preferred to be able to control every detail of the data subset creation even if it meant having a larger learning curve. Knowing which user feedback to prioritize was a significant challenge.

Progress towards Long-Term Outcomes:
To achieve the long-term outcomes, we established a robust feedback mechanism to collect insights from users and incorporate their suggestions into the development process. This iterative approach allowed us to refine the GUI interface, add new features, and improve user experience.

Looking ahead, we anticipate submitting grant applications to secure additional funding for expanding the capabilities of the ADM GUI tool. We also plan to collaborate with other research institutions and industry partners to leverage their expertise and resources. Furthermore, based on the positive outcomes and promising findings, we intend to prepare manuscripts for publication in reputable scientific journals, highlighting the advancements and novel insights gained from utilizing the ADM GUI tool in clinical trial enrichment.

Additionally, we have made significant progress towards the long-term goal of increasing adaption of the ADM tool by adding to the amount of data records which are available in the ADM tool. CPAD achieved a significant milestone recently when the CODR dataset passed over 100,000 individual patient records. The data acquisition efforts have helped to make the ADM tool even more important to the data curation and processing tasks which are undertaken by modelling experts involved with CPAD.

**Conclusion:**
The progress made in the development of the ADM GUI tool has been substantial, making great strides towards the one-year outcomes of delivering the first version of the GUI and demonstrating its value in clinical trial enrichment. Challenges encountered during the development process were addressed, leading to a robust and user-friendly tool. The long-term outcomes of integrating the tool into standard practice and observing increased adoption are well underway, supported by user feedback and iterative improvements. Future grant applications, publications, and collaborations will contribute to further enhancing the ADM GUI's impact on clinical trial design, execution, and the scientific understanding of Alzheimer's disease.
MAYO CLINIC ARIZONA
PROJECT PROGRESS REPORTS

**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, Molly Maxfield, Li Liu), USC (Berislav Zlokovic), Mayo Clinic (Oana Dumitrascu, Otto Pedraza, Leslie Baxter, Cynthia Stonnington), and Banner Alzheimer Institute (Eric Reiman and his team).

4. Capitalizing on the longitudinal design of our program we took the opportunity created by the COVID-19 pandemic to directly compare the neuropsychological outcomes of COVID-19 disease among members of our cohort by comparing test scores before and after COVID-19 disease. We performed a similar analysis using NACC data. In both cases we found no significant impact among participants who almost entirely had mild disease treated as outpatients as well as in a small subset from the NACC cohort of hospitalized patients (9).

5. From the MRI studies added this past year we examined altered connectivity of the hippocampus among APOE carriers and noncarriers and showed preclinical alterations affecting the left hippocampus among APOE e4 carriers (10). This particular project also supported training of a medical student who participated in the data analysis.

References:


Specific Aims:
Specific Aim 1. To obtain non-mydriatic retinal CFP and OCT in subjects with pre-clinical AD (amyloid-positive) and age-matched normal controls (NC) (amyloid-negative), and to compare the retinal changes on CFP (vascular analysis) and OCT (structural analysis) between pre-clinical AD and NC.
Specific Aim 2. To characterize the effect of APOE phenotype on retinal CFP and OCT changes in subjects with and without amyloid biomarkers.
Specific Aim 3. To train multi-modality (demographic, genetic, neuropsychometric, comprehensive brain and retinal imaging) deep CNN models, test their ability to detect pre-clinical AD, and to identify the most accurate and cost-effective automated CNN model to predict pre-clinical AD.

Background and Significance:
The retina is a central nervous system organ that exhibits vascular changes, amyloid and tau deposition, inflammatory and neurodegenerative changes that correlate with the AD brain “A, T, N, I” changes. The retina has the advantage of being more accessible for repeated and high-resolution imaging, hence retinal imaging has emerged as a safe and non-invasive tool to study both cerebral vasculature, neurodegeneration, and cognitive disorders. We have previously reported that specific retinal imaging features on specialized retinal autofluorescence imaging could predict AD-related neurocognitive dysfunction and brain imaging changes. We have also developed a DL model based on retinal color fundus photography (CFP) to identify AD and automatically classify AD retinal biomarkers. Yet, retinal CFP changes and retinal OCT analysis in pre-clinical AD are not well-characterized. We hypothesize that retinal changes could predict AD development in subjects with normal cognition. Additionally, we hypothesize that a deep convolutional neural network (CNN) that includes comprehensive retinal imaging could be trained and tested to predict development of AD in asymptomatic patients or patients with mild cognitive symptoms.

Preliminary Data, Experimental Design and Methods:
To date, we have shown that retinal vascular changes, especially vascular tortuosity changes and retinal amyloid deposits correlate with AD-specific neurocognitive measures and hippocampal volumes. Prior studies have shown that retinal vascular geometric changes on CFPs and retinal OCT morphometric changes have potential linkage to early AD diagnosis. As hand-crafted identification of the features is subjective and laborious, we used DL through weakly supervised localization and Gradient-weighted Class Activation Mapping to develop an automatic framework to classify AD and extract AD retinal CFP biomarkers. Our trained U-net based model achieved an AUC-ROC of 0.938 on the testing set. The generated heatmaps 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 were highlighted in NC. Our innovative DL model is
feasible and could be applied in pre-clinical AD subjects to identify retinal regions mostly suggestive of AD development.

**Proposed One-Year and Long-Term Outcomes:**
We plan to complete the proposed aim 1 and 2 within the 1-year timeframe, by collecting data from all subjects in the Arizona APOE cohort that present at Mayo Clinic AZ for their regular visits. The CNN will be trained in year 1 without retinal imaging and further developed, with adding the comprehensive retinal imaging, at the end of year 1. Afterwards, we plan on incorporating retinal imaging in every longitudinal visit, to determine the ability of retinal imaging to monitor pre-clinical AD. Our overarching goal is to train and test a DL model in preclinical AD stages and fine-tune it for translation into clinical practice for AD screening. We plan on achieving this by examining the effect of retinal imaging (CFPs and OCT) markers on AD screening, and then modulating DL models to determine inputs that are highly accurate and cost-effective for AD prediction. Once tested, we plan to validate the DL model in real-world patients in future studies.

**Year End Progress Summary:**
We collected retinal images (non-mydriatic CFPs and OCT) from all subjects in the Arizona APOE cohort that presented at Mayo Clinic AZ for their regular research visits with Dr. Richard Caselli’s group (n=54). Retinal vascular fractal analysis is currently being analyzed, aiming for completion once all 60 subjects will be imaged. The analysis that aims to characterize the effect of APOE phenotype on retinal CFP and OCT changes in subjects with and without amyloid biomarkers is pending.

In collaboration with Dr. Yalin Wang from ASU, we trained the CNN on retinal images derived from participants with AD and MCI due to AD (obtained form Mayo Clinic AZ). Next, we will test this model on retinal images obtained from subjects with preclinical AD and their matched controls. We also plan on increasing the number of retinal images by including the AD participants that had retinal images collected in the UK biobank. We have learnt that one of the obstacles of the CNN tool training is the expected excellent-quality retinal images. Hence, we worked on developing a methodology to enhance the quality of retinal color fundus photographs. We have applied for the Patent Invention ID D23-15 “Systems and Methods for enhancing retinal color fundus images”. To further develop and test this methodology, we are putting together an R01 application to NIA in August 2023 titled “Deep Learning-Based Retinal Imaging Screening Tool for Preclinical Alzheimer’s Disease”. Additionally, to continue this work, I was awarded a 24-month Developmental Project Grant from Arizona Alzheimer’s Consortium and Arizona Department of Health services titled “Retinal Imaging Application in Preclinical Alzheimer’s Disease”, anticipated start date July 1, 2023.

Below are key abstracts, publications and oral presentations form our work.

2) Zhu W, Qiu P, Lepore N, Dumitrascu OM, Wang Y. Self-supervised equivariant regularization reconciles multiple instance learning: joint referable diabetic retinopathy classification and lesion segmentation. Presented at the 18th International Symposium on Medical Information Processing and Analysis (SIPAIM), Valparaiso, Chile by Dr. Zhu


8) Deep Learning Application in Retinal Imaging Classification of Alzheimer’s Disease. AI Summit Oral Presentation by Dr. Oana Dumitrascu in 06/2023. Mayo Clinic Rochester, MN
Interventions for those caring for those with cognitive impairment (CarePRO-VA). Dona E.C. Locke, PhD, David Coon, PhD. Mayo Clinic Arizona, Arizona State University, Arizona Alzheimer’s Consortium.

Specific Aim:
With support from the AAC in the 2021-2022 funding period, the Mayo Clinic team was successfully trained by the ASU staff to become a research sight for the CarePRO-VA caregiver intervention. We ran two sessions of the program with the direct support from the ASU team. For the 2022-2023 period, the aim was for the Mayo Clinic team to independently recruit and run two additional sessions of the research intervention at our site.

Background and Significance:
In the recent Alzheimer’s Association facts and figures report, Arizona shows the highest average amount of caregiving hours out of all states in the nation. Our goal is to continue to build support programs that help our caregivers in their caregiving journey. The Mayo Clinic already has a clinically available multi-component therapy for those with MCI and their partner, the HABIT Healthy Action to Benefit Independence & Thinking ® program. Though partners are included, the program itself is very patient oriented. CarePRO VA has the potential to support caregivers very directly.

Preliminary Data:
As of July 2023, we have completed two additional sessions with a total of 15 subjects recruited from the Mayo Clinic Arizona practice. All groups have completed their 12-week follow-up points as well. We are in the process of sharing that deidentified information with the ASU team (with IRB approval) for entry into the master dataset for CarePRO VA. We continue to communicate with ASU and remain available to help support data analysis, presentations, or manuscript writing with that dataset.

Proposed One-Year and Long-Term Outcomes:
By July 2024, it is the goal of the Mayo Clinic team to have run additional sessions independently of the ASU team to demonstrate success in recruitment and delivery of the program as well as consistency of the quality of the data collected at Mayo Clinic when compared to ASU. Eventually we hope to offer the CarePRO program routinely to our clinical practice.
Western diet induced Alzheimer's pathology: assessment of the brain-gut-bone axis. Layla Al-Nakkash, PhD, Thomas Broderick, PhD, Minsub Shim, PhD, Seungyong Lee, PhD. Midwestern University; Arizona Alzheimer’s Consortium.

Specific Aims:
1. Determine ability of genistein and exercise to reverse build-up of Alzheimer’s-associated brain markers.
2. Determine the impact of genistein and exercise to reverse Alzheimer’s-associated senescence.
3. Determine the effects of genistein and exercise to reverse Alzheimer’s-associated bone loss.

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. Moreover, HFD alone increases peripheral neuropathies and bone loss, and the presence of neuropathy is an independent predictor of fracture incidence or poor fracture repair. Metabolic syndrome is a major contributor towards cardiovascular disease, type II diabetes, insulin resistance and inflammation, which are all risk factors for Alzheimer’s Disease (AD) and dementia. Such dietary habits are correlated with increased deposition of amyloid beta, increased formation of neurofibrillary tangles and reductions in synaptic plasticity. Given the epidemic of obesity in the US, this proposed study is 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 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. In addition, low bone mass, osteoporosis, and increased risk of fractures are common comorbidities in AD and dementia. AD-associated bone loss is not explained solely by low bone mass, and obesity-induced diabetic neuropathy may be a contributing factor to AD-related bone loss.

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 µM, 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: jejunum chloride secretion (basal Iₜₛｃ) 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. Exercise has been shown to improve hippocampal-dependent learning and memory in older individuals and voluntary wheel running has been shown to ameliorate some of the memory dysfunction in HFD C57BL/6J mice. Our group has recently demonstrated that exercise training (along with resveratrol) provided benefits in cardiac function and aortic elastin morphology in the 3xTg mouse model of AD.

**Preliminary Data, Experimental Design and Methods:**
We utilized male C57BL/6J mice purchased from 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. 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 build-up of Alzheimer’s-associated brain markers.**
We examined the effect of HFHS diet in male mice and assessed the influence of genistein, exercise, or both, on the diabetic obese phenotype and the associated changes in brain markers for Alzheimer's Disease. Data to date indicates that HFHS incuses increased the level of protein expression of CT20, CP13, caspase-3 as determined by standard western blot. This was associated with a concomitant decrease in GSk and an increase in pGSK. Genistein and exercise combined induced significant decreases in CP13 and pGSK. We are currently assessing other markers of AD.

**Aim 2. Determine the impact of genistein and exercise to reverse Alzheimer’s-associated senescence.**
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 pH2AX expression with HFHS feeding versus leans and switching to standard diet/water reversed this.
In jejunum tissue, we found a significant increase in pH2AX 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. We are currently assessing senescence in additional tissues such as liver and comparing to brain tissue.

**Aim 3. Determine the effects of genistein and exercise to reverse Alzheimer's-associated bone loss.**

This aim will be assessed in more detail over the coming year. The faculty member that was dedicated to this aim, resigned his position at Midwestern University and returned to South Korea. He has set up a new lab and is able to collaborate again. Delays were also attributed to turnover of the IACUC committee and delays in approval of our protocol. We have recently run another cohort of mice to examine the effects of exercise only on HFHS-fed mice and we will send him tissues/bones as samples are collected (July 2023). With bones collected from this new animal cohort we will examine microCT based quantifications of bone volume (BV), fractional BV (BV/TV), trabecular thickness, trabecular number, trabecular separation, and bone mineral density for trabecular bones.

**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 “Beneficial 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, Lee 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 and we predict this current study assessing reversal effects will be submitted in the next AY for publication.

We are generating extramural grant aims based on the data to date.
Identifying probiotics and the bacterial genes that ameliorate motor dysfunction in a Drosophila Parkinson’s disease model. Gerald B. Call, PhD, Shaleen B. Korch, PhD. Midwestern University; Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: Isolate 15 unique bacterial strains from over-the-counter probiotic supplements.
Aim 2: Identify probiotic bacteria that have motor effects in a Drosophila PD model.
Aim 3: Perform a meta-genome wide association (MGWA) analysis to predict the bacterial genes that influence climbing ability.

Background and Significance:
Early studies have identified specific probiotic strains that ameliorate non-motor and possibly motor symptoms in PD patients. Work in mouse models of PD has supported these encouraging human studies by identifying probiotics that are neuroprotective and improve motor function. The major drawback to current PD probiotic work is that there are no systematic, mechanistic investigations. The types of microorganisms (species) and their dosages varied widely across studies and were apparently randomly selected. Systematic, mechanistic studies with model organisms have the potential to identify probiotics with greater therapeutic potential than current studies have found. In light of this, much of what is known about autosomal recessive-juvenile parkinsonism, a familial form of PD, has been realized using Drosophila melanogaster that are mutant for the parkin gene (park25). These flies exhibit many PD-like symptoms, including, motor dysfunction, loss of olfaction, decreased lifespan, and decreased dopaminergic neurons. We propose that we can utilize this model to screen for potentially therapeutic probiotics.

Preliminary Data, Experimental Design and Methods:
Preliminary bacterial mono-association data with park25 flies indicated that different bacterial species could affect motor function. We set out to expand these studies in a systematic approach with readily available probiotic bacterial strains that could be of immediate potential therapeutic use in PD patients. For Aim 1 we planned to isolate 15 unique bacterial strains from over-the-counter probiotic supplements. We will continue to purchase new probiotic supplements with the goal of isolating 15 additional unique probiotic species. Isolation and identification of unique bacterial strains will occur with standard microbiological techniques and PCR amplification of the 16S rRNA gene and sequencing at the ASU Genomics Core facility. For Aim 2 we will identify probiotic bacteria that have motor effects in a Drosophila PD model. We will individually mono-associate those probiotic bacterial species with PD model (park25) and control (w1118) flies and measure their climbing ability. This involves making the fly embryos germ-free (axenic) using bleach and sterile techniques, placing these embryos on sterile food and letting them culture for one generation. The sterile F1 generation flies are then used to deposit embryos on new sterile food that are then inoculated with a specific bacterial strain. Seven days later, the homozygous park25 pupae are selected based on morphology and placed in new sterile food and allowed to develop to adulthood. The adult flies are transferred to new sterile food one last time, 24 hours before tested in the climbing assay to measure their motor function using a multibeam monitor. Following climbing, the flies are homogenized and the homogenates are cultured on MRS media to verify axenic or mono-association status. This is a laborious undertaking, as only 10 different
mono-associations can be performed at a time, due to pupal transfer time constraints, with the entire experiment taking one month to complete. For Aim 3 we will perform a meta-genome wide association (MGWA) analysis to predict the bacterial genes that influence climbing ability. We will sequence the genomes of the 15 unique probiotic species identified in Aim 1. This is by far the single most costly process of the entire proposal but is absolutely necessary to perform the MGWA. From these sequences (along with the genomic sequences we already have) and Aim 2 climbing data, the MGWA will be performed. The MGWA is a powerful technique that will permit us to predict the bacterial genes that influence climbing ability in both control (w^{118}) and mutant (park^{25}) flies. The MGWA will be performed by first determining the gene presence-absence patterns in the 40 bacterial strains used in Aim 2, by using OrthoMCL software. Finally, we will predict the bacterial genes that are associated with fly climbing ability (beneficial, neutral or detrimental) in each host genotype separately using the MAGNAMWAR R package. We will perform this analysis with assistance from Dr. John Chaston, a Drosophila microbiome researcher at Brigham Young University, who developed this technique for fly microbiome analysis. The result of the analysis is a list of bacterial genes that are statistically associated with variation in fly climbing rate in the two different genotypes.

**Proposed One-Year and Long-Term Outcomes:**
Successful completion of this proposal will characterize the motor effects of 40 different bacteria in a PD model fly, enabling us to identify genes and pathways in the bacteria contributing to the observed effects in mammalian PD models and PD patients. Additionally, this will establish our fly PD model as a fundamental investigational platform/tool that can be routinely used to reveal/evaluate the potential of different probiotic strains and provide key genetic information to systematically explain the mechanistic basis for microbiota-derived effects in PD. Data obtained from this proposal could substantiate the microbiome and probiotic findings in PD patients as well as lead to novel genetic pathways in the microbiome that could alleviate motor symptoms in PD. This finding might be the impetus to a novel therapeutic approach in PD patients. Our results may help explain some of the observational data regarding microbiota differences in PD patients, making the future publication of our screen findings very relevant to the PD-microbiome field. These aims will also yield preliminary data for future grant applications. We plan to use the genes identified in the MGWA as the basis for a future R15 grant proposal.

**Year End Progress Summary:**
We started work immediately on Aim 2 and performed two rounds of mono-association experiments with 10 individual bacterial species in the park^{25} flies. Unfortunately, all of the climbing data showed no significant bacterial effects on climbing as had been observed in our preliminary data. We reasoned that the survival rate of the park^{25} flies through the mono-association technique was very low and that we may be selecting for healthier flies to climb. Therefore, we set out to identify a more vigorous parkin mutant stock with the idea that this may provide more meaningful climbing data. However, upon analysis of more bacterial mono-association climbing data from other experiments, we determined that the MGWA would likely not provide meaningful data. Therefore, we changed the directions of our project.

For the new direction of our genomic sequencing aim, our previous data in different PD model flies indicated that Acetobacter tropicalis was more enriched in conventional microbiome PD model flies (four different genetic mutants from different laboratories) compared to their controls. Additionally, A. tropicalis dominates the overall bacterial load when park^{25} flies are inoculated with equal amounts of four different bacterial species after being made axenic. These
data strongly suggest that *A. tropicalis* is interacting with PD model flies in some way. Therefore, we believe that a more comprehensive analysis of different *A. tropicalis* strains from the different PD model and control flies may reveal the basis for this interaction. We have cultured *A. tropicalis* from 11 different fly stocks and have sequenced their genomes in order to analyze genetic differences that may exist between the *A. tropicalis* strains that are present in PD model flies versus control flies. We will also be performing mono-association experiments with these different *A. tropicalis* strains to determine which of them has the capacity to dominate the fly microbiome, as observed with our two previously identified strains.

We have very recently identified the presence of “kidney stones” in our *park*²⁵ PD fly model. This is a completely novel phenotype in this very well-characterized PD fly model. The Malpighian tubule (MT) is the excretory organ of the fruit fly that is analogous to the kidney. The MT is a blind-ended, monolayer epithelial tube that filters the hemolymph of the fly. MT cells regulate ionic balance by transporting ions, including H⁺ and organic cations, and water through aquaporins through their main two cell types: principal and stellate cells. There are hard concretions within the MTs of the *park*²⁵ flies that are not present in control flies. We believe these are analogous to kidney stones. We decided to change the direction of our research supported by the AAC to the characterization of these kidney stones.

Our overall hypothesis is that mitochondrial dysfunction induced by the *park*²⁵ mutation leads to reduced pump function in the MT promoting stone formation, contributing to the decreased lifespan of these flies. Given that the identification of this phenotype is only months old, we are still in the initial characterization phase of this project; however, we have collected some data. We have determined that the stones are mostly composed of an organic material, with some calcium phosphate nodules. Stone development happens throughout larval development and their presence continues through metamorphosis into the adult fly with 72% of newly eclosed adults having stones present. The amount of MT area that the stones occupy increases as the fly ages, going from 0.6% on day 0 post-eclosion to 2.5% on day 20 post-eclosion.

In addition to this stone analysis, we have also observed that the MTs in the *park*²⁵ fly are much larger than control flies upon initial dissection and following tissue fixation. Preliminary analysis suggests that this size difference appears to be reduced following the tissue fixation process, suggesting that the cells may be hypertrophied by fluid accumulation. In addition to this, a marked cellular proliferation occurs in the lower tubule and ureter portion of the MT in the *park*²⁵ flies that is not present in control flies. This is very similar to a phenotype observed in flies with a mutation in the *xanthine oxidase* gene that have xanthine stones in their MTs. In these flies, the renal stem cell population expands and differentiates into small principal cells in order to allow the lower tubules and ureters to expand in size and allow passage of the stones, thereby improving the flies’ ability to deal with the stone and live longer. We believe that this is what is happening in the *park*²⁵ flies, which is readily observed by nuclear staining.

We understand that the work which we performed was not in line with what we proposed. However, the overall goal of our laboratory, to better understand PD through the characterization and use of *Drosophila* PD models was advanced significantly with the AAC funding and we believe that two publications will arise from this support.
The Telomere Protection Protein RAP1 and the epsilon isoform of glial fibrillary acidic protein activate gamma-secretase activity. Mark J. Swanson, PhD, Nancy S. Bae, PhD. Midwestern University; Arizona Alzheimer’s Consortium.

Specific Aims:
Specific aim 1. Test known γ-secretase protein modifiers in our yeast system.
Specific aim 2. Test the effects of RAP1/GFAPε on the Notch1 cleaving activity of γ-secretase.
Specific aim 3. Determine the effects of RAP1 and GFAPε overexpression in human cells.

Background and Significance:
Deposition of amyloid peptides in senile plaques is a hallmark of AD. Early-onset, familial AD (eFAD) afflicts individuals from their 30s to their 60s and is due primarily to mutations in APP, PSEN1 or PSEN2. APP encodes the amyloid precursor protein (APP). β-secretase and γ-secretase sequentially cleave APP producing amyloid β (Aβ) peptides. γ-secretase contains a catalytic subunit, either presenilin 1 or 2 proteins (PS1 or PS2, encoded by the PSEN1 and PSEN2 genes, respectively) and three non-enzymatic subunits Aph-1A, Nicastrin, and Pen-2. γ-secretase cleaves APP to produce Aβ peptides that are released into the environment and the amyloid precursor protein intracellular domain (AICD), which enters the nucleus to affect gene expression. Normally, most Aβ peptides produced are 40 amino acids in length (Aβ40) and are soluble. Less frequently, less soluble Aβ42 peptides are made. When the ratio of Aβ40:42 favors Aβ40, the brain functions without AD-related pathology. Higher levels of Aβ42 promote self-aggregation resulting in senile plaque formation. Mutations associated with eFAD either increase the overall amount of Aβ peptides or increase the ratio of Aβ42 to Aβ40.

Regulation of γ-secretase is being explored through naturally occurring proteins (γ-secretase protein modulators or GSPMs), which include the γ-secretase activating protein (GSAP), the hypoxia inducible transcription factor 1α (HIF-1α), interferon-induced transmembrane protein 3 (IFITM3), and the stress-associated endoplasmic reticulum protein 1 (SERP1). Among the proteins interacting with γ-secretase is an isoform of the glial fibrillary acidic protein (GFAP), the most abundant isoform of which is GFAPα. GFAPε is a minor isoform that interacts with the PS1 and PS2 proteins. GFAPε was shown to be expressed by neurogenic astrocytes in the granular zone of the hippocampus, a site of adult neurogenesis. Our lab has identified an interaction of GFAPε and PS1 with RAP1, a telomere protection protein. This is important since telomere shortening is a cellular aging mechanism, and a meta-analysis showed evidence of shorter telomere length in AD patients. Thus, our work is the first to link a protein involved in cellular aging with Alzheimer’s disease, an age-related disorder.

Preliminary Data, Experimental Design and Methods:
GFAPε and RAP1 interact with PS1, and the interaction likely modulates γ-secretase activity. To test this, we developed a yeast γ-secretase system that expresses the four subunits of γ-secretase with PS1 as the catalytic subunit as most mutations leading to eFAD are in PSEN1. Our target gene for γ-secretase activity is a fusion of the γ-secretase cleaved portion of APP and the yeast GAL4 transcriptional activator. When this fusion protein is expressed in yeast, the APP
portion is embedded in the plasma membrane, trapping the GAL4 protein at the cellular periphery, preventing it from entering the nucleus. When γ-secretase is active, and the APP portion is cleaved, GAL4 will be released from the membrane and enter the nucleus where it can activate reporter genes. Reporter gene activity is measured by growth in certain media or by the expression of an enzyme to provide quantitative data. Our preliminary data showed that when GFAPε and RAP1 were expressed in these cells, γ-secretase activity only increased severalfold when both proteins were expressed.

**Methods/Experimental Plans:**

**Specific aim 1. Test known γ-secretase protein modifiers in our yeast system.** We will test each of the four known GSPMs (GSAP, HIF-1α, IFITM3 and SERP1) in our yeast γ-secretase system to show that our reconstituted system functions like human γ-secretase. We will compare γ-secretase activity when RAP1 and GFAPε are expressed side-by-side with the known GSPMs. The results of this work should validate our yeast γ-secretase system for us to use in additional studies on γ-secretase and additional modifier proteins.

**Specific aim 2. Test the effects of RAP1/GFAPε on the Notch1 cleaving activity of γ-secretase.** γ-secretase has numerous target proteins. The Notch 1 protein has been used to characterize most of the known GSPMs. We will determine the effects of RAP1 and GFAPε on cleavage of Notch1 in our yeast γ-secretase system. The vector and plasmids expressing the GSPMs and RAP1/GFAPε will be transformed into the yeast γ-secretase/Notch1-GAL4 strain. We will use phenotypic and colorimetric enzyme assays to measure γ-secretase activity on Notch1. Establishment of a Notch1-reporter assay in yeast will also be important for our future screens for novel γ-secretase protein modifiers to classify them as APP specific or general modifiers affecting γ-secretase activity on multiple targets.

**Specific aim 3. Determine the effects of RAP1 and GFAPε overexpression in human cells.** In addition to using the yeast system, ultimately, we will need to verify our results using human cells since this AD is a human disease. We are proposing experiments that can be done in our labs that should provide enough data for us to be competitive for grants in which we can get funding for more expensive experimental options. For our work, we have chosen to use the U251 glioblastoma and SH-SY5Y neuroblastoma cell lines since these immortalized cell lines are neuronal. We will clone RAP1, GFAPε and RAP1/GFAPε into human expression vectors to determine their effects on γ-secretase cleavage of APP by detecting Aβ peptides secreted into the cell growth medium by ELISA.

**Proposed One-Year and Long-Term Outcomes:**

The research in this application is significant because we have identified novel protein modulators of γ-secretase activity that may be useful in identifying new AD susceptibility loci and targets of therapeutic intervention, and this work provide insight into the mechanisms for the production of amyloid peptides leading to plaque formation, a hallmark of AD pathology. The research proposed in this application has been designed to address the concerns reviewers of our R15 REAP application had. One of the main concerns was that the γ-secretase complex in yeast was not stable, and the interaction with RAP1 and GFAPε may merely be stabilizing the complex, leading to an increase in activity as opposed to being true GSPMs. Thus, we will use known GSPMs to validate our system. The use of a second γ-secretase target protein, Notch1, may also show differential cleavage compared to APP when RAP1 and GFAPε are co-expressed, which would indicate that the complex is not merely being stabilized. Finally, we will assess the
effects RAP1 and GFAPε have in human cells, which is more complicated but required for publication. It is important for us to validate our yeast γ-secretase system since we will use it for additional studies on γ-secretase and its modifiers, including functional screens that cannot be easily done in human cells. The data obtained from this work will be used to support the research proposed in our R15 REAP application as well as preliminary data for additional applications. The data will also be used in publications.

Year End Progress Summary:

**Specific aim 1. Test known γ-secretase protein modifiers in our yeast system.** Each of the known GSPMs (GSAP, HIF-1α, IFITM3 and SERP1) were amplified by PCR, sequence verified, cloned, and expressed in our yeast γ-secretase system. We used the activation of an enzyme encoding gene (β-galactosidase) to provide quantifiable data. Amongst the four, only GSAP resulted in a significant, ~3-fold increase in γ-secretase activity. GFAPε does not alter γ-secretase activity on its own, but RAP1 expression resulted in a 10-fold increase. Co-expression of GFAPε with RAP1 increased the activity an additional 2-fold. The increase in γ-secretase activity by GSAP validates our yeast system. Although the other GSPMs did not show any effects on γ-secretase activity in the yeast system, it may be a consequence of removing these proteins from the human cell context. This may be an indication that there are additional regulatory proteins that would be of interest.

**Specific aim 2. Test the effects of RAP1/GFAPε on the Notch1 cleaving activity of γ-secretase.** The human Notch1 gene has been difficult to clone. We are still working to clone this into our system since it is the best studied target of γ-secretase second only to APP. It is still of interest to determine whether RAP1 is a specific or general regulator of γ-secretase activity. Towards this end, we are attempting to clone N-cadherin as another target of γ-secretase in addition to Notch1.

**Specific aim 3. Determine the effects of RAP1 and GFAPε overexpression in human cells.** Our data from the yeast γ-secretase system indicated that RAP1 alone could increase γ-secretase activity. Thus, we transfected a plasmid overexpressing RAP1 into both SH-SY5Y and U251 human cell lines. Aβ40 and Aβ42 levels in the medium were measured using ELISA. The peptides were undetectable from the SH-SY5Y cell samples. However, U251 cell growth medium showed a modest (~1.7-fold) but significant increase in Aβ production with RAP1 overexpression compared to the vector alone. We have obtained a dual promoter vector for human cells, and we are cloning both RAP1 and GFAPε into it to test the effects of overexpressing both proteins in human cells.

Results from this project were used in a publication:

Swanson MJ, Lewis KN, Carpenter R, Whetzel A, Bae NS. The human RAP1 and GFAPε proteins increase γ-secretase activity in a yeast model system [published online ahead of print, 2023 Mar 17]. G3 (Bethesda). 2023;jkad057. doi:10.1093/g3journal/jkad057
PMID: 36929840

In this article, we showed:
- RAP1 specifically interacts with GFAPε not GFAPα (Yeast 2-hybrid and in vitro)
- RAP1, GFAPε, and PS1 can form a complex in vitro
- RAP1 can directly interact with PS1 in vitro
- Immunoprecipitation of RAP1 can coprecipitate GFAPε from human cells
• RAP1 and GFAPε co-localize with subunits of γ-secretase (nicastrin and PS1) using immunofluorescence microscopy
• RAP1 increased γ-secretase activity, and GFAPε was able to potentiate this in our yeast γ-secretase system,
• Overexpression of RAP1 in human U251 cells gave a significant increase in Aβ levels indicating it could increase γ-secretase activity

The results from this project will also be used for a future application for federal funding, which will be supported by the above publication.
Geroscience approach to Alzheimer’s disease: mitigation of cellular senescence by intermittent fasting. Minsub Shim, PhD, Layla Al-Nakkash, PhD, Seungyong Lee, PhD, Midwestern University; Arizona Alzheimer’s Consortium.

**Specific Aims:**
Senescence Accelerated Mouse-Prone 8 (SAMP8) mice are a sub-strain of senescence-accelerated mice (SAM) and are characterized by an early manifestation of age-related phenotypes, including age-related deficits in learning and memory. 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 the impaired cognitive function and pathological changes in the brain of aged SAMP8 mice.

The research conducted during this funding period was an extension of the previous project, which would allow for complete behavioral, histopathological, and biochemical analyses with additional animals.

**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 the goal of “healthy aging”. The evidence increasingly supports the connection between cellular senescence and organismal aging.

Recently, intermittent fasting has emerged as a more palatable alternative to caloric restriction. Many studies have shown that intermittent fasting can have similar effects as caloric restriction. In humans, intermittent fasting has been shown to improve numerous health conditions. Similarly, intermittent fasting has also 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 for 9 months. Before the termination of the experiment, behavioral tests were conducted with nine-month-old mice. The mice were then 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). Four medical students are currently working on this project as their summer research program. The findings from this study will be presented at Kenneth A. Suarez Research Day at MWU as well as in the 2023 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 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 the behavioral tests including the Novel Object Recognition test, Barn’s maze test, and Morris water maze (MWM) test. 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 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.
Progranulin & lysosomal pH: implications for potential new therapeutic strategy for neurodegenerative diseases. Elizabeth Hull, PhD, Kathryn Leyva PhD. Midwestern University, Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: Lysosomal pH differences between SW13 subtypes with and without PGRN knockdown
   A. Assessment of lysosomal pH using the lysosensor DND-160 pH sensitive ratiometric fluorophore
   B. Assessment of lysosomal pH using the lysosensor DND-189 pH monochromatic fluorophore
   C. Assessment of lysosomal pH after knockdown of endogenous PGRN

Aim 2: Lysosomal pH and lysosomal function with expression of granulin units
   A. Lysosomal pH differences in the SW13+ subtype expressing C-terminal granulin units
   B. Lysosomal function in SW13+ and SW13- subtypes expressing C-terminal granulin units

Background and Significance:
The central question investigated by this proposal is the proposed causal link between PGRN and lysosomal pH and how this may impact the development of neurodegenerative diseases (NDD). Both lysosomal pH and progranulin (PGRN) are independently linked to but how each contributes to NDD pathology is unclear. Several lines of evidence suggest that there is a functional link between PGRN and lysosomal pH. First, mutations in PGRN lead to lysosomal dysfunction and restoring PGRN supports lysosomal protease activity. Second, PGRN promotes the trafficking of lysosomal proteases such as prosaposin to the lysosome. Third, not only is PGRN processed by lysosomal proteases, the resultant granulin units bind to and stabilize lysosomal proteases. Fourth, suggestive of a homeostatic mechanism, PGRN insufficiency is linked to increased lysosomal protein and gene expression levels. Thus, reductions in PGRN levels appear to be correlated with lysosomal dysfunction and altered lysosomal processing of PGRN but how these are linked to NDD is an open question. This work addresses the link between lysosomal pH and PGRN. As the measurement of lysosomal pH using non-disruptive dyes in living cells has only recently become an accessible technique, the link between PGRN and its cleavage products with lysosomal pH has not been investigated and is an open question which can now be addressed. If the proposed causal link between PGRN processing and lysosomal pH is substantiated, it will lay the foundation for new therapeutic strategies for delivery of PGRN to the brain and/or restoring lysosomal function in neurodegenerative disease.

Preliminary Data, Experimental Design and Methods:
Measurement of pH will be conducted using fluorescent dyes. The ratiometric DND-160 dye will be performed to provide verification of pH differences between subtypes using the most reliable pH sensitive dye currently available. As a standard curve is generated for each experimental sample, a specific pH value is generated by these experiments [18]. A second pH sensitive dye, DND-189 will be performed to confirm the data in cells treated with lysosomal pH disruptors or stabilizers. Experiments determining lysosomal pH and function (as measured by protease activity) will be performed with and without expression of siRNA for PGRN and expression of PGRN and granulin units. Each of these C-terminal granulin units will be expressed using a
tetracycline inducible expression vector system which will enable the modulation of expression levels and establishment of stable cell lines if required for future experiments.

**Proposed One-Year and Long-Term Outcomes:**
At the end of the one-year grant period, we anticipate the submission of an initial manuscript combining existing data with the addition of results from Aim 1 on differences in pH between the two SW13 subtypes. Data generated in the completion of Aim 2 will provide the groundwork for an extension of this project. If expression of any of the C-terminal granulin units alter lysosomal pH in SW13 subtypes, future experiments will investigate the ability of these expression constructs to alter lysosomal function in neuronal cell lines. In addition, if appropriate samples can be obtained, we plan to assay levels of these C-terminal granulin units in clinical samples and/or disease models.

**Year End Progress Summary:**
Progress was made on both aims of the proposal despite a myriad of challenges. Specific progress, challenges encountered, and ongoing experiments are summarized below by Specific Aim. It is anticipated that the initial will be submitted by the end of the calendar year. In addition, we have broadened part of this initial work to include microglial cell lines to lay the foundation for future experiments addressing the potential role of PGRN and lysosomal function in promoting neuroinflammation.

**Aim 1: Lysosomal pH differences between SW13 subtypes with and without PGRN knockdown**

**A. Assessment of lysosomal pH using the lysosensor DND-160 pH sensitive ratiometric fluorophore.**

pH differences between the lysosomes of each of the SW13 subtypes has been confirmed with the ratiometric DND-160 fluorescent dye with a pH difference of >1 pH unit. Data with this dye after treatments with hydroxychloroquine and treatments to modulate lysosomal proton pump V-ATPase activity are ongoing but preliminary data is promising. Progress has been slow due to data analysis challenges presented by use of the DND-160 dye. Specifically, lysosomes in each image must be manually identified for fluorescent intensity measurement in each image. To accelerate progress, we have shifted experimental approaches. Use of the DND-160 dye in dextran form (rather than diffusible DND-160 dye) removes the necessity for manually identifying the lysosome in each image and this new experimental approach has replicated existing data and dramatically reduced analysis time.

**B. Assessment of lysosomal pH using the lysosensor DND-189 pH monochromatic fluorophore**

Use of this dye was originally proposed to facilitate more rapid data analysis than would be possible with the DND-160 diffusible dye. With the experimental advantages of DND-160 dextran which retains the advantages of a ratiometric quantitation, these advantages are no longer applicable. Therefore, aside from some preliminary experiments, we have not pursued use of diffusible DND-189, and current experiments focus on use of DND-160 dextran to take advantages of pH calibration and loading control.

**C. Assessment of lysosomal pH after knockdown of endogenous PGRN**

shRNA constructs for PGRN knockdown have been selected and all reagents necessary for routine transient transfection. Initial siRNA transfections have been performed but quantitation of
knock-down and additional experiments have not been completed. To facilitate overall progress on grant aims, experiments on these siRNA knockdowns will be performed in parallel with the expression of PGRN and granulin units and further experiments on this sub-aim have been delayed until the stable transfectants in Aim 2 are complete.

Aim 2: Lysosomal pH and lysosomal function with expression of granulin units

A. Lysosomal pH differences in the SW13+ subtype expressing C-terminal granulin units
The sixteen required expression constructs for full-length and C-terminal fragments with and without flag-tag have been made and establishment of stable, inducible cell lines from each is ongoing. The number of transfections and selection has proved challenging as selection conditions have needed to be adjusted to allow for PGRN expression. Currently, stably transfected lines have been obtained for approximately two thirds of the cell lines and, now that conditions have been modified, progress in obtaining stable cell lines is expected to be rapid. pH measurements with DND-160 dextran are commencing in these cell lines.

B. Lysosomal function in SW13+ and SW13- subtypes expressing C-terminal granulin units
Assays determining lysosomal proteolytic activity have developed in the laboratory and collection of data is ongoing. Currently, differences in overall protease activity within the lysosomal compartment are visualized in living cells using a fluorescently quenched casein particle (Lysoview 488). We have developed both a 96-well plate-based assay and a fluorescent microscopy-based approach. Data substantiate reduced lysosomal protease activity within the lysosomes of SW13+ cells and in a pH dependent fashion. The efficacy of PGRN and granulin unit expression to restore proteolytic activity within the lysosome is currently being addressed.
Preparedness of Arizona physical, occupational, and speech therapy practitioners for working with clients with Alzheimer’s disease and related dementias: A pilot study. Tamara Turner, EdD, OTR/L, Patrice Ayala, PT, DPT, Stephanie Christensen, PhD, CCC-SLP. Midwestern University; Arizona Alzheimer’s Consortium.

Specific Aims:
The intent of this study is to better understand physical, occupational, and speech therapy practitioners’ readiness to work with clients with Alzheimer’s and Related Dementias (ADRD).

Background and Significance:
Dementia is a general term used to describe a progressive neurodegenerative disease that impairs one’s ability to remember, think, or make decisions that interfere with everyday activities (CDC, 2019). 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. Individuals lose their mobility, ability to communicate, and independence to complete daily living activities or meaningful tasks by themselves (Alzheimer’s Society of Canada, 2019).

Training for dementia care is essential for those working with persons living with dementia (Takizawa et al., 2017). Professionals need to be able to work with the persons living with dementia (PwD) and their carepartners. They need a broad set of skills to most effectively do so (De Vriendt et al., 2018). One study found that assessment for cognition and delirium were inadequate in acute care despite access to physical, occupational, and speech therapy services (Timmons et al., 2016). Another study found an increase in rehabilitation clients with dementia diagnoses and a lack of knowledge regarding dementia care and an accurate understanding of capabilities of a PwD (O’Brien et al., 2019). It is important to understand the preparation and readiness of physical, occupational, and speech therapy practitioners to treat PwD in order to improve dementia care.

Preliminary Data, Experimental Design and Methods:
The researchers on this team each teach the dementia content in their respective programs. The accreditation standards for doctoral degree physical therapy programs, doctoral degree and master’s degree occupational therapy programs, and doctoral degree speech language pathology programs do not specify dementia specific knowledge or treatment strategies (CAPTE 2021, ACOTE, 2018, & CAA, 2021). Although, accreditation standards do not specifically mention diagnoses, but rather therapeutic processes, it does leave the content to be taught up to each individual program. This means that an entry-level practitioner may or may not have a baseline knowledge of ADRD and appropriate treatment strategies.

Proposed One-Year and Long-Term Outcomes:
The researchers plan to publish the results of their study. The researchers expect the findings of this study to lead to the development of survey items for a national survey. That survey in turn will better inform postsecondary education and continuing education regarding the educational needs
of practitioners regarding dementia care. The most important deliverable is to lead to a positive impact in the lives of care partners and persons living with ADRD.

**Year End Progress Summary:**
A purposive sample was used to recruit practitioners from each discipline (Physical, Occupational, and Speech Therapy) and from the following adult practice settings: Acute Care, Acute Rehab, Skilled Nursing, Home Health, and Outpatient Rehab. It was aimed to recruit 5 practitioners from each setting and each discipline for a total of 75 participants. Researchers were able to recruit 75 participants, however some setting/discipline categories had less than 5 participants and others had more than 5 practitioners.

Each participant completed a demographic/background survey. Sixteen Focus groups were held with mixed disciplines and settings. The Focus Groups were moderated by one of the investigators. The discussion focused on practitioner knowledge of ADRD and comfort level in working with clients with an ADRD diagnosis. Focus sessions were recorded.

Focus sessions are in the process of being transcribed. Transcripts, notes, documents, and any other related materials will be gathered, reviewed, coded, and then combined into themes. 6 work study students have been hired to assist with transcription and qualitative data analysis. Coding and Thematic analysis will be completed by the PI/Co-PI of the same discipline and 2 work study students of the same discipline.

Preliminary findings show a lack of knowledge of how to and where to find quality intermediate and advanced level continuing education. Also noted was the barrier of time and a desire for therapy managers to provide guidance on furthering education.

The researchers plan to publish the results of their study. The researchers expect the findings of this study to lead to the development of survey items for a national survey. That survey in turn will better inform postsecondary education, continuing education, and mentoring regarding the educational needs of practitioners for the provision of dementia care. The long-term goal is to lead to a positive impact in the lives of care partners and persons living with ADRD through the findings and applications identified.
Defining the role of gut microbiome enrichment of *Bacteroides* spp. in mice modeling Alzheimer’s disease pathologies using an integrated multi'omics approach. Emily K Cope PhD, J Gregory Caporaso PhD, Jonathan Lifshitz, PhD. The Pathogen and Microbiome Institute, Northern Arizona University, Barrow Neurological Institute at Phoenix Children's Hospital, University of Arizona College of Medicine, 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 of interest in Alzheimer’s Disease (AD). We have demonstrated that *B. fragilis* is enriched in 3xTg-AD mice compared to the WT genetic background. We hypothesize that *B. fragilis* contributes to AD pathologies by driving a neurotoxic inflammatory milieu, mediated by *B. fragilis*-derived metabolites in the context of a dysbiotic gut microbiome.

**Specific Aim 1.** Assess the growth dynamics of orally-administered *Bacteroides fragilis* and association with neuroinflammation, amyloidosis, and cognitive function in 3xTg-AD and wild-type B6129SF2/J mice aged to 52 weeks.

**Specific Aim 2.** Build a multi’omic model of the gut microbiome-brain axis to determine the microbial and metabolic features that predict amyloidosis, tauopathy, and neuroinflammation in naïve and *B. fragilis*-treated mice.

**Background and Significance:**
The gut microbiota-brain axis is the bidirectional communication between the gut and brain through immune, nervous, metabolic, and endocrine signaling.¹ These collective mechanisms regulate a number of physiological processes, including gut motility and permeability², and inflammation at extra gastric sites, such as the brain.³ Major perturbations to the gut microbiota-brain axis signaling is associated with diseases affecting brain, including Alzheimer’s disease (AD).³ Alterations in the gut microbiome can contribute to inflammation in the brain via diverse pathways, including microbial-derived metabolites entering circulation and acting on systemic immune population.⁴ Since neuroinflammation is a key feature of Alzheimer’s Disease (AD), and contributes to characteristic AD pathologies, understanding the aging gut microbiome is critical to understanding AD progression.

In our prior studies supported by the AAC, we observed a marked increase in *Bacteroides* in the gut microbiome of 3xTg-AD mice prior to the time point at which amyloid-β plaques are prevalent. *Bacteroides* have been implicated in health status and are likely key contributors to host-microbial interactions via the gut microbiome-brain axis. Several species of *Bacteroides*, including *B. fragilis*, function ecologically as keystone species, indicated by low relative abundance and disproportionately numerous interactions within the microbial community.² *B. fragilis* can influence the gut microbiome-brain axis by modulating serum metabolites and GI inflammation in a mouse model of Autism Spectrum Disorder.⁸ In other studies of AD, *Bacteroides* were increased in abundance in mice expressing a variant of human APP (APPSwe [Tg2576]) compared to control mice and were positively correlated with amyloid-β burden.⁹ Another study using 5xFAD mice, which model amyloidosis at an earlier time point than 3xTg-AD mice, demonstrated increased relative abundance of *Bacteroides* in 5xFAD mice at 10 weeks of age. The 10 week time point in 5xFAD mice and the 24 week time point in 3xTg-AD mice (where we observed the first increase in *Bacteroides*) both represent development of amyloidosis in the
We hypothesize that enrichment of Bacteroides contributes to amyloidosis and neuroinflammation through production of proinflammatory metabolites that enter systemic circulation.

**Preliminary Data:**
Our group and others have demonstrated an altered relative abundance of Bacteroides in rodents modeling AD pathologies and human participants with AD. We have demonstrated that gut microbiome alterations in 3xTg-AD mice generally precede onset of pathologies, which was recently supported in a human study of AD. This human study demonstrated robust changes in the gut microbiome of participants with preclinical AD, suggesting that the gut microbiome may change early in the disease process. Our study contributes mechanistic insights that will inform our understanding of the contribution of gut microbiome dysbiosis to development or progression of AD pathologies. Because the gut microbiome is strongly influenced by lifestyle factors, including those related to AD risk, we hope that these results will contribute to the prevention or early detection of AD pathologies.

**Experimental Design and Methods:**
This is a continuation of the study initiated in the past year of AAC support. Mice have been bred at NAU and were challenged with Bacteroides fragilis (10^10 CFU in 1mL of applesauce) or vehicle control (PBS in applesauce). To measure growth dynamics, mice were also randomized into groups receiving 16-O and isotopically labeled 18-O. The following experimental groups will be included for both 3xTg-AD and B6129SF2/J wild-type mice: 1) oral PBS (vehicle control), mice maintained on H_2O_16, 2) oral PBS, mice maintained on H_2O_18, 3) Bacteroides fragilis, mice maintained on H_2O_16, and 4) B. fragilis, mice maintained on H_2O_18. Upon sacrifice, the GI tract (ileum, cecum, colon, and a fecal pellet), blood, and cerebrospinal fluid (CSF) will be collected. Hippocampus and frontal cortex 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. For 16S rRNA gene sequencing, the universal primers 515F and 806R will be used to amplify the V4 region as previously described. Amplicons will be sequenced on the Illumina MiSeq. For metabolomics, serum and fecal samples are collected at terminal timepoints for untargeted metabolomics. We will analyze a total of 240 samples from 120 mice (paired fecal and serum). This will enable detection of significant differences with 82% power, and was determined by a power calculation, our pilot data demonstrating a moderate effect size, and feasibility within the proposed budget and timeline. We will focus on 3xTg-AD and WT mice from terminal samples described above (8, 24, and 52 weeks). Flash frozen fecal, serum, hippocampus, and frontal cortex samples will be sent to Dr. Aron for untargeted metabolomics using LC-MS as previously described.

**Proposed One-Year and Long-Term Outcomes:**
These studies will be the first mechanistically to assess the role of a gut microbiome characterized by predominance of Bacteroides fragilis in driving AD pathologies. The work proposed here is a logical extension of our prior AAC-supported findings and is a continuation of our past year’s support so that we can evaluate mice up to 52 weeks of age. As a result of our funding in the AAC, we received an NIH/NIA R21, the goal of which is to develop a qSIP to study microbiome dynamics in the GI tract of 3xTg-AD mice, a technique that we are leveraging in this study. We anticipate that results from this year will support an additional NIH submission.
Year End Progress Summary:

Aim 1 (B. fragilis intervention and gut microbiome dynamics). We have analyzed ~500 fecal samples from 115 mice that were treated with B. fragilis or vehicle control, and randomized to consume isotopically enriched 18-O or normal 16-O water. Microbiome analyses were performed using QIIME2. Microbiome bioinformatics were performed with QIIME 2.18 q2-DADA2 was used for sequence quality control and generation of amplicon sequence variants (ASVs) to provide the highest taxonomic specificity.19 Alpha diversity, including Faith’s Phylogenetic Diversity,20 Shannon Diversity Index,21 and Observed ASVs were computed with q2-diversity.20 Beta diversity (community dissimilarity) metrics were computed with q2-diversity, including Bray-Curtis dissimilarity, Jaccard dissimilarity, weighted UniFrac,22,23 and unweighted UniFrac distances. Longitudinal analysis was performed with q2-longitudinal to assess temporal changes in bacterial communities.24 Group comparisons of alpha diversity were performed with non-parametric Wilcoxon tests, and group comparisons of beta diversity were performed with non-parametric PERMANOVA.25 Cage effects were assessed using volatility analysis with PC1 of Jaccard and Unweighted UniFrac distances, and a multivariate PERMANOVA was performed using genotype and cage as covariates using adonis in R.26 ASVs and taxa that were differentially abundant across mouse strains were identified using ANCOM.27 All P-values were corrected for multiple comparisons using the Benjamini-Hochberg False Discovery Rate correction. We demonstrated several key findings. First, B. fragilis colonized 3xTg-AD mice more successfully than in WT mice. In 3xTg-AD mice, B. fragilis colonized 100% of treated mice, and indigenous Bacteroides were depleted. In WT mice, B. fragilis colonized at a lower relative abundance, and indigenous Bacteroides were present at a high relative abundance. Indigenous Bacteroides were defined as features that were present in pre-treatment samples and in mice treated with PBS. We have performed two cognitive tasks that test spatial memory (Morris Water Maze) and temporal memory (Temporal Order Recognition), and data analysis is underway. Immunohistochemistry and gene expression analyses have also been performed on terminal samples at 8, 24, and 52 weeks and data analysis are underway.

Aim 2 (multi’omic model of the gut microbiome-brain axis). Frozen fecal, serum, frontal cortex, and hippocampus samples were extracted with a mixture of water/methanol, sonicated, and centrifuged to separate soluble components for liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis on a Thermo Vanquish UPLC coupled to a Thermo Q Exactive HF mass spectrometer. Data processing was performed using the feature finding software MZmine 3 along with the molecular networking platform Global Natural Products Social (GNPS), and univariate and multivariate statistics were performed using custom codes in R Studio. Multivariate analysis demonstrates that metabolome trends similarly with the microbiome observations that we reported in our recent paper, with a largest separation at week 8 (PERMANOVA p=0.03), that continues until the endpoint at week 52 (PERMANOVA p=0.002).10 Integrated analyses are currently underway.

Toward our 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 also published a manuscript in Microbiology Spectrum describing our findings in a longitudinal cohort of 3xTg-AD and WT mice.10


TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
PROJECT PROGRESS REPORTS

**Specific Aims:**
The specific aim of this project is to utilize the genome-wide SNP data from the MindCrowd cohort to calculate and identify those polygenic risk scores (PRS) associated with verbal memory performance.

**Background and Significance:**

*MindCrowd.* The MindCrowd cohort was founded by Drs. Huentelman and Ryan in 2013. It currently includes approximately 300,000 non-demented participants from around the world who have provided basic demographic information as well as completed two brain tasks – simple visual reaction time and verbal memory paired associates learning. Genome-wide SNP data is available for ~1,000 participants and we have funding to increase this to 20,000 during the course of the next five years.

*Polygenic Risk Scores (PRS).* PRS are based on the existing catalog of human genome-wide association studies (GWAS). GWAS include both human diseases and traits. We have downloaded and pre-processed hundreds of GWAS studies that are both large and have data available for public use. Using these data, we can calculate a PRS for each disease/trait in any individual with genome-wide SNP data. PRS act as an aggregate, genetic-based risk score for each disease/trait of interest.

*Integration.* We propose to integrate the PRS approach with the verbal memory results obtained in MindCrowd. This will be performed across the hundreds of high-quality PRS currently available – and more, in the future, as they evolve. This will allow us to determine which PRS are most correlated with performance.

*Significance.* PRS can act as genetic-based predictions for common complex diseases and traits. However, it is currently unknown if PRS may cross-correlate with other diseases and traits. For example, would a PRS for Alzheimer’s disease also predict an individual’s memory performance decades before diagnosis? If this is true, what are the parameters for the sensitivity and specificity of such a measurement? What other PRS may correlated with verbal memory performance? For unanticipated correlations, what implications does that hold for a better understanding of verbal memory?

**Preliminary Data, Experimental Design and Methods:**

*SNP genotype data processing.* As new SNP data is generated for MindCrowd participants we will process the data, impute it with standardized approaches and stage it for PRS calculation.

*PRS curation.* We will continue to curate our internal PRS database on a monthly basis. This includes to assessment and incorporation of qualifying GWAS results.

*Statistical correlation between PRS and verbal memory.* Regression analysis will examine the correlation between each PRS and verbal memory results as assessed in MindCrowd. Co-variates will be included and association p-values will be corrected for the number of PRS investigated in parallel. Additionally, we will utilize an 80:20 split between discovery and validation.
coHORTS – only considering those PRS scores that were significant during discovery for replication in the validation cohort.

**Proposed One-Year and Long-Term Outcomes:**
At the end of one-year, we will have genotyped a large (1,000+) cohort of MindCrowd participants and have completed the genetic PRS analysis. For the longer term, we will continue to collect DNA from MindCrowd participants and grow our cohort to ~5,000 participants over five years. This will provide us with the opportunity to confirm our results and refine our PRS-based analyses.

**Year End Progress Summary:**
During the grant period, we collected and genotype 1,328 samples from MindCrowd participants. Each genotyped sample was imputed to ~30 million genome-wide SNP profiles. The resulting data was used to determine each participant’s APOE status as well as their PRS results for our entire catalog of human traits and diseases (~100 different conditions). We also performed a genome-wide association study (GWAS) that attempted to relate each individual’s performance on the MindCrowd verbal memory test to their common genetic SNP variants.

**APOE.** We examined the relationship between APOE genotype and verbal memory performance. We found that APOE e4 carriers had worse verbal memory performance across the aging spectrum [modeling total correct by age, sex, mc_version, and APOE genotype, p=0.000569]. Additionally, it was noted that no APOE e4 homozygotes were noted in the participants who scored in the top 5% of their age group. These findings suggest that the APOE e4 allele is associated with cognitive performance on verbal memory tasks across the aging spectrum.

**PRS.** 148 individual PRS were calculated using public GWAS data and each one was examined for its ability to predict verbal memory performance within the genotyped MindCrowd cohort. Surprisingly, no PRS was found to be statistically significant after correcting for multiple testing via Bonferroni’s method. However, it is interesting to note some of the top associated PRS which included “Intelligence” [GCST006250, p-corrected=0.079], “Parental longevity” [GCST006697, p-corrected=0.079], and Occupational attainment [“GCST90102253”, p-corrected=0.121]. We hypothesize that the lack of statistical significance is simply due to sample cohort size. Therefore, we expect this to be addressed in the coming year(s) as we collect more samples for genotyping.

**GWAS.** Finally, we also examined the panel of genotyped genome-wide SNPs for any association with verbal memory performance using a genome-wide association study (GWAS) approach. It was found that one region in the genome achieved statistical significance just below the standard genome-wide threshold – top SNP located at chr12:23571754 (rs11046979) within the SOX5 gene. Of note, it was recently reported that rare missense variants in SOX5 may contribute to Alzheimer’s disease risk and that the SOX5 protein accumulates in synaptic boutons and silencing it in a fly model results in abnormal neuron development and behavioral deficits. These data suggest that the SOX5 locus may be associated with verbal memory performance in humans without dementia. As our study increases in size we will continue to examine this association.
Validation of single nuclei sequencing in Alzheimer’s disease across multiple cell types.
Kendall Van Keuren-Jensen, PhD, Eric Reiman, MD, Thomas Beach, PhD. Translational Genomics Research Institute, Banner Alzheimer’s Institute, Banner Sun Health Research Institute, Arizona Alzheimer’s Consortium.

**Specific Aims:**
Validate changes in RNA expression, identified in single nuclei RNASeq, on a spatial transcriptomics platform

**Background and Significance:**
We have been working on two large collaborative single nuclei sequencing projects, one in collaboration with Eric Reiman, Ben Readhead, Diego Mastroeni and Thomas Beach, titled: 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, funded by the NOMIS Foundation. And a second project with Dr. Rita Sattler at BNI titled: Cryptic exon detection and transcriptomic changes revealed in single-nuclei RNA sequencing of C9ORF72 patients spanning the ALS-FTD spectrum, funded by the Department of Defense. The goal is to generate widely used public resources of single nuclei transcriptomic (RNA sequencing) data from fresh frozen brain tissue. We recently completed the single nuclei sequencing for 195 frontal cortex samples, 100 posterior cingulate samples, and are currently completing 125 visual cortex samples across these two projects. As we are working on analysis, it would be ideal to validate a large number of the differentially expressed genes in each cell type, on a second assay. Our goal for this project was to use a recently released spatial transcriptomics platform for validation of gene expression changes. The specific aim of the proposal is to validate changes in RNA expression, identified in single nuclei RNASeq, on a spatial transcriptomics platform.

**Preliminary Data, Experimental Design and Methods:**
We have performed analysis of the frontal cortex data across diseases. We have lists of differentially expressed genes between groups and we ordered a custom probe panel from VizGen.

**Proposed One-Year and Long-Term Outcomes:**
We will optimize tissue preparation, processing and staining for pathology compatible with VizGen. We will then complete the data acquisition and analysis for a custom gene panel on 15 AD SFG and 15 control SFG samples.
Longer-term outcomes: These data will be used as validation in papers that we are completing – such as assessments of transcriptional changes in FTD and AD. These data will also serve as comparison data for PDD and FTD samples that we will also process.

**Year End Progress Summary:**
We recently had a paper accepted with Dr. Sattler on Cryptic exon detection and transcriptomic changes revealed in single-nuclei RNA sequencing of C9ORF72 patients spanning the ALS-FTD spectrum. In this paper, it became clear that specific cell types were more transcriptionally altered.
than others, and that confirming these cell identities and their transcriptomic changes with respect to the microenvironment and single cell resolution would be very important. We identified rare cell types that were more significantly affected by disease pathology. We purchased a custom probe kit for targeted gene hits and cell marker genes that we were interested in validating through spatial transcriptomics on the VizGen platform. There were technical issues that hindered our progress with the data acquisition. We have also began the process of examining the 10x Genomics Xenium spatial transcriptomics platform for comparison. We are in the process of designing the probes necessary for validation on this platform. These tools are evolving and we are confident that we will be able to achieve our goals for single nuclei validation in a spatial context.
A CRISPR knockout negative screen to identify genes that lead to enhancement of efficacy of antibodies targeting amyloid beta (Aβ) in Alzheimer’s disease. Raffaella Soldi, PhD, Tithi Ghosh Halder, PhD, Sunil Sharma, MD, PhD, FACP, MBA. Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.

Specific Aim(s):
The specific aim of this project is the identification of genes that interact with the efficacy of the antibodies targeting amyloid β (Aβ) peptides in Alzheimer’s Disease (AD) settings through the analysis of CRISPR knockout negative screen in neuronal cell lines generated from AD patient’s skin puncture. By Knocking down one by one genes in cells treated with antibodies against Aβ peptides, we will identify genes that influence the expression of Aβ and PTau in the presence of treatment. This study will allow the identification of genes that enhance the efficacy of the treatment, resulting in a better patient selection in clinical trials as well as development of combination therapy to enhance the current treatment in AD patients.

Background and Significance:
Alzheimer’s disease (AD) is a debilitating disorder that accounts for almost 70% of the cases of dementia worldwide [1], and it has no effective treatment to date. Amyloid-β (Aβ) deposits and hyperphosphorylated tau proteins are the main pathological hallmarks, along with oxidative stress, N-methyl-d-aspartate (NMDA) receptor-mediated excitotoxicity, and low levels of acetylcholine. Particularly, the accumulation of the Aβ peptides leads to synaptic dysfunction, neurodegeneration, and ultimately AD symptoms [2]. A pharmaceutical intervention that has received great attention in recent years for treating AD is the use of antibodies targeting Aβ peptides in the brain [3]. Recruiting the immune system may prevent Aβ peptides from clumping into plaques or remove Aβ plaques that have formed and help the body clear the Aβ peptides from the brain. Reducing these plaques by means of passive or active vaccination against Aβ peptides has been a long-running endeavor but with disappointing results as the impact on disease progression has been minimal. Recently, a Phase III trial in patients with mild-to-moderate AD has provided ambivalent evidence for the efficacy of this intervention [4] [5]. The data gathered to date could suggest that antibodies do not work, mainly because the studies have not been performed in an optimal fashion. The emerging views are that patients should be treated earlier, ideally in the prodromal or symptom free stage, antibody levels have to be high and the correct epitope must be targeted. More studies and clinical trials to fully explore the potential of vaccines are therefore warranted. In this study we propose the use of a new approach and techniques to identify genes that interfere with the efficacy of the antibodies against Aβ peptides, enhancing the efficacy of the vaccine and can be potentially used to develop new combination therapies for AD patients.

Proposed One-Year and Long-Term Outcomes:
The primary screen and secondary studies outlined above are anticipated to lead to the discovery of genes that interfere with the efficacy of the antibodies against Amyloid β peptides, and either by promoting resistance or enhancing the efficacy in the first year of study. The knowledge of these genes’ effects is anticipated to be beneficial in the treatment and prevention of AD, other dementia and neurodegenerative disorders in general, and can be the basis for future drug
development. Our data also support the validity of the arrayed CRISPR screening to identify new therapeutic strategies in AD, and highlights the potential for drug treatment in combination with antibodies against Amyloid β peptides in AD patients.

**Year End Progress Summary:**

During the past year we performed the analysis of CRISPR knockout negative screen in neuronal cell lines generated from AD patient’s skin puncture to identify genes that influence the expression of Aβ and PTau. For our initial screening we used the kinase inhibitor CRISPR library (Synthego) which 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.

We performed our screening on neurons to assess the effect of the kinase’s inhibitors on the tau phosphorylation levels estimated by MSD assay. In parallel we run the same screening focusing on neuron survival as final readout. This assay allows us to identify kinase inhibitors that affect neuron survival, resulting in false positive for reduction of tau hyperphosphorylation. The results from the two assays provided hit lead of drugs that can be used in combination with the antibodies against Aβ in AD patients.

Screening analysis showed that knock down of CDK5 results in significant reduction of tau phosphorylation. Cyclin-dependent kinase 5 (CDK5) is considered a major tau kinase that contributes to tau pathology via its activators p35/p25 (1-4). CDK5 is activated by interaction with the non-cyclins, p35 and p39, which are regulatory proteins expressed almost exclusively in postmitotic neurons (2). p35 and p39 are cleaved by calpain to generate p25 and p29, respectively, and these proteins promote prolonged activation of CDK5 (2, 5-8). Increased activation of calpains in AD brains leads to overexpression of CDK5 and p25, but not p35, resulting in increased tau phosphorylation at specific sites (5, 7, 8). CDK5 might also indirectly regulate the kinases and phosphatases that act on tau, such as phosphatase 1 (PP1) inhibitors I-1 and I-2, resulting in augmentation of tau phosphorylation (9, 10). Deregulation of CDK5 also result in the dysfunction of many other pathways such as neuroinflammation, neuronal fragmentation, mitochondrial fragmentation and JNK pathway (11) that lead to generation of β amyloid plaques. Importantly, inhibition of CDK5/p25 has proven to reduce the pathological hallmarks of AD and improve cognitive performance in vivo (4, 12, 13), suggesting CDK5 as a prime therapeutic target for AD.

This serine/threonine kinase expression is predominant in the nervous system, where it is involved in a variety of processes including neurite outgrowth, axonal guidance, neuronal migration, learning and memory (4, 14, 15). Silencing of CDK5 reduces the phosphorylation of tau in primary neuronal cultures and in the brain of wild-type C57BL/6 mice. Furthermore, the knockdown of CDK5 strongly decreased the number of neurofibrillary tangles (NFTs) in the hippocampi of triple-transgenic mice (4, 16).
Although several classes of CDK5 inhibitors have been developed, generally they are not selective and are associated with toxicity thus significantly impairing their efficacy in the treatment (17-20). Discovery of more specific CDK5 inhibitors is an unmet need.

We have developed a new class of trisubstituted pyrazolo pyrimidine compounds that show high specificity and potency for CDK5 inhibition. During the past year, we tested the ability of these compounds to reduce tau phosphorylation in AD models. The lead candidates will be further characterized for their ability to affect AD phenotype in combination with antibodies against Aβ peptides.

AD patient iPSC-derived neuron cells were treated with 5μM of selected compounds (TGN-102, TGN-1091, TGN-1099, TGN-1102, and TGN-1104) up to 12 h, then lysed and subjected to MSD analysis of phosphorylated tau (THR231) (Ptau), known to be targeted by CDK5. As positive control we used flavopiridol, a CDKs pan-inhibitor. Our data shows that all the compounds tested are able to significantly reduce Ptau levels similarly to the positive control Flavopiridol. The selected compounds were then tested for efficacy on expression of total tau. Upon treatment, only one of the selected compounds, TGN-1099, shows an effect on total tau expression after 12h incubation suggesting a possible cytotoxic effect of the drug on the cells.

Next, we tested the selected compounds for ability to reduce Ptau in AD neurons versus healthy neurons. Our data show very limited effect on Ptau levels in healthy neurons compared to AD neurons. Among the compounds selected, TGN-1062, TGN-1102 and TGN-1104 show higher efficacy, and were tested further on AD and healthy neurons for efficacy on Ptau upon long exposure (4 weeks). Briefly, healthy (WT) and AD iPSC-derived neurons were incubated with the selected compounds at 10 and 1 nM respectively for 4 weeks. Every 7 days a portion of the samples were tested for Ptau levels by MSD assay. All the compounds tested shown limited to no effect on Ptau levels in healthy neurons during the period of 4 weeks, while they promoted a significant reduction of Ptau in AD neurons already at week2 of treatment.

The next step was to determine the toxicity, CDK5 selectivity, and brain absorption for the final hit compounds TGN-1062, TGN-1102 and TGN-1104.

To determine whether our compounds promote toxicity at neuronal level, we performed viability assays using AD iPSC-derived neurons. Approximately 5x10³ cells/well were seeded in a 96-well tissue culture-treated plate and after 24h, cells were treated with a ten-point serial dilution of compounds at final assay concentrations of 100 µM to 0 µM. A ten-point serial dilution of DMSO was used as a control. Following a 72h incubation at 37 ° cell viability was quantified by CellTiter-Glo using the Envision Plate Reader. All three compounds induced toxicity at micromolar concentrations, with an average IC50 = 7.4μM. However, our previous data have shown that nanomolar doses for extended time periods (2 weeks) resulted in inhibition of hyperphosphorylated tau, well under toxicity levels. Next, to verify the selectivity for CDK5, we performed a kinase profiling on the selected compounds. This assay is an active site-directed competition binding assay to quantitatively measure interactions between the selected compounds and more than 489 kinase assays and disease relevant mutant variants through arrayed screening. Compounds that bind the kinase active site and directly (sterically) or indirectly (allosterically) prevent kinase binding to the immobilized ligand, will reduce the amount of kinase captured on the solid support. Conversely, test molecules that do not bind the kinase have no effect on the amount of kinase captured on the solid support. Our data shown that although TGN-1062 displays higher affinity for CDK5 (0.639 nM), it is not selective for the kinase, revealing an even higher affinity for CDK7 and CDK2. In comparison, TGN-1102 and TGN-1104 display a lower affinity for CDK5 than TGN-1062 (15 and 22 nM respectively), but are more selective toward
the targeted kinase, thus we decided to move forward with TGN-1102 and TGN-1104 for further studies.

Finally, we investigated the ability of the selected compounds to cross the blood-brain barrier. We conducted pharmacokinetics and brain accumulation studies in mice following an intravenous (IV) or oral (PO) administration of TGN-1102 and TGN-1104. Both compounds showed a good brain penetration, particularly TGN-1102, with 3-fold more drug in the brain that in the plasma, while TGN-1104 shown approximately 40% drug in the brain. Our ongoing studies are focused on optimizing these initial hits to improve their pharmaceutic properties and activity towards CDK5. No publications/posters are currently in preparation. Further studies are needed and in progress.

No new collaborations arose from this project.

References:


Behavioral biomarkers in brain aging & Alzheimer’s disease. Gene Alexander, PhD, David Raichlen, PhD, Ali Atri, MD, Tom Beach, MD, PhD, Richard Caselli, MD, Yi Su, PhD, Matt Huentelman, PhD, Steve Rapcsak, MD, Eric Reiman, MD, Ted Trouard, PhD, University of Arizona; University of Southern California; Banner Sun Health Research Institute; Mayo Clinic Arizona; Banner Alzheimer’s Institute; Translational Genomics Research Institute (TGen); Arizona Alzheimer’s Consortium.

Specific Aims:
1) to determine how physical activity (PA) and sleep quality (SQ) influence cognitive and brain aging in highly active versus typically active older adults with differential risk for Alzheimer’s disease (AD); and 2) to further develop, evaluate, and implement novel methods for processing and analysis of PA and SQ data, as well as for remote cognitive assessments, to identify new lifestyle and behavioral biomarkers for age-related cognitive decline and AD risk. Additionally, we expect this proposal will provide important added value by: 1) evaluating novel wearable biomarkers for use in the NIA Arizona ADRC Biomarker Core, 2) helping to create the infrastructure, methods, and a unique dataset to support cognitive aging and AD research across Arizona and nationally, 3) exploring how neuroimaging measures of key brain structures, including the hippocampus and frontotemporal white matter relates to PA and SQ in older adults; 4) evaluating how PA 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 is expected to grow rapidly over the next two decades. It will be important to address the associated growth in AD across Arizona and nationally. It is well-established that APOE ε4 genetic and cerebrovascular health factors increase the risk for AD. Engaging in PA, however, can improve cognition in aging and 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 with highly active older adults are needed to identify how PA supports healthy brain aging and the reduction of AD risk. SQ is another critically important aspect of our daily activity that influences brain aging and AD risk.

Preliminary Data, Experimental Design and Methods:
We have 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 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). We also 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 further develop and implement methods to conduct remote behavioral and neuropsychological evaluations by telehealth video calls and mailings to
administer actigraphy and collect health histories, cognitive measures, self-report scales of PA and SQ, and dried blood spots. We also plan to enroll healthy older adults, 70 - 84 years of age with differing levels of PA engagement. For this proposal, we will continue 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 AAC 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 influence 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 to further support our ADRC Biomarker Core efforts. Specifically, this project will provide key data and methods to support planned grant submissions, including a follow up to a currently funded NIA R56 grant (MPIs: Alexander, Raichlen) to support a new NIA R01 submission to investigate how engaging in high levels of PA influence the risk of AD.

Year End Progress Summary:
We have made significant progress in the past year in support of our efforts to understand how lifestyle factors and physical activity influence brain aging and the risk for AD. In support of this project, we have published articles this past year investigating 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; Kraft et al., Geroscience, 2022; Hardcastle et al., Geroscience, 2022), how frontal control networks are related to executive function in healthy aging (Hausman et al., Geroscience, 2022), and how the Covid-19 pandemic influenced health behaviors, psychosocial factors and cognitive function in older adults (Hausman et al., Frontiers in Aging Neuroscience, 2022). We have published a genome-wide association study identifying genetic factors associated with the liking of physical activity (Klimentidis et al., Medicine & Science in Sports & Exercise, 2022); we have applied a novel methodological approach to demonstrate a causal relation between PA and cognitive function (Cheval et al., Scientific Reports, 2023); and we have used mendelian randomization to show that the blood metabolite glutamine may have a causal role in reducing risk for AD (Ramadan et al., submitted). We have shown that exposure to air pollution is an important risk factor for dementia (Parra et al., Environmental 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., Medicine...
& Science in 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 study of companion dogs living in the community, as part of a large-scale collaborative canine study of aging and dementia (Bray et al., Geroscience, 2022).

We have shown, in an article published in the Proceedings of the National Academy of Sciences, that sedentary behavior can increase the risk of dementia depending on the type of sedentary activity (Raichlen et al., Proceedings of the National Academy of Sciences USA, 2022). This work garnered media attention and was highlighted in multiple news outlets following a journal press release. Furthermore, in follow up work we have found that the risk for dementia related to sedentary behavior rises rapidly in a non-linear manner in older adults that is distinct from engagement in other types of PA, providing implications for behavioral interventions that may help reduce dementia risk (Raichlen et al., submitted). We plan to extend our work on sedentary behavior in the context of aging and risk for dementia with a new collaborative NIH grant application. We have also demonstrated the novel application of a multimodal network covariance analysis to identify how a blood-based biomarker of vascular risk is related to subcortical brain structures and white matter lesion load in healthy aging (Song et al., Neurobiology of Aging, 2023).

This AAC project has also directly supported methodological developments and data collection to advance our wearable/digital biomarker efforts for our $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 leveraged as part of our $5M Biomarker Core (Core-Leader: Alexander; Core Co-Leaders: Atri, Su), as part of our renewed and ongoing $15.7M NIA Alzheimer’s Disease Research Center grant (ADRC PI: Reiman). This new Biomarker Core provides access, methodological support, expertise, analyses, and data to the community of Arizona-wide investigators in the use of neuroimaging, fluid, and behavioral/wearable biomarkers to support research in AD and brain aging.

In the past year, a new collaborative $4.6M NIA R01 grant was awarded (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 SQ 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, 85 years of age and older. This ongoing complementary effort reflects collaborations between teams of investigators at the University of Arizona, University of Florida, University of Alabama, and the University of Miami. Initial findings from this work, has helped to validate the use of the NIH Cognitive Toolbox battery for oldest-old adults (Sims et al., JINS, 2022) and has identified functional connectivity brain networks associated with cognitive function in this cognitively unimpaired oldest-old cohort (Sims et al., submitted). In addition, work investigating the relation between self-reported levels of PA and cognitive performance has shown an association in the context of oldest-old healthy aging (Ho et al., submitted).
Fast parametric imaging of the hippocampus sub-regions. Maria Altbach PhD, Ali Bilgin PhD, Kevin Johnson BA, Craig Weinkauf MD, PhD. University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
The overall aim of this work is to combine novel radial MRI methods for T2 and T1 mapping with deep learning (DL) methods for high-resolution parametric mapping of the hippocampal internal structures. The specific aims in this project are:

Aim 1: To optimize and test 2D and 3D radial MRI methods developed by our team at the UA (RADTSE and IR-RADGRE) for optimal visualization and parametric mapping of the hippocampus (HC).

Aim 2: To develop a DL model that can achieve optimal image quality and accurate T2 and T1 mapping (as determined from Aim 1) within a shorter scan. Our goal is to achieve high-resolution parameter mapping of the HC at 3T in < 5 min.

Background and Significance:
The HC is an early site for pathologic changes related to Alzheimer’s disease (AD) with volume loss detected in early AD and early stages of dementia. There has been progress made in the past two decades in assessing volume changes in the hippocampal sub-fields based on ultra-high resolution MRI data acquired in high-field 7 Tesla (T) scanners. Limitations of the technology are (i) the long acquisition times (~10 min) which increases the lengths of scans aimed at evaluating brain structure and function in patients that may already have difficulty staying still during 40-60 min imaging sessions. (ii) Limited availability of 7T scanners and (iii) data obtained with conventional pulse sequences that only allow for anatomical evaluations (e.g., volume changes).

Recently, there has been an increased interest in incorporating quantitative imaging into clinical and research MRI protocols with the goal of extracting parameters related to molecular or cellular changes in tissue due to pathology. A major limitation in quantitative MRI is the need for acquisition of data at several time points for parametric accuracy, resulting in unacceptable scan times (sometimes hours) when spatial and temporal resolution are paramount.

Our team at the University of Arizona (UA) has developed quantitative techniques based on radial MRI methods. The major advantage of the technology is that parameter maps derived from data acquired with high spatial and temporal resolution can be obtained from a small fraction of the data compared to conventional methods (~4% of data required by conventional methods). The fast quantitative MRI technology developed at the UA has caught the attention of the imaging community and the technology is being distributed as “beta versions” worldwide but primarily for abdominal MRI applications. The goal of this application is to translate the technology for fast high-resolution quantitative mapping of the HC to detect pathologic changes that predece volumetric loss. The technology will be developed for 3T scanners for wide accessibility.

Preliminary Data, Experimental Design and Methods:
Recently, we started focusing on high-resolution brain quantitative T2 and T1 mapping imaging in support of an ongoing grant on the impact of carotid artery disease on cognition (R01-AG070987; PI: Weinkauf).

Our intial results on quantitative HC imaging obtained with a T2 mapping MRI method developed at the UA (RADTSE) show that we can obtain similar image quality to ultra-high spatial resolution
(0.48x0.48x2mm) protocols for hippocampal imaging at 7T. The advantage of RADTSE is that it provides anatomical images at each of the TE time points (typically 15-32) and a quantitative T2 map within an 8 min scan.

In the preliminary results (included in the FY 23 AAC application) we compared anatomical T2-weighted images as well as T2 maps from a patient with carotid artery disease and to those from a normal volunteer. We showed that while the anatomical T2-weighted images between these two subjects were similar, the quantitative T2 maps exhibited remarkable differences. This preliminary results show the promise of the technique to quantify pathological changes beyond volume loss.

Experimental design and methods:
Aim 1: To optimize T1 and T2 MRI methods developed by the UA team for parametric mapping of the HC, we will fine tune the acquisition parameters of the current versions of the RADTSE and IR-RADGRE pulse sequences (using phantoms and health volunteers) for optimal signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and T2/T1 repeatability. The best pulse sequence parameters in terms of in vivo SNR, CNR, and T2/T1 mapping repeatability will be used as our REFERENCE pulse sequences. We will recruit 20 subjects (10 healthy and 10 subjects with mild cognitive impairment recruited from a cohort of subjects assessed as part of Dr. Weinkauf’s R01-AG070987-01) and image them with the REFERENCE T2 and T1 sequences (each expected to be 8-10 min long). Scans will also be acquired with a REDUCED scan time by reducing the number of radial views to 1/3 and 1/2 relative to the REFERENCE.

Aim 2: To overcome the reduction of acquired data proposed in Aim 1 to shorten the scan time, we will develop deep learning (DL) reconstruction techniques for RADTSE and IR-RADGRE. We will split the in vivo HC data obtained in Aim 1 into training, validation, and test datasets and use these to train the corresponding DL networks. We will use the REDUCED scans as input and REFERENCE scans as target in our supervised learning approaches, with the goal of matching the T1/T2 mapping accuracy of the REFERENCE scan using the REDUCED scan data.

Proposed One-Year and Long-Term Outcomes:
1-year outcomes: We expect multiple publications from this work. Results obtained as preliminary data will be used in extramural funding applications for the development of novel brain imaging technologies (e.g., NIBIB Brain Imaging Initiative). The data obtained will also benefit other investigators in the Arizona neuroimaging community to strengthen their grant applications. Long-term: Our long-term goal is to investigate the use of the proposed quantitative imaging techniques to monitor molecular/cellular changes in the HC subfields in vascular related dementias and other applications for which we will seek collaborators within the Arizona neuroimaging community.

Year End Progress Summary:

Progress in Aim 1
Protocol optimization: We completed the protocol optimization planned in Aim 1. The evaluation yielded pulse sequence parameters for high-resolution (0.48x0.48x2 mm) quantitative mapping of the HC with scan times of 8 minutes for T2 mapping (RADTSE) and 6 minutes for T1 mapping (IR-RADGRE). Since a main goal of the project is to reduce scan time, the protocol also included a version of the pulse sequences with twice the slice thickness (4 mm instead of 2 mm); the latter covers the HC volume in half the time compared to the 2-mm slice thickness protocol. The 4- and 2-mm slice thickness datasets were acquired to be used in conjunction with the super-resolution DL network described below. Other pulse sequences added to the human protocol were: T1 MPRAGE (1 mm³) for HC volumetric analysis and high-resolution (0.48x0.48x2 mm) T2 SPACE for anatomical comparisons and HC subfield segmentation.
Testing in volunteers: We had some challenges in scheduling subjects for the MRI scans due to the large number of MRI studies that are being carried out by the neuroimaging community in our 3T research scanner. To overcome this challenge our imaging facility opened weekends and after hour scanning. Thus, we were able to acquire 14 volunteer datasets (4 of them with repeatability scans). It is important to note, that the facility will add a new brain-optimized 3T scanner (planned for October 2023) thanks to a successful NIH high-end instrumentation grant; this will alleviate scheduling issues going forward with the project.

Reconstruction of RADTSE and IR-RADGRE images and maps: We adapted the reconstruction algorithms developed by our group for T1 and T2 mapping of the HC. These included adjusting the regularization in our iterative algorithms which depends on the specific application. The images produced by the iterative algorithm are used as REFERENCE and input to the DL networks.

HC subfield segmentation: To be able to evaluate T1 and T2 mapping in the HC subfields we evaluated segmentation approaches using Free Surfer. These included using (i) T1 MPRAGE alone or (ii) a combination of T1 MPRAGE and high-resolution T2 SPACE. The latter gave better results. Going forward, we plan to develop a segmentation approach based on the RADTSE and/or IR-RADGRE images and maps.

Progress in Aim 2
DL networks: To obtain T1 and T2 maps from acquisitions with reduced data our group has implemented several deep learning networks including: one unrolled network for RADTSE T2-weighted and T2 mapping, one for efficient anatomical coverage based for IR-RADGRE T1 mapping, and one for super-resolving thin slices from thick-slice acquisition. This one is the most promising for HC parametric mapping since it can reduce scan time for RADTSE to 4 min and IR-RADGRE to 3 minutes. Adaptation and testing of the networks is underway and will continue as part of the new funded FY24 AAC.

Publications and future grant applications: FY23 was the first year of the project. We have made steady progress in technical developments and have been able to acquire sufficient data to start analyzing results. These will be the base of publications in FY24. We also started putting together a multi-center grant application to look at the effect of plaque composition in brain health. The quantitative T1 and T2 mapping of the HC is novel and will be included as preliminary material for the grant application. The technical developments will also provide material for a grant application focused on technology development for parametric imaging of the HC subfields. This will align with our long-term goal of providing a new way to monitor molecular/cellular changes in the HC subfields to the neuroimaging community.

**Specific Aims:**
1) Specific Aim 1: We plan to implement an integrated set of high-resolution and multi-contrast 3T MR imaging protocols capable of mapping hippocampal subfields of human subjects. Specifically, we plan to develop protocols for T2-weighted MRI, multiplexed sensitivity encoded (MUSE) diffusion-tensor imaging (DTI), and T2*-weighted quantitative susceptibility mapping (QSM) at uniform spatial-resolution (0.4 x 0.4 x 2 mm^3) and voxel geometry. We would like to point out that, as compared with conventional DTI of relatively limited spatial-resolution (e.g., 2 x 2 x 2 mm^3), our unique MUSE technology enables DTI at a resolution (0.4 x 0.4 x 2 mm^3) capable of mapping the structural connectivity for different hippocampal subfields.
2) Specific Aim 2: 2a) In collaboration with other AAC projects (PI: Ying-hui Chou), we plan to acquire high-resolution and multi-contrast MRI data from 16 adults (including subjects with mild cognitive impairment); and 2b) we will develop post-processing pipelines to jointly analyze high-resolution hippocampal MRI data, aiming to achieve a more reliable automatic segmentation of hippocampal subfields.

**Background and Significance:**
Efforts have been made by many research groups on segmenting hippocampal subfields from high-resolution MRI data, with significant implication to studies of Alzheimer's disease. However, hippocampal subfield segmentation still largely relies on manual procedures, partly because a single-contrast high-resolution MRI data set (e.g., T2-weighted fast-spin echo MRI at 0.4 x 0.4 x 2 mm^3 resolution) might not always provide contrast that is sufficiently robust for an automatic segmentation of hippocampal subfields.

To address the above-mentioned limitation, here we propose to implement multi-contrast MRI protocols (all at 0.4 x 0.4 x 2 mm^3 resolution) to improve the robustness of segmenting hippocampal subfields in automatic data processing pipelines. Specifically, we plan to add high-resolution MUSE diffusion MRI data (of which we are the developers), revealing different structural connectivity patterns that are unique to each of the hippocampal subfields. The integration of T2, diffusion, and T2*-weighted images makes it possible to convert segmentation of hippocampal subfields to a high-dimensional classification procedure.

**Preliminary Data, Experimental Design and Methods:**
Our research team has expertise in developing high-resolution and multi-contrast MRI protocols, including multi-shot echo-planar imaging (EPI) based MUSE-DWI, in human studies. In our recent studies we have compared high-resolution 2D MUSE DWI (0.375 x 0.375 x 5 mm^3) and conventional DWI (1.5 x 1.5 x 5 mm^3), illustrating that MUSE-DWI achieves significantly higher anatomic resolvability. In our other preliminary studies we have compared high-resolution T2-weighted fast-spin-echo MRI (0.4 x 0.4 x 2 mm^3) and high-resolution 3D MUSE DWI (0.8 x 0.8 x 0.8 mm^3), demonstrating the feasibility of visualizing hippocampal subfields from high-resolution and multi-contrast MRI. Built upon these preliminary data, we propose to implement multi-contrast MRI protocols of uniform resolution (0.4 x 0.4 x 2 mm^3) for mapping hippocampal subfields, and evaluate the developed methods in 16 human subjects.
Proposed One-Year and Long-Term Outcomes:
We will make the high-resolution multi-contrast MRI protocols (including MUSE-DWI) available to our neuroimaging community. The validated hippocampal segmentation procedures will also be shared. We expect that the proposed methods can be used to quantitatively evaluate changes of gray matter volume in each of the hippocampal subfields due to neurodegeneration.

Year End Progress Summary:
1. Pulse sequence development: The PI, Nan-kuei Chen, has been working on developing and implementing the proposed high-resolution MRI pulse sequences, capable of providing multiple types of MRI contrasts (e.g., T2-weighted; T2*-weighted; QSM; and diffusion-weighted imaging) at a spatial-resolution suitable for resolving hippocampal subfields (0.4 x 0.4 x 2 mm³). We have made the following progresses in pulse sequence development between 07/01/2022 and 06/30/2023.
   a. We have implemented a segmented echo-planar imaging (EPI) sequence template, using an open-source pulse sequence programming environment, termed Pulseq [https://pulseq.github.io](https://pulseq.github.io), in our 3 Tesla Skyra MRI scanner. We have implemented the pulse sequence template in such a way that it is compatible with various acceleration schemes (e.g., in-plane SENSE acceleration scheme; through-plane multi-band or simultaneous multi-slice accelerations scheme) and contrast preparation modules (e.g., T1, inversion-recovery, T2, T2*, perfusion, diffusion among others).
   b. When assessing the segmented EPI quality in data obtained from healthy adults, the PI realized that the residual chemical-shift artifact (i.e., the remaining fat signals that are inconsistently displaced along the phase-encoding direction as compared with water signals) remains significant even after applying the existing tools. In order to address this concern, the PI has invented a technology “Flyback Echo-Planar Imaging (EPI) Pulse Sequence with Embedded Chemical-Shift and Field Inhomogeneity Compensation Schemes and Artifact-Free Image Reconstruction Procedures”, so that various EPI artifacts (including chemical-shift artifact, Nyquist artifact, geometric distortions) can be effectively removed. The PI has filed an invention disclosure (Ref. No.: UA23-253, May 2023), and Tech Launch Arizona is currently working with a law firm on a provisional patent application.
   c. We have evaluated the newly invented MRI pulse sequence on healthy adult volunteers, assessing improvement in EPI image quality by the new approach as compared with existing methods. Based on these results we have drafted a manuscript, which will be submitted to scientific journal for consideration of publication, after a provisional patent application is filed by Tech Launch Arizona.
2. Assessing the pulsation artifact in MRI data in the medial temporal lobe: The brain pulsation, like other types of head motion, could make the actual spatial-resolution of MRI data lower than the nominal spatial-resolution. In order to achieve the targeted spatial-resolution (0.4 x 0.4 x 2 mm³), Nan-kuei Chen (PI) and Aidan Dolby (PhD student) have been working on evaluating the impact of brain pulsation on EPI spatial-resolution. Specifically, we have implemented a post-processing procedure that 1) matches the simultaneously acquired MRI k-space data and physiological recording (e.g., from ECG, pulse oximeter, and breathing monitoring belt), 2) re-arranges the acquired MRI k-space data based on the corresponding cardiac and respiratory phases, 3) produces multiple sets of imaging data that are specific to selected cardiac and respiratory phases, and 4) assess the impact of brain pulsation (due to cardiac and respiratory effect) on MRI signal intensity and spatial accuracy. We have implemented the procedures, and have acquired data sets for evaluating the implemented procedures.
3. **Producing multi-contrast MRI protocols of high-spatial-resolution:** With the progresses in both EPI pulse sequence development and pulsation artifact assessment (described above), our research team has begun the implementation of high-resolution and multi-contrast EPI for acquiring functional and structural MRI data from hippocampal subfields. In addition to our implementation efforts, Nan-kuei Chen (PI), Ying-hui Chou (Co-I) and Aidan Dolby (PhD students) have had a series of meetings with collaborators (e.g., researchers with expertise in arterial-spin-labeling MRI for measuring cerebral blood flow) to ensure our pulse sequences are optimized for measuring the targeted physiological information.

4. **Evaluation of the developed technologies in human subjects:** As discussed above, we have evaluated 1) the new “Flyback Echo-Planar Imaging (EPI) Pulse Sequence with Embedded Chemical-Shift and Field Inhomogeneity Compensation Schemes and Artifact-Free Image Reconstruction Procedures”, and 2) “physiological signals based EPI data rebinning for reducing pulsation artifact and improving spatial-resolution” in healthy adult volunteers, with results demonstrating the success of our technical development. The multi-contrast MRI protocols, on the other hand, require more time to be evaluated in human subjects. Although this specific AAC funding expired on 6/30/2023, our research team will continue the development and evaluation of high-resolution MRI technologies.
Concurrent theta burst stimulation and electroencephalography study for individuals with amnestic mild cognitive impairment. Ying-hui Chou, ScD. University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
Theta burst stimulation (TBS) is a brain stimulation technique that has emerged as a promising therapy for mild cognitive impairment (MCI). However, little effort has been undertaken to optimize the application of TBS for individuals with MCI. Previous animal in vitro studies have found that TBS could induce long-term potentiation (LTP) in adult rat hippocampal slices in a dose-dependent manner. The maximum LTP effect was observed after TBS sessions were repeated three times, with a 60-minute break between each session. The dose-response curve was flattened when TBS applications did not have adequate interludes. This points to an array of parameters that must be properly tuned to achieve the desired TBS effects. The purpose of the study is to investigate the effects of spaced TBS on cortical activity as measured by electroencephalography (EEG) in individuals with MCI. The specific aims of this proposed study include:

1) Specific Aim 1: Determine TBS effect on TMS-evoked potentials in individuals with aMCI
2) Specific Aim 2: Establish dose-response relationship of the TBS effect

Background and Significance:
Previous studies using rat hippocampal slices have found that synapses stimulated by a single session of theta burst stimulation (TBS) were remodeled over a period of at least 60 minutes, leading to enlargement of the existing functional postsynaptic density and presynaptic active zone. However, this single session of TBS only initiated consolidation and strengthening at a subset of synaptic contacts. In this experimental model, subsequent TBS sessions applied at intervals of 60 or 90 minutes cumulatively increased long-term potentiation (LTP). These in vitro studies report a dose-response relationship between spaced TBS sessions for the first 3 exposures before the cumulative effect saturates. Specifically, they report that 3 TBS sessions spaced at least 60 minutes apart produce an LTP effect 3 times greater than a single TBS exposure (with no additional potentiation by the 4th TBS exposure). This suggests that sequential TBS exposures spaced with an interval of 60 minutes or more are necessary for optimal reinforcement of LTP. Furthermore, the spaced applications have been found to elicit more durable long-term facilitation of synapses that lasted for more than 24 hours. Spaced TBS protocol has recently been investigated as a potential treatment strategy for patients with major depressive or bipolar disorders. Multiple TBS sessions with an intersession interval of 50 minutes applied daily for 5 consecutive days improved depressive symptoms (i.e., ≥ 50% decrease in the HDRS17) and increased anti-correlation of functional connectivity between the stimulation site (i.e., the left dorsolateral prefrontal cortex) and the subcallosal cingulate cortex in 5 out of 6 patients.

Overall, the above findings from animal in vitro and human studies have demonstrated the immediate and lasting effects of spaced TBS on LTP and LTP-like plasticity and suggested the importance of leaving at least 50-60 minutes between TBS sessions for cumulative TBS effect. However, spaced TBS effects have not yet been investigated in Alzheimer’s disease (AD) and mild cognitive impairment (MCI). Theta-band fluctuations generated by the hippocampus have long been implicated in learning and memory, and therefore, non-invasive stimulation such as TBS using theta-band patterns has great potential in synchronizing and normalizing the hippocampal network. The purpose of the proposed project is to maximize response to...
hippocampal stimulation with spaced TBS in individuals with amnestic MCI (aMCI). Of all the MCI subtypes, patients with aMCI are at greatest risk for the development of AD\textsuperscript{12}. Previous longitudinal studies have reported that 25-61\% of aMCI individuals converted to AD within 3 years\textsuperscript{13-18}. Therefore, it is crucial to provide an early and effective intervention in people with aMCI to attenuate neurodegeneration before it becomes medically refractory.

**Preliminary Data, Experimental Design and Methods:**

Our laboratory recently completed a pilot study investigating the effects of single-session hippocampal TBS on memory function and resting-state functional connectivity in 8 individuals with MCI\textsuperscript{11}. We leveraged white matter tractography from each participant’s diffusion-weighted MRI data by using their hippocampal structural connectivity map as a guide to identify individualized superficial stimulation sites that were anatomically connected to the left hippocampus for all participants. Our preliminary data demonstrate the feasibility of the tractography-guided hippocampal TBS approach and reveal that, compared to the inhibitory TBS and sham TBS, excitatory TBS improved associative memory performance and increased resting-state functional connectivity along the left inferior longitudinal fasciculus to the hippocampus\textsuperscript{11}.

**Aim 1: Determine TBS effect on TMS-evoked potentials in individuals with aMCI**

**Study:** Sixteen individuals with MCI will be enrolled in the TBS-EEG study. Participants will be randomly assigned into one of the two TBS groups: active TBS or sham TBS. Participants will receive 3 TBS sessions with each TBS session separated by 60 minutes to maximize the TBS effect\textsuperscript{4,5}. Participants in the active TBS group will receive 3 active TBS sessions. Participants in the sham TBS group will undergo a procedure identical to the active TBS except that no TBS will be provided. Research participants and outcome assessors will be blinded for participants’ allocated group. Outcome measures assessing memory function and TMS-evoked potentials will be acquired immediately before the first TBS session and immediately after the third TBS session.

We hypothesize that active spaced TBS will enhance memory function and increase TMS-evoked potentials compared to the sham TBS condition. Each active TBS session will consist of 600 pulses, and it only takes approximately 200 sec to complete a TBS session. Structural T1-weighted MRI (6 mins), structural T2-FLAIR MRI (2.5 mins), diffusion-weighted MRI (DWI, 8.5 mins), and memory task fMRI (36 mins) will be used to determine each participant’s superficial brain region with the greatest degree of connectivity to the left hippocampus. TBS will be applied to the individualized superficial brain region (within the left parietal lobe) that is structurally connected to the peak activation area within the left hippocampus during an associative memory fMRI task. Resting-state EEG data will be acquired immediately before and after each block of TBS session. EEG data will also be continuously acquired through a TMS-compatible EEG system during TBS using 32 Ag/AgCl ring electrodes, arranged in an elastic cap according to the standard 10-20 layout.

**Aim 2: Establish dose-response relationship of the spaced TBS effect**

To estimate dose-response relationship, we will acquire additional points of EEG data. Specifically, TMS-evoked potentials will be acquired immediately before the first TBS session and immediately after each TBS session in the 16 individuals with aMCI recruited for Aim 1. Participants in both active and sham TBS groups will receive 3 TBS sessions with each TBS session separated by 60 minutes, yielding a total of 6 sets of EEG data. We expect to observe a dose-dependent effect of TBS on TMS-evoked potentials in the active TBS group. The power of theta-band, alpha-band, and gamma-band oscillation will be the outcome measures of linear mixed effects models. Each model will include fixed predictors for the EEG data for time (4 levels:
baseline, post-TBS 1, 2, and 3), group (2 levels: active TBS and sham TBS), their interaction, age, sex, and education. A random intercept per participant will be included.

**Proposed One-Year and Long-Term Outcomes:**
We greatly appreciate the support from the Arizona Alzheimer’s Consortium (AAC). The pilot data acquired from previous AAC support have helped us receive NIH R01AG062543 and R21AG077153 awards. In this proposed pilot project, we plan to enroll 16 participants with aMCI this year and additional 16 participants next year. For the long-term outcomes, we plan to submit an R01 proposal to examine spaced TBS effects on memory and brain function measured with functional MRI, EEG, and neuropsychological tests. The data we will acquire carrying out this pilot project will prepare us to submit the R01 grant in October 2023. The goal of the R01 will be to conduct a large-scale clinical trial to systematically examine spaced TBS 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 enhance treatment efficacy and adherence, which are of relevance for patients with cognitive dysfunction.

**Year End Progress Summary:**
We enrolled 10 participants in the pilot TMS-EEG study, during which each participants underwent 3 sessions of TBS within one day. We used the activation cluster within the left hippocampus during the Face-name fMRI task as a seed to plan for an individualized superficial stimulation site within the left parietal lobe. Participants received either 3 sessions of active TBS or 3 sessions of sham TBS. No adverse responses to the TBS sessions were reported. Results of the EEG data analysis revealed that active TBS suppressed oscillation of theta band (4-7 Hz) and alpha band (9-11 Hz) activity compared to the sham TBS. We are currently enrolling more participants in this ongoing project and will report more comprehensive results to report once it is completed.

Additionally, we conducted a literature review evaluating the potential of TMS-induced EEG parameters as biomarkers for AD and MCI. Eighteen studies assessed TMS responses with EEG and reported significantly different temporospatial characteristics between those on the AD spectrum and healthy controls in corticospinal excitability, plasticity, and brain connectivity. Furthermore, TMS-induced EEG features were found to be associated with cognitive performance and AD pathological biomarkers. Across the studies included, the integration of TMS and EEG appears to have provided unique insights into the underlying neurophysiology of MCI and AD, and has potential for early diagnosis, monitoring disease progression, and prediction of treatment responses. Future research will be needed to explore how TMS-EEG can be utilized to optimize treatment for MCI and AD. This manuscript will be submitted to “Neuroscience and Biobehavioral Reviews”.
High-density neural ensemble recording from hippocampus in behaving aged and young rats during a spatial sequential memory task. Stephen L. Cowen, PhD, Carol A. Barnes, PhD.

Specific Aims:
Millisecond-level coordination between ensembles of neurons is required for neural communication and plasticity. Evidence suggests that such coordination is disrupted in normal aging and age-associated disorders such as Alzheimer's and Parkinson's disease. Simultaneous measurement of the activities of large groups of neurons is required for the effective assessment of coordination between neurons and its role in memory and decision making. Traditional approaches using wire or silicon probes resolve < 50 neurons during a typical recording session, which 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 > 1000 electrode sites and hundreds of neurons. This order-of-magnitude improvement allows for robust assessment of interactions between neurons and brain regions, and how interactions are affected by age. The objective of this proposal is to use this system to record from large ensembles of neurons in awake behaving young and old rats. This is required given our hypothesis that neural coordination is disrupted in aging. We propose here to adapt this system for chronic recording in behaving rodents. This involves developing an implant device capable of protecting and lowering the probe into the brain in behaving rodents. In addition, systems must be developed for the synchronized video tracking of the animal’s behavior during recording.

The working hypothesis is that communication between hippocampal subregions is disrupted in aging. Specifically, we predict that 1) neural coordination between hippocampal subregions (CA1, CA3 and dentate gyrus), and between the dorsal and ventral hippocampus will be disrupted in aged rats (e.g., reduced inter-region cell-pair measure of correlation), and 2) that correlated activity between task-active neurons will be disrupted in the older animals. While we will not be able to perform an entire age comparison in a one-year period, obtaining proof that we are able to set up the Neuropixels system to recording from rats while they are performing a challenging behavioral task, will provide key preliminary data for a future RO1 grant to specifically study aging. Our approach is to use the Neuropixels system to collect ensemble data from CA3, CA2, and CA1 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 the sequence learning behavior. The Experiment Proposed has Two Specific Aims:

Aim 1 is to develop a fully functional Neuropixels system capable of collecting high-density neural signals from behaving rats. Outcome measures will include assessments of cell stability, longevity of recording probe functionality, and the effect of the chronic device on the animal’s behavior.

Aim 2 is to finish developing the novel spatial sequence memory task that we have called the “Fan Maze”, and to test young and old rats’ performance on this task.

Background and Significance:
It has been hypothesized that changes in the communication between individual hippocampal subregion neurons is altered in aging, and that these deficits contribute to age-associated decline in memory formation, recall, and consolidation. This hypothesis has not been explicitly examined due to the formidable challenges involved in acquiring sufficiently large populations of neurons simultaneously from regions across the hippocampus. To achieve this, an order of magnitude increase in the number of simultaneously recorded neurons is critical for a more robust
assessments of how coordination between neurons in different hippocampal subregions is affected by age.

**Preliminary Data, Experimental Design and Methods:**

**Preliminary Data Neuropixels Recording System:** Because of the grant provided by the Alzheimer’s Consortium last year, we were able to set up and demonstrate that we can implement the necessary acquisition procedures and utilize the Neuropixels recording system in house. Indeed, no system exists at the University of Arizona and very few systems are in use across the country. While this is a very new technology, we are excited to be on the forefront of implementing this system. We were able to provide a proof-of-principle demonstration that we can successfully record with these high-density probes made possible through the previous year’s funding. The next step is to move this technology into an awake, behaving animal system.

**Preliminary Data on the novel Fan Maze:** Memory for sequences of spatial locations visited is impaired in aging rats, and this is related to the integrity of the hippocampus. Furthermore, there is evidence that neurons in the aged hippocampus improperly 'reactivate' sequences during sleep. While tasks for spatial memory have been developed and are in wide use, these mazes pose problems for tethered recording systems, as the Barnes maze requires that the rat descend into a dark box. Additionally, the tethered recording system developed for the Neuropixels probe is not compatible with commutators that prevent tangling of the recording wires. Thus, we have developed the Fan Maze that is designed to assess sequential spatial memory but deters rotation that would lead to twisting of the tether. We have begun to train 4 young and 4 old rats on this prototype, without automated food delivery, but automation will be included in later versions. We will use “DeepLabCut” to track animal behavior. So far, 7 out of 8 rats have moved on from a simplified 2 arm alternation phase, to a more difficult 3 arm alternation phase of the task. The final phase is a 4-arm alternation phase (one young rat has achieved thus far). Thus, we believe that this task will enable the measurement of the animal’s capacity to retain memories of past spatial choices and allow simultaneous recording from multiple hippocampal regions.

**Proposed One-Year and Long-Term Outcomes:**

Our goals are: 1) Develop chronic recording procedures with the Neuropixels system, 2) complete the development of the Fan maze, and 3) to collect preliminary data that demonstrates that we can obtain Neuropixels recordings from the Fan maze, which will allow us to apply for an RO1 grant using these methods. We expect to behaviorally characterize 8 young and 8 old rats on the Fan maze, and to record from at least 3 rats on the Fan maze with the Neuropixels probes.

**Year End Progress Summary:**

During the 07/01/22 to 06/30/23 funding period we accomplished the following objectives:

1) We built a fully functional Neuropixels system (960 electrode sites per probe) and collected data from >1500 neurons in anesthetized rats and mice. Data was collected from the hippocampus, striatum, motor cortex, parietal cortex, thalamus, and medial prefrontal cortex.

2) This system was adapted to work in behaving rats and collected data from >200 neurons from 2 behaving rats trained to run on a circular track and trained to perform a novel string-pulling task. This was a key objective of our original proposal.

3) An entire suite of Matlab software for efficiently processing and analyzing data collected from this system was developed.

4) We designed and built a novel 3D-printed encasement for the probes to allow probes to be implanted in awake and behaving rats. The encasement has been used successfully in two rats.
5) By evaluating the behavior rats implanted with the probes we determined, contrary to our initial expectations, that the Neuropixels system is compatible with an established W-maze spatial working memory behavior rather than the proposed ‘Fan Maze’ that was originally proposed. This is an essential finding as it improved the feasibility of our submitted R01 proposal as it allowed us to use a well-tested paradigm rather than our less established task.

6) Experiments with the Neuropixels system were performed involving electrical stimulation of the ventral hippocampus with simultaneous measurement of ensemble and local-field activity in the medial prefrontal cortex. These data will be essential for our recently funded R01 as it allowed us to map the functional projections of the hippocampus to the prefrontal cortex so that we can better position electrodes.

7) The system was integrated with a voltammetric system for measuring dopamine in anesthetized rats. This allowed us to examine how neural ensembles in the striatum are affected by dopamine release.

8) AAC 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.

The behavioral and neural ensemble data collected with AAC support and described above were essential for the R01 Dr. Barnes and Dr. Cowen were awarded in 2023 (R01 AG031581, $3,266,421 Total).

Data collected using the Neuropixels system were used for 2 posters presented at the Society for Neuroscience meeting in 2022 (San Diego), one poster at the 2023 BRAIN Initiative meeting (Bethesda, MD), and for 2 poster abstracts submitted for the upcoming 2023 Society for Neuroscience meeting (Washington DC). Posters were presented by trainees supported by AAC funding.

Near-term next steps include 1) enhancing the system to permit the implantation of multiple probes in a single animal for assessment of prefrontal-hippocampal interactions, 2) improving anatomical targeting, 3) publishing our work on mapping functional projections between the hippocampus and frontal cortex, and 4) integrate probes with LEDs to allow optogenetic stimulation/inactivation of neuronal subpopulations to identify the roles interneurons play in age and Alzheimer’s related memory loss.
Evaluating social and cognitive factors relevant to understanding age and Alzheimer's disease-related cognitive decline in uncontrolled environments. Matthew D. Grilli, PhD, Katelyn S. McVeigh, MA, Emily C. Edmonds, PhD. University of Arizona; Banner Alzheimer’s Institute, Arizona Alzheimer’s Consortium.

Specific Aims:
Assessing cognition naturalistically with smartphones is a promising direction for improving early detection of age-related and Alzheimer’s disease (AD)-related cognitive decline, and for improving accessibility of cognitive assessment to an increasingly diverse population. A challenge for smartphone-based assessment, however, is the uncontrollability of the context in which cognition is evaluated. Recently, we showed that autobiographical memory (AM), memory for personal events, can be assessed naturally in older adults using a smartphone application that captures the sound of everyday conversations (Wank et al., 2020). While preliminary results are promising and suggest that smartphone applications can detect age and AD-related risk factors in AM sharing in naturalistic contexts, we know very little about the role of key contextual factors on the naturalistic assessment of memory sharing, including the impact of the social environment where memories are shared, and how recent conversations may affect subsequent ones. In this project, we will begin to close these gaps in knowledge by examining in the laboratory 1) a key feature of social conversation that may impact how memories are shared, and 2) whether recent mode of memory retrieval influences how young and older adults’ approach later memory retrieval. Accurately assessing AM is especially important given that changes to AM may be an indicator of early changes associated with AD-related decline.

1) Specific Aim 1: To determine the impact of inter- vs. intra-generational conversation on the specificity of AM in young and older adults, and individuals with objectively-defined subtle cognitive decline (Obj-SCD) or mild cognitive impairment (MCI). In daily life, both inter- and intra-generational conversations are common (Demiray et al., 2019). However, how these different social contexts affect the way AMs are shared remains underspecified. Using a within-subjects experimental design in the laboratory, we will examine whether AM “specificity” (i.e., vivid, event-specific details used to describe a memory) shared in an intra-age group conversation differs from the specificity of memories shared in an inter-age group conversation. We hypothesize that cognitively normal older adults are responsive to the assumed general knowledge of their conversation partner and therefore are more specific when engaged in an intra- vs. inter-generational conversation. In comparison, we hypothesize that specificity in individuals with Obj-SCD and MCI is less flexible and therefore specificity variation is dampened for intra- vs. inter-generational conversation partners. Whether young adults alter their memory specificity according to intra- vs. inter-generational conversation is an empirical question.

2) Specific Aim 2: To reveal the impact of recent memory retrieval on subsequent memory retrieval in young and older adults at varying risk for AD. Research has shown that the mere act of engaging in memory retrieval can temporarily alter how a person engages in subsequent memory retrieval (Grilli et al., 2019; Madore et al., 2014). While this phenomenon affects young and older adults, it remains unclear whether older adults who are at higher risk for AD because of lower neuropsychological functioning show as strong of a mode-of-retrieval effect. There also remain questions about the impact of focusing on the “gist” vs. the detail of a memory on later specificity. In a within-subjects experimental design conducted in the lab, we will examine the impact of inducing gist, detailed, and no-recent memory retrieval on later AM retrieval in young and older adults. We hypothesize that, relative to baseline (i.e., no-recent memory retrieval), a detail-induction will increase specificity on later AM retrieval in older adults. However, we expect
this detail effect to be dampened in those with Obj-SCD or MCI. We also expect that, relative to baseline, the gist induction will have a weaker impact on later memory retrieval compared to the detail induction, reflecting that older adults naturally adopt a gist mode of thinking. In young adults, we predict that the gist induction will have a greater impact on later AM retrieval (i.e., reducing specificity relative to baseline) in comparison to the detail induction (i.e., smaller effect relative to baseline), reflecting that young adults naturally adopt a detail mode of thinking in their approach to memory retrieval.

Background and Significance:
Research focused on evaluating the quantity and quality of AM has largely taken place in a laboratory. Recently, research has shifted to using smartphone-based ambulatory assessment technology, such as the Electronically Activated Recorder (EAR) (Mehl, 2017), to study AM objectively outside of the lab (Wank et al., 2020). Despite the evident importance of naturalistic data collection, the real world is still an uncontrolled setting. We lack a clear understanding of the impact that variable environmental factors may have on participants’ day-to-day lives. One way to address this challenge is to use a controlled, laboratory setting in a way that will provide insight into naturalistic data collection. In this project, we took this approach by manipulating social and cognitive factors in the laboratory that we can then detect and measure, but not control, with smartphone-based data collection. This work will contribute to the on-going effort of earlier detection of AD-related risk factors by characterizing the impact that key environmental factors have on memory alterations among individuals experiencing normal age-related changes, Obj-SCD, or MCI.

Preliminary Data, Experimental Design and Methods:
We have demonstrated that AM specificity assessed naturalistically with the EAR is associated with older age (Wank et al., 2020) and the presence of APOE4 (unpublished data), which motivates the importance of understanding contextual factors that may moderate memory assessed in daily life. We have also shown that we can reliably detect the nature of a conversation (e.g., with a friend vs. a grandchild) in young and older adults using the EAR. Data from our lab further suggests that recent memory retrieval alters a person’s immediate mode of thinking (Grilli et al., 2019). In the current project, we used laboratory-based experimental designs to examine the impact of inter- versus intra-generational simulated conversations, and recent mode of retrieval, on the specificity of autobiographical memory retrieval in young and neuropsychologically characterized older adults.

Proposed One-Year and Long-Term Outcomes:
One-year outcomes: 1) Completion of data collection and analyses, presentation of results at the AAC Annual Meeting; 2) Incorporation of outcomes into the analytical plan for an R56 project and a pending R01 project. Long-term outcomes: 1) These results are expected to serve as key preliminary data for a planned AD/ADRD R01 application submission in Fall 2023 focused on examining the impact of multiple social, temporal, and other contextual factors on AM in older adults at varying risk for AD; 2) Publication of results in Spring 2023.

Year End Progress Summary:
We are on track to achieve our one-year and long-term outcomes. In regard to our one-year outcomes, we will complete our proposed data collection by July 1, 2023, and we will have made good progress on data analyses. Inspired by this project, we developed a novel, theory-driven scoring protocol that we believe will provide critical insight into how intra- versus inter-generational conversations may affect the way memories are shared, as well as give new insight into the impact of gist and specific modes of thinking on remembering. Applying this scoring protocol to our
findings, our initial impressions are consistent with the specific aims. Older adults appear to calibrate the way they describe autobiographical memories based on their conversation partner. That is, older adults appear to be more specific in intra-generational conversations relative to inter-generational conversations. Older adults seem to be including more gist-based content in inter-generational conversations, perhaps reflecting their awareness that young adults may not have relevant background knowledge. At this early stage of data analyses, it is less clear if young adults are calibrating their use of gist or specific details for autobiographical memory sharing depending on inter- vs. intra-generational conversation. We are interested to see if these patterns are present when the data analyses are complete. We will submit an abstract related to this project to the 2023 AAC Annual Meeting. Based on these preliminary outcomes, we will continue data collection through the upcoming year (unfunded) to address follow-up questions.

One of our one-year goals was to incorporate the ideas of examining conversation partner and mode of retrieval into what at the time was a pending R01. That R01 is now funded (MPIs: Grilli & Andrews-Hanna R01 AG068098). We have an EAR scoring protocol in place that will allow us to examine how an individual’s conversation partner relates to the specificity of autobiographical memory. The results of the present project will inform our hypotheses for how conversation partner might relate to autobiographical memory specificity captured with the EAR, and they will enable us to examine whether outcomes translate from lab to uncontrolled environments. The related R01 is examining how preclinical biomarkers of Alzheimer’s disease in cognitively unimpaired older adults are associated with autobiographical memory in naturalistic environments, including measured with the EAR. We look forward to seeing if we might have evidence from the present AAC project to predict that the presence of preclinical biomarkers is associated with a similar memory sharing profile as what we find in obj-SCD or MCI. If there is similarity in memory profiles across these groups, it could mean that the presence of preclinical biomarkers is an early sign of later subtle cognitive decline and transition to MCI. In addition to incorporating conversation partner into our EAR scoring protocol, we also have established a multilevel modeling analytic plan for the EAR that will allow us to track how memory sharing may evolve over time. Using laboratory-based data, we recently introduced this multilevel modeling approach (Knoff et al., preprint). This manuscript received positive peer reviews and is being revised for resubmission. This approach is directly inspired by the present AAC project’s investigation of how retrieval modes might influence autobiographical memory sharing.

Regarding our long-term goals, we are on track to submit an R01 application in Fall 2023 or Winter 2024. This application will build on a novel theoretical proposal that was partly inspired by the current AAC project and recently proposed in a Trends in Cognitive Sciences article (Grilli & Sheldon, 2022). Here, we are proposing that gist autobiographical memory may be spared in cognitively normal older age, but not in abnormal cognitive and brain aging, and that spared gist memory adaptively serves older age. The data gathered with the current AAC project is providing key preliminary and pilot data for this R01 application. We expect that both aims will provide strong support for two of the three aims that we propose in this new R01 application.

In addition to the Trends in Cognitive Sciences article, we recently had accepted for publication an article titled “Differences in the Content and Coherence of Autobiographical Memories Between Younger and Older Adults: Insights from Text Analysis.” This study shows that older adults appear to rely on gist memory to shape the content and narrative style of their autobiographical memories (Sheldon, Sheldon, Zhang, Setton, Turner, Spreng, & Grilli, Psychology & Aging, in press). We also are on track to submit at least one manuscript related to the present AAC project in Spring 2024. We anticipate several additional manuscripts will follow.
Assessing the diagnostic sensitivity of ecological navigation tasks as a behavioral measure of preclinical Alzheimer’s disease. Paul F. Hill, PhD, Arne D. Ekstrom, PhD.
University of Arizona, Arizona Alzheimer's Consortium.

Specific Aims:
The overarching goal of the proposed project is to collect MRI data and blood samples for future plasma biomarker analyses as part of ongoing and future studies in the Human Spatial Cognition Laboratory. The data obtained from this project will supplement ongoing studies in the lab, permit testing of novel hypotheses regarding the effect of normal and pathological aging processes on spatial cognition, and provide preliminary data for future extramural grant applications.

Background and Significance:
The concept of an asymptomatic, preclinical stage has gained importance in Alzheimer’s disease (AD) research due to the recognition that AD pathological processes begin years before appearance of pronounced cognitive deficits and clinical symptoms. This preclinical period represents a critical window for early disease detection, monitoring, and intervention. However, individuals at this stage often perform normally on standard neuropsychological tests designed to detect more overt memory and cognitive impairments. Consequently, the nature of cognitive and behavioral changes that occur during this asymptomatic and potentially elevated risk period are poorly understood and ill defined.

Our lab currently uses a variety of experimental approaches to examine the effects of healthy aging on episodic memory and spatial navigation. With this award, we have begun collecting additional biological measures (plasma samples, structural MRI) in order to better define the earliest asymptomatic stages of AD pathologic change. Our goal is to uncover subtle behavioral and cognitive markers that can be used to identify those at elevated risk for developing AD and related dementias. The insights gained from these data will break new ground in understanding the nature of cognitive deficits in older adults and those at heightened risk for AD. This information therefore has the potential to impact not only scientific understanding of cognitive aging and brain health, but also the development of novel biomarkers and rehabilitative interventions targeting aspects of cognitive function most vulnerable to advancing age and incipient AD.

Preliminary Data, Experimental Design and Methods:
The principal objective of the initial proposal was to collect blood samples and structural MRI data from older adults enrolled studies of episodic memory and spatial navigation. These data were meant to support multiple pilot studies and full-scale investigations ongoing in the Human Spatial Cognition Laboratory. To date, we have collected samples from participants enrolled in the following studies: 1) three behavioral studies using state-of-the-art virtual reality technology to examine effects of age on spatial navigation in ecologically valid environments, 2) an fMRI study investigating the effects of age and AD biomarker status on source memory and mnemonic precision, and 3) an eye tracking study examining interactions between gaze fixations, self-motion, and episodic memory.

Proposed One-Year and Long-Term Outcomes:
We anticipate amassing a database of blood samples and structural MRI data from approximately 60 older adult volunteers by the end of the one-year award period. This sample will include cognitively healthy community dwelling older adults recruited directly by our lab, as well as older adults with MCI referred to our lab through existing collaborations with Drs. Eric Reiman, Matthew
Grilli, and Steven Rapcsak. Importantly, each of these older adult volunteers will have undergone extensive neuropsychological testing and participated in at least one spatial navigation study in our lab.

This multimodal dataset will allow us to perform hypothesis-driven and exploratory data analyses examining the impact of normal and pathological aging processes on spatial navigation, memory, and brain health. At the culmination of the award period, we will submit abstracts to national meetings and begin drafting manuscripts for publication. Results obtained from the proposed research will support an application for the NIA Small Research Grant program (RFA-AG-19-003), which we intend to submit in February 2023. This funding would be used, in part, to cover the costs of plasma biomarker testing. We believe the research proposed in this application is also well suited for the NIA Notice of Special Interest in promoting digital technology for early detection and monitoring of AD and related dementias (NOT-AG-21-048).

The long-term goal of this research is to better understand the behavioral and neurobiological factors that underlie age-related navigation deficits. The information gained from the proposed research will inform an emerging program of research investigating the neurobiological determinants and diagnostic sensitivity of navigation impairments in older adults at heightened risk for AD and related dementias.

**Year End Progress Summary:**
To date, we have collected plasma samples and high-resolution structural MRI data from a total of 30 healthy older adults and older individuals meeting criteria for mild cognitive impairment (MCI). Although our laboratory has extensive prior experience collecting and analyzing MRI data, we do not have prior experience obtaining or analyzing blood samples. The first 4 months of this award period were spent consulting with other research groups in the Department of Psychology and clinical personnel at the Clinical and Translational (CATS) Research Center to develop a protocol for performing blood draws. To date, we have collected blood samples and structural MRI data from 30 older adults. Critically, each of these participants have also contributed behavioral data in at least one study in the Human Spatial Cognition Laboratory (a majority have participated in multiple studies).

Given unforeseen delays, it was determined that it was unlikely we would reach our initial recruitment goal of 60 participants during the award period. For this reason, we elected to run an older adult cohort through an fMRI version of a novel item-location associative memory task. The preliminary data obtained from this study (described in the following paragraphs) form the basis of an NIA R03 grant application (PAR-23-179; PI Paul Hill) that will be submitted in early July.

We have collected behavioral data for an item-location associative memory task in 30 healthy older adults and seven older individuals with MCI. Eligible participants underwent high-resolution structural MR imaging of the hippocampus and entorhinal cortex (N = 25 to date) and contributed a blood sample for future AD biomarker analyses. A subset of these participants (N=20 to date) have also contributed functional MRI data obtained while performing the item-location association task.

Provisional results indicate that a continuous measure of mnemonic precision explains a unique source of variance in memory performance that cannot be accounted for by recollection accuracy or standardized assessments of verbal and visuospatial memory performance. We believe that this measure may be particularly sensitive to early stages of AD-related pathologic change (e.g., amyloid plaques, tau tangles, neurodegeneration), even in otherwise asymptomatic (i.e., cognitively unimpaired) older adults. We are in the process of submitting an R03 application to the NIA to build on these novel findings. The overarching aim of this application is to collect a highly powered dataset of behavioral, MRI, fMRI, and biomarker data so that we can examine whether continuous measures of mnemonic precision can reliably differentiate between older adults at varying risk for AD.
An analysis of high-resolution ex vivo MRI from aging macaque brains to estimate white matter and microstructural parameters and to align histological atlases with MRI images. Elizabeth Hutchinson, PhD, Carol A. Barnes, PhD, Ted Trouard, PhD, Kelsey McDermott, BS, Laurel Dieckhaus, BS. University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
1) Perform probabilistic tractography analyses on postprocessed DTI data to isolate brainstem-specific white matter tracts for quantitative analyses with respect to age and cognition. We will postprocess and validate high-resolution ex vivo MRI data that was collected with the support of the Alzheimer’s Consortium from 12 macaque brains that range in age from 15 to 32 years.
2) Perform voxel-wise tract-based spatial statistics (TBSS) to determine white matter regions of vulnerability to aging and cognitive status.
3) Develop and refine methods for registering ex vivo MRI data with histologically-prepared brain sections from the same animals for evaluation of hippocampus anatomy and microstructure.

Background and Significance:
The hippocampus, cerebral white matter and some brainstem regions are preferentially vulnerable in age-related disorders with cellular and molecular underpinnings that may be accessible to microstructural MRI techniques. In these structures, myelin especially is a critical component of brain microstructure that have been shown to be altered during aging including loss of myelinated nerve fibers, myelin pallor, malformation of myelin sheaths, and an enlargement of the extracellular space. 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. Ex vivo MRI or ‘MRI microscopy’ has superior sensitivity and resolution compared to in vivo MRI and has recently been appreciated as an important ancillary method to combine with higher-resolution histological studies to provide novel opportunities to study the microstructural condition of previously unobservable white matter projections, particularly those originating in subcortical brain regions in the midbrain and brainstem, which are notoriously difficult to resolve and of small gray matter regions such as the hippocampal subfields, which are undergo well characterized pathologic changes in Alzheimer’s disease. Because these regions sustain age-associated changes in structure and function relatively early in the aging progression, a quantitative assessment of microstructural associations with aging and cognitive status confirmed by comparison with cell-level changes is timely and an important problem.

Preliminary Data, Experimental Design and Methods:
With the funding obtained from the AAC in FY2022, we previously achieved goals of 1) collection and processing of a complete set of microstructural MRI maps in 12 bonnet macaque brains over an age range of 15-32 years, 2) development of processing and analysis pipelines including targeted tractography of brainstem projection systems related to the LC, and 3) sectioning and staining of two brains from the set – one young and one old.

ROI-based analysis has been performed and while (as expected) we have not found a strong correlation of any metric with age in the regions examined, we have found differential relationships
between several key microstructural MRI parameters in the hippocampus and white matter which has compelled us to focus on the hippocampal radiologic-histologic correspondence and the TBSS approach.
Additionally, based on previous evidence from the Barnes lab and others in the AAC community showing imaging correlations with cognitive status in the absence of age-dependent correlations for other macaque species have compelled us to emphasize new analyses to related imaging outcomes with cognitive scores in these 12 bonnet macaques.

**Proposed One-Year and Long-Term Outcomes:**

1) Analyze 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 in brainstem nuclei and our estimates of cognitive function. [Barnes lab]
3) Create standardized templates for the adult and aged monkeys separately and perform targeted white matter comparisons using tract-based spatial statistics to identify regions in which white matter structure show robust age- and cognition-associated correlations. [Hutchinson and Trouard labs]
4) Finalize the methods for alignment of MRI and histology images in the two serial sectioned and Nissl stained brains from one young and one old monkey. [Barnes Lab]
5) Use the data obtained from these aims to prepare an R21 or RO1 in the summer of 2023 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. We will share the results from the histologically validated anatomical MRI, and all other data obtained with the community.
6) Preliminary results from these experiments will be presented at the Arizona Alzheimer's Consortium meeting and at the Society for Neuroscience meeting when available. We will also begin to prepare manuscripts reporting the results of these data during this period.

**Year End Progress Summary:**
All quantitative MRI maps for all 12 brains have been generated, analyzed with native space ROI analysis (*Outcome 1*) and warped into a common template space for voxelwise analysis (*Outcome 3*). Four were removed from the final analysis due to tissue processing (fixative) differences or outlier brain volume. Template building techniques were compared between anatomical MRI and diffusion tensor MRI (DTI) based registration methods and it was found that the DTI-based registration methods were optimal for template generation. Two templates were then made using this method one from non-aged adult brains (n=4) and one from aged adult brains (n=4). The aged template was then warped to the adult brain template to generate tensor-based morphometry (TBM) maps that report local volume differences between the two groups. Each individual brain volume in the common adult brain space was then used to perform template-based ROI analysis and for voxelwise analysis.

There were no reportable differences between age groups in the whole brain white-matter or hippocampus, but there were some observed correspondence findings with behavioral scores during life. Additional analyses were initiated and are ongoing to assess individual tracts, especially the uncinate fasciculus. TBM results appeared to show that the cortex but not the hippocampus of the aged group was reduced in volume compared to the adult group suggesting that the hippocampus is selectively preserved during healthy aging. We have reported some of these findings at the SfN and AAC meetings in 2022 (*Outcome 6*) and are currently preparing a
manuscript describing the quantitative MRI findings across the whole brain. This paper will also describe technical aspects of template generation and microstructural MRI metric differences.

Tractography of the LC projections via the central tegmental tract were performed for brains in this study (Outcome 2) and those results were presented to the AAC meeting in 2022 (Outcome 6). These results showed no difference in tract length or number of tracts generated between the two age groups and also no differences in DTI diffusivity or anisotropy values related to age. These data provide support for the hypothesis that robust changes in the LC and its projections are characteristic of pathological but not normative brain aging. The integrity of this tract could thus be a promising biomarker for differentiating healthy aging from pathological aging. Ongoing work using this data is focused on the correlation of LC-CTT metric values with behavioral scores during life.

The current data were used to support an application and award for additional AAC funding to follow up our results with targeted experiments focused on the hippocampus and brainstem. A tangential R21 application related to a rat model of AD was submitted and we do expect to propose future work related to the results of the current period work once the findings are more mature and supported by additional experiments in the next year.

Overall, the majority of proposed milestones were met early in the project period and used to expand the analysis of quantitative microstructural MRI metrics across the whole brain and by tractography in the LC projections specifically. The main findings support preservation of key structures, especially the hippocampus, white matter and LC during healthy aging. We have presented this work in conference abstracts and the first manuscript related to this project is currently being written.
Cerebrovascular tortuosity changes in cerebral amyloid angiopathy and Alzheimer’s Disease. Kaveh Laksari, PhD, Paulo Pires, PhD, Chelsea Kidwell, MD. University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
The overarching hypothesis in this study is that vascular alterations in AD lead to higher wall shear stress levels in the luminal blood flow which is associated with higher amyloid deposition and in turn cerebral tissue atrophy in the perivascular space. We will test this hypothesis through the following specific aims:

Aim 1: Validate tortuosity index in a pre-clinical model of AD to determine effect of vascular morphology on amyloid deposition. We will use middle-aged (12 months-old) and aged (18 months-old) Tg-SwDI mice, a validated pre-clinical model of CAA (Fig. 2) to assess regional vascular tortuosity by time-of-flight MRI angiography and brain anatomy / microhemorrhages by T1. We will correlate these findings with histopathology and cognitive tests (nesting test, dry Barnes maze) to identify which factors within distinct brain regions strongly correlation with cognitive decline.

Aim 2: Correlate vascular tortuosity and tissue atrophy in retrospective human dataset. We will use an existing dataset of 75 healthy, 75 mild AD (CDR=0-5), and 75 moderate AD (CDR=1-2) subjects that have both T1 MRI scans and time-of-flight MRI angiography. After co-registering to the standard MNI space, each scan will be categorized based regional brain territories, and the changes will be quantified using multiple regression.

Aim 3: Simulate cerebral blood flow and wall shear stress to correlate with white matter hypointensities. We will use a computational fluid dynamic (CFD) code augmented with physics-informed neural networks machine learning established at the Laksari Lab, to simulate blood flow in each of the subjects’ brains and extract wall shear stress and other hemodynamic features and correlate with white matter hypointensities.

Background and Significance:
This project aims to assess and quantify vascular morphology alterations in Alzheimer’s disease (AD) and cerebral amyloid angiopathy (CAA). Our hypothesis is that vascular alterations in AD lead to higher wall shear stress levels in the luminal blood flow which is associated with higher amyloid deposition and in turn cerebral tissue atrophy in the perivascular space. Cognitive impairment is a critical health problem in the elderly population. An estimated 16 million people are living with cognitive impairment in the United States and with increasing prevalence due to the aging population it is estimated that the number of elders living with dementia will surpass nine million by 2040. Tools that provide early dementia screening are critical to allow for patients and physicians to begin secondary prevention and plan for future care. The more common type of dementia is AD, which affects approximately 7% of the elderly population in both the United States and globally. The accumulation of amyloid-β (Aβ) on cerebral blood vessels (CAA) is associated with cognitive decline and is one of the hallmarks of AD pathology. CAA is increasingly recognized as a major contributor of AD pathogenesis. Importantly, vascular deposits, rather than parenchymal plaques, are better predictors of dementia. Aβ deposition in and around cerebral blood vessels plays a central role in blood-brain barrier disruption, leading to extravasations of plasma proteins, edema formation, release of inflammatory mediators and matrix metalloproteases, which, in turn, produce partial degradation of the basal lamina with the potential to develop microhemorrhages. In addition, the progressive buildup of Aβ deposits in CAA chronically impair brain hemodynamic responses, thus causes focal nutrient deprivation and
triggering a secondary cascade of metabolic events resulting in oxidative stress and cell toxicity. As such, understanding vascular morphology changes during the progression of AD may provide a novel non-invasive clinical biomarker of disease severity and prognosis. Recent advances in medical imaging and automatic image processing may provide significant benefits to the controversies observed in brain atrophy by presenting changes not easily observed by visual inspection. However, no comprehensive and quantitative methodology is currently available to investigate these changes.

**Preliminary Data, Experimental Design and Methods:**
The Tg-SwDI model of CAA shows extensive microvascular angiopathy (Fig. 1). Brain slices from 12-month-old Tg-SwDI were immunolabeled for markers of vasculature (collagen IV, blue) and an amyloid-β antibody (red). Note the extensive CAA in this model, including in larger vessels (white arrows).

Time of Flight Magnetic Resonance Angiography (TOF-MRA) scans and T1 Weighted (T1W) scans were obtained from the OASIS3 Database for both subjects with Alzheimer’s disease or dementia (n=56) and subjects who were defined as cognitively normal (n=55) during clinical assessment. TOF-MRA scans underwent image segmentation to obtain a binary segmentation of the vascular architecture. Image registration was performed using FSL. Subject T1W scans were registered to the TOF scan for the same subject, taken during the same MR sessions. Subject T1W scans were then registered to the Montreal Neurological Institute’s (MNI) standard brain template (2mm isotropic resolution).

In a previous cross-sectional study (6), we showed that several brain regions are vulnerable to structural changes in MCI and AD patients, using results from T1 MRI scans and automatically quantifying tissue atrophy per individual. We reported cerebral atrophy in MCI and AD patients that begins in the medial temporal lobe (MTL) including areas, such as the fusiform gyrus, and other smaller volumes, that is, hippocampus, parahippocampus, amygdala, and entorhinal cortex.

The Automatic Anatomical Labeling atlas (AAL) was utilized to label the vasculature for assessment of geometric features by region. The Statistical Parametric Mapping (SPM) program in Matlab was utilized to generate standardized ROI binary masks for each region of interest. The saved transformation matrix from T1W to MNI registration was inverted and concatenated with the matrix to register the T1w to the TOF scan. This final transformation matrix was applied to the AAL atlas to move the labels to subject TOF space to label the vasculature. This transformation matrix was applied to all standardized ROI masks using FSL, once the masks were transformed to subject specific space, they were applied to the vessels and each region was saved separately. Feature extraction was performed to extract geometric features from each region using an automated feature extraction code. Features were compared by region between healthy subjects and AD subjects using one way ANOVA and a Tukey Post Hoc analysis. Paired T-tests were performed to compared left and right hemisphere geometry to look for any significant patterns in Alzheimer's Subjects.

**Proposed One-Year and Long-Term Outcomes:**
We expect from this project to detect early changes in the AD brain as a clinical non-invasive marker associating with prognosis and quantify the associations between brain tissue atrophy and vascular tortuosity using medical imaging. The research team consists of Dr. Laksari, from the Department of Biomedical Engineering, and Dr. Paulo Pires, from the Department of Physiology. This AFS funding mechanism will allow us to initiate this multi-disciplinary collaboration between different colleges and completely distinct fields of science that coincide and complement each other to provide a novel perspective on the AD disease. Accomplishing the proposed project will provide the preliminary results for a major R01 submission to the NIH NOSI.
in aging research (NOT-AG-21-020). Within the proposed project, we will aim to show significant differences in the brain vasculature of AD patients with the goal to distinguish these morphological changes as a major contributor to amyloid deposition and as a marker for AD. The PIs have been and will continue to promote underrepresented minority education in groundbreaking research. Dr. Laksari is currently engaged in multiple campus activities, including College of Engineering’s ENGAGE (ENGiengineering Access, Greater Equity, and Diversity) program for undergraduate students as well BIOS5’s KEYS program for high school students in the Tucson area.

**Year End Progress Summary:**
TOF MRA scans from 56 AD subjects and 55 Healthy subjects were segmented to obtain the cerebral vascular architecture. Of these subjects, 40 AD subjects and 34 Healthy subjects have undergone the FSL registration pipeline detailed above to obtain labeled vascular segments for feature extraction. Feature extraction has been performed on 33 of these subjects and preliminary analysis has been performed to compare the two cohorts.

Analysis of Temporal Lobe geometry showed a significant increase in tortuosity, total length and total volume of the vasculature in Alzheimer's subjects versus the Healthy subjects. Previous studies have demonstrated atrophy in early Alzheimer's Disease begins in the medial temporal lobe, these changes in vascular complexity could follow such atrophy and potentially contribute to the aggregation of amyloid in these regions of the brain. These results also show a significant increase in fractality for both the occipital lobe and the frontal lobe, which mirrors patterns of increasing vascular complexity found in our previous study.

**Temporal Lobe:**
Tortuosity, Total Length and Volume were significant higher in AD subjects
- Tortuosity no significant difference for symmetry (n=32 for AD and Healthy), Anova Results P = .0053
- Fractal Dimension Symmetry t-tests were not significant for either group Anova P value = 0.105
- Total Length Symmetry t-tests were not significant for either group Anova P value = 0.00502
- Number of Branches Symmetry t-tests were not significant for either group Anova P value = 0.331
- Max Branch Length Symmetry t-tests were not significant for either group Anova P value = 0.754
- Total Volume Symmetry t-tests were not significant for either group Anova P value = 0.00724
- Diameter Symmetry t-tests were not significant for either group Anova P value = 0.91

**Frontal Lobe:**
- Tortuosity Symmetry stats – not significant Anova Results not significant
- Fractal Dimension Symmetry stats – not significant Anova Results p = 0.0419
- Total Length Symmetry stats – not significant Anova Results not significant
- Number of Branches Symmetry stats – not significant Anova Results not significant
- Max Branch Length Symmetry stats – not significant Anova Results not significant
- Total Volume Symmetry stats – not significant Anova Results not significant
- Diameter Symmetry stats – not significant Anova Results not significant
Endothelial K+ channel dysfunction in menopause: identifying novel targets to improve Alzheimer’s dementia. Paulo W. Pires, PhD, University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
The overarching hypothesis of this project is that menopause impairs arteriolar SKCa/IKCa channels in AD, thus blunting vasodilation, functional hyperemia and accelerating progression of dementia, an effect that will be prevented by gene therapy aimed at rescuing SKCa/IKCa function. We will test this hypothesis in 2 specific aims:

Aim 1: To investigate if menopause reduces SKCa/IKCa function in brain arterioles, impairing functional hyperemia and accelerating dementia in menopausal AD mice.

Aim 2: To test if gene therapy to rescue SKCa or IKCa function will restore vasodilation, brain functional hyperemia and improve cognition in menopausal AD mice.

Background and Significance:
Our original proposal was aimed at investigating the effects of menopause on cerebral microvascular dilation in a mouse model of rapidly-progressing AD, the 5x-FAD. We focused on endothelial small- and intermediate-conductance Ca2+-activated K+ channels (SKCa/IKCa), as they are central players in functional hyperemia and the final effectors of most signals leading to dilation. Further, we used the physiologically-relevant 4-vinylcyclohexene diepoxide (VCD) model of menopause, which causes progressive menopause by accelerating natural atresia, closely modeling human menopause.

Preliminary Data, Experimental Design and Methods:
Due to space restraints, these are omitted from this report.

Proposed One-Year and Long-Term Outcomes:
Aim 1. We expect that menopause will impair brain arteriolar SKCa/IKCa function in AD mice, thus blunting vasodilation to endogenous signals or direct SKCa/IKCa activation. We expect that functional hyperemia will be reduced in menopausal AD mice, associated with poor cognition.

Aim 2. We expect that brain endothelium-specific gene therapy to rescue SKCa or IKCa function will restore brain arteriolar function in menopausal AD females, increase functional hyperemia and cognitive performance.

Year End Progress Summary:
Progress on Aim 1.
Menopause impairs endothelial Ca2+-dependent K+ channels, but not inwardly rectifying K+ channels in 5x-FAD arterioles. One of the major goals of Aim 1 was to investigate if menopause affects endothelial function of cerebral parenchymal arterioles in the 5x-FAD mouse model of AD. Corroborating our preliminary data, we observed that the vasodilatory response of arterioles to NS-309, a pharmacological activator of endothelial Ca2+-dependent K+ channels (IKCa/SKCa), was significantly blunted in menopausal 5x-FAD females when compared to regularly cycling 5x-FAD. Interestingly, the activity of other endothelial K+ channels, particularly the inwardly rectifying K+ channel KIR2.1, was unaltered by menopause.
Menopause induces extensive inward eutrophic remodeling in cerebral parenchymal arterioles of 5x-FAD mice. In order to fully characterize the extent of cerebral vascular dysfunction in menopausal 5x-FAD mice, we performed a thorough assessment of structural and biomechanical properties in isolated arterioles. We observed that arterioles from menopausal 5x-FAD females showed extensive inward remodeling, characterized by a reduction in both the outer and lumen diameters of the arterioles in passive conditions (i.e. fully dilated arterioles). This inward remodeling was not accompanied by an increase in wall thickness (thus, eutrophic). Further, we observed that the biomechanical properties of parenchymal arterioles of 5x-FAD mice was not affected by menopause. Distensibility, stiffness and compliance were similar between menopausal and regularly cycling females.

Lower resting lumen diameter in cerebral arterioles of menopausal 5x-FAD mice. The combination of endothelial dysfunction and inward remodeling has the potential to reduce the resting lumen diameter of cerebral arterioles. The resting lumen diameter is the purported physiological diameter while within the brain, and is a semi-constricted state that provides a vasodilatory reserve to the tissue. We observed that the contractile state of the arterioles (i.e. myogenic tone) was not different between groups. However, the resting lumen diameter of arterioles from menopausal 5x-FAD females was significantly lower than those from regularly cycling 5x-FAD.

Progress on Aim 2.
Issues with viral delivery. Aim 2 was focused on using a cerebral endothelium-specific viral vector, the AAV-BR1, to induce overexpression of IKCa/SKCa channels as a putative therapeutic to improve cerebral microvascular function in menopausal 5x-FAD. However, to date, we have been unable to generate the vector and transfect mice in a reproducible manner. This issue is recurring and not specific to the targets of interest for this proposal, but for other targets in the laboratory as well (KIR2.1 and MT-MMP1). Due to these technical difficulties, we shifted our focus to investigate other mechanisms of microvascular dysfunction in 5x-FAD mice, as described below.

Overall Research Progress During Fiscal Year 2022-2023
BKCa nitrosylation is associated with cerebral microvascular dysfunction in female 5x-FAD mice. Large conductance Ca2+-activated K+ channels (BKCa) play an essential role in vasodilatory responses and maintenance of myogenic tone in resistance arteries. BKCa can be modified in a pro-nitro-oxidative environment, resulting in decreased activity and vascular hyper-contractility, which can compromise cerebral blood flow regulation. We hypothesized that reductions in BKCa function in cerebral arteries, as a consequence of nitro-oxidative stress, are associated with blunted neurovascular responses in the 5x-FAD model of AD. We observed that posterior communicating arteries (PComA) from 5 months-old female 5x-FAD mice showed higher spontaneous myogenic tone than wild-type (WT) littermates. Constriction to the BKCa blocker iberiotoxin (30 nM) was smaller in 5x-FAD than WT, suggesting lower basal BKCa activity, which was independent of alterations in intracellular Ca2+ transients or BKCa mRNA expression. These vascular changes were associated with higher levels of oxidative stress in female 5x-FAD and a higher level of S-nitrosylation in the BKCa α-subunit. In females, pre-incubation of PComA from 5x-FAD with the reducing agent DTT (10 μM) rescued iberiotoxin-induced contraction. Female 5x-FAD mice showed increased expression of iNOS mRNA, lower resting cortical perfusion atop the frontal cortex, and impaired neurovascular coupling responses. No significant differences between male 5x-FAD and WT were observed for all parameters above. These data suggest that the exacerbation in BKCa S-nitrosylation contributes to cerebrovascular and neurovascular impairments in female 5x-FAD mice. These findings will be used as preliminary data for a R01 submission in October 2023 by the PI.
Evaluating neurofilament light (NFL) protein as a marker of neuronal damage in older and middle-aged adult survivors of SARS-CoV2. Lee Ryan, PhD, Meredith Hay, PhD, Sairam Parthasarathy, MD, Matt Huentelman, PhD. University of Arizona; Translational Genomics Research Institute (Tgen); Arizona Alzheimer’s Consortium.

Specific Aims:
Aim 1: To determine how post-recovery cognitive functioning relates to COVID-19 severity in middle-aged and older adults with varying levels of (1) respiratory symptoms post-recovery from COVID-19 and (2) circulating NFL and inflammatory markers in blood. We predict that more severe post-COVID-19 respiratory symptoms will result in poorer cognitive performance, particularly on tasks that are dependent on the hippocampus. However, our pilot data suggest that NFL levels will be a better predictor of cognitive performance than ongoing respiratory symptoms among COVID-19 recovered individuals.
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. Similarly to cognitive functioning, we predict that NFL levels may be a better predictor of brain MRI measures, or may add significantly to the prediction of MRI differences post-recovery.

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 previous study suggested 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. Levels were highest in COVID-19 patients with neurologic complaints and systemic inflammation, suggesting that NFL is a possible biomarker for disease severity. Preliminary data collected over the past year demonstrate that NFL also predicts individual differences in memory...
performance, and that this relationship is evident among COVID-19 survivors, regardless of whether or not they experience ongoing respiratory symptoms post-recovery. Taken together, we hypothesize that middle-aged and older adults who survive COVID-19 are at risk for experiencing cognitive impairment and changes to brain structure and function following recovery. These changes may be particularly pronounced in measures of hippocampal integrity.

**Preliminary Data, Experimental Design and Methods:**
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. The results show a negative relationship between increasing levels of circulating NFL and lower scores on a memory task that is known to be sensitive to hippocampal function (pattern separation). These data were presented at the McKnight Brain Institute annual conference, and the Cognitive Aging Conference in Atlanta Georgia (April, 2022).

In the previous funding period, we recruited older adults ages 55-79. We will recruit an additional 25 participants, ages 35-54, who are experiencing ongoing respiratory dysfunction post-COVID-19 recovery. An additional 25 participants in the same age range will be recruited who had confirmed COVID-19 infection but without respiratory dysfunction post-recovery. Groups will be matched on demographics including age, education, and other health factors such as cardiovascular disease and diabetes.

Cognitive testing will include 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. Blood samples will be collected for evaluation of NFL levels, inflammation, and immune function. MRI will be obtained including:
- T1-weighted 3D MPRAGE for gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes.
- 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.
- Cerebral blood flow and BBB permeability will be measured using arterial spin labeling (pCASL) with variable post-labeling 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:**
Recruitment goals for the previous funding period will be met by June 30th, 2023. We are already in the process of recruiting middle-aged participants to the study, and IRB approval has been obtained. We expect that the expanded study will be completed by June 30th, 2023, and will provide excellent pilot data for an RO1 submission in Spring, 2022. Preliminary data from the study has been presented at the McKnight Brain Institute Annual Conference (Tucson AZ, March, 2022) and the Cognitive Aging Conference (Atlanta GA, April, 2022).

**Year End Progress Summary:**
The recruitment goals of the study have been met. A total of 101 participants have been recruited, including 43 younger adults (ages 30 to 55) and 58 older adults (ages 56 to 79). Participants include 19 controls (without COVID infection), 37 mild COVID (COVID positive, no respiratory symptoms), 25 moderate COVID (COVID positive, with respiratory symptoms including difficulty
breathing), and 18 severe COVID (COVID positive, hospitalized due to severe respiratory symptoms).

Preliminary behavioral outcomes were presented at the fall annual meeting of the Arizona Alzheimer’s Consortium, based on data from 85 participants. On an associative memory task, the three COVID positive groups performed more poorly relative to the control group in their ability to identify correct face-name pairs. The lowest scores on this test were among the severe COVID group, which showed a 35% drop in performance relative to the controls. On a test of object recognition, the mild and moderate COVID groups did not differ substantially from the control group. However, the severe COVID group performed worse than all other groups, showing a 60% drop in performance relative to the control group.

Consistent with our hypothesis, these results suggest that COVID may have a detrimental effect on hippocampally-mediated forms of memory, including associative memory and object discrimination (pattern separation) that lasts well beyond the resolution of COVID infection. Additionally, respiratory severity may increase the negative impact on memory performance, particularly for object recognition.

**Future plans.** Blood samples for NFL and other blood biomarkers will be analyzed in summer 2023. Neuroimaging data analysis is underway, and will continue through summer and fall of 2023. Once neuroimaging and blood biomarkers are available, analyses will be conducted to determine how NFL levels predict memory performance, and whether the impact of COVID on memory is mediated by brain changes as measured by MRI. We anticipate that manuscripts will be written in spring 2024. We plan to submit the results at the Society for Neuroscience meeting in fall 2024.
Quantifying amyloid beta levels in Alzheimer’s Disease patients using FLOWER. Judith Su, PhD, Gene Alexander, PhD, Thomas Beach, MD, PhD. University of Arizona; Arizona Alzheimer’s Consortium; Banner Sun Health Research Institute.

Specific Aims:
1) Specific Aim 1. Detect the presence of amyloid beta from postmortem serum samples from healthy patients and those with confirmed AD.
2) Specific Aim 2. Quantify the amount of amyloid beta present in these samples using the standard addition method to minimize matrix effects.

Background and Significance:
Ultra-sensitive sensors that can operate in complex fluids are needed for diagnostics and prognostics. FLOWER’s ultra-sensitivity enables us to significantly dilute our samples but still detect our marker of interest thus minimizing non-specific binding.

Preliminary Data, Experimental Design and Methods:
Our preliminary data indicates that we can successfully distinguish between patient groups (healthy, mild cognitive impairment, and Alzheimer’s disease), from cerebral spinal fluid using FLOWER. We are currently working on this in serum. Microtoroid optical resonators will be functionalized with monoclonal antibodies for amyloid beta 42 using standard EDC/NHS chemistry. We will then dilute our serum samples 1000x and record the signal from our sensor as they are flowed over our system. These serum samples already exist in our lab. After we record the signal from the diluted serum sample, we will spike in three higher concentrations of amyloid beta 42 to generate a curve from which we can determine the unknown concentration of amyloid beta from both healthy and diseased samples. This will hopefully remove the need for a separate calibration curve for each patient sample.

Proposed One-Year and Long-Term Outcomes:
Our proposed one-year outcome is to quantify the amount of amyloid-beta 42 present in healthy and diseased postmortem patient serum using FLOWER. Our long-term outcome is to establish FLOWER as an early diagnostic tool for AD.

Year End Progress Summary:
We have obtained data on using FLOWER to screen patient CSF samples. From this data, FLOWER can clearly distinguish between patients with Alzheimer’s, mild cognitive impairment, and Alzheimer disease negative patients. This is based on detecting levels of amyloid-beta 42.
With regards to distinguishing between patient groups in serum, the data has a larger spread, and more data is needed to decrease the error bars.

**Figure 2.** CSF samples screened using FLOWER. FLOWER can distinguish between Alzheimer disease positive (AD+) patients, people with mild cognitive impairment, and Alzheimer disease negative (AD-) patients. The box height is one standard deviation from the sample mean and the whiskers are 1.5.

**Figure 3.** Serum samples screened using FLOWER. More patient samples need to be screened to form a conclusion regarding whether FLOWER can distinguish between patient groups in serum. The box height is one standard deviation from the sample mean and the whiskers are 1.5.

Specific Aims:
The purpose of the current project is to establish a new algorithm to identify signs of cognitive impairment by assessing deficits across brain and motor systems. Instead of basal resting state condition, we will challenge older adult participants to perform an upper-extremity function (UEF) test, while we measure brain function using functional near-infrared spectroscopy (fNIRS) and motor performance using motion sensors. Although fNIRS has become more acceptable in neuroscience research, for estimating absolute (concentration of oxygenated (HbO) and deoxygenated hemoglobin (HbR) values, additional MRI-based anatomical information is required (1-3). This in turn limits absolute hemoglobin concentration assessment, due to differences in wavelength-dependent scattering properties of the head layers in different experimental setups and different population (4, 5). To address this problem and limit the influence of such random errors, in a controlled testing condition with defined duration (stress), we will measure brain function changes due to the stress (response) with reference to the baseline condition. Using a nonlinear dynamic model of stress-response we will quantify the interaction between brain function and motor task. The ultimate goal is to enhance the accuracy and reliability of cognitive impairment assessment using the proposed stress-response model compared to direct measures of HbR and HbO. We will further measure brain function complexity (function patterns instead of absolute HbO and HbR), to be able to normalize our outcomes based on the resting-state condition. The specific aims of the current project are:

**Aim 1** Quantitatively assess the directional nonlinear interactions between neural network function and motor task performance using convergent cross mapping (CCM) (6, 7).

Hypothesis: In addition to system-specific performance within motor and brain units, assessing dysregulation of interaction between motor and brain systems will reveal novel signs of cognitive impairments, which will be significantly different between CN vs. MCI.

**Aim 2** Assess test-retest reliability of CCM model and complexity analysis, and compare these measures with previously established direct measures of brain function using fNIRS.

Hypothesis: using the stress-response model (CCM and complexity analysis) we will provide a higher reliability for fNIRS parameters compared to direct measures of HbR and HbO.

**Background and Significance:**
The proposed project is to develop and validate a novel stress-response nonlinear dynamic model for identifying MCI compared to CN using wearable sensors. To minimize between-subject variability, we will target only MCI of the Alzheimer’s type, as the most common types of dementia. However, our approach is expandable to general early-stage dementia as it measures dual-task deficits, which is also common across frontotemporal, Lewy body, and vascular dementia (8-10). Early cognitive impairment screening provides an opportunity to begin secondary prevention and plan for future care, safety concerns, and financial arrangements, while decision-making capacity remains (11). Unfortunately, less than half of patients with Alzheimer’s disease (AD) having never received a formal diagnosis (12), while there is gathering policy support for AD screening, such as with the IAGG-GARN consensus panel recommendations (4, 8). Current neuropsychological screening tools are subjective and affected by education and language biases (e.g., clock-drawing test), and are insensitive to changes over time (13-17). Our proposed approach is objective, and
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requires minimum staff training, and the cognitive score is available immediately and automatically after testing. In aging-related neurodegenerative diseases, compensatory processes in “cortical brain regions” allow maintenance of motor and cognitive performance (18). Assessing deficits in dual-tasking due to an impaired attention and motor plan development can, therefore, provide a powerful tool for screening cognitive impairments (19-22). In our previous research, we developed an upper-extremity function (UEF) for screening cognition, based on dual-task “motor performance” assessment using wearable sensors (NIA R21AG055852), and validated this tool among clinically diagnosed aMCI/AD older adults (23, 24). In the proposed research, we will assess brain function using fNIRS during our UEF dual-task test. The proposed fNIRS methodology in combination with UEF provides several unique advantages over other approaches for cognitive impairment screening. For older adults with AD or other dementia, fNIRS application in the clinical setting is fast (~10 minutes), inexpensive (<$15000), and practical. We showed 82% sensitivity and specificity in detecting aMCI/AD based on UEF motor performance alone (n=91,(25, 26)), and we will further improve the accuracy of our screening approach using the proposed multimodal brain and motor function assessment. We previously, as outlined below, proved the additional value of brain function assessment in our pilot data, where we achieved 27% increase in MCI identification using combined fMRI and motor data compared to original UEF motor score.

Preliminary Data, Experimental Design and Methods:
Eight cognitively healthy (age=74±4) and nine MCI older adults (age=81±9) performed tasks inside the fMRI, including counting (one minute), elbow flexion (one minute), and dual-task UEF (one minute) with one-minute rest between the tasks, repeated in four trials. Our preliminary findings showed greater activation in frontal lobe, especially in middle frontal gyrus in MCI compared to CN. We observed significant differences in complexity of task-dependent fMRI data between MCI and CN for frontal, occipital, and temporal brain regions. Using both complexity data and motor function we were able to identify MCI with a sensitivity and specificity of 89% and 88%, which was a 27% improvement in accuracy compared to our original UEF motor score. fMRI results demonstrated that cortical brain, rather than deep brain regions are associated with UEF dual-task, which provides evidence that fNIRS can be efficiently used to capture brain function for UEF cognitive screening. Subsequently, we tested the application of fNIRS for identifying brain function complexity when healthy young participants (age=25±5 years) were exposed to UEF dual-tasking. We observed 39% increase in fNIRS data complexity in left pre and post central, temporal, and frontal brain regions for two-minute UEF dual-task compared to resting (p<0.03). These pilot studies showed promise for developing the proposed multimodal cognitive score. We will recruit 15 CN and 15 MCI older adults (≥65 years), to perform two minutes of resting and two minutes of dual-task trials, involving simultaneous counting backward by three and UEF motor task. All participants will repeat this test within seven days from the first session. Participants will be selected and stratified into cognitive groups, based on National Institute of Aging – Alzheimer’s Association (NIA-AA) (27, 28) diagnosis. Clinical measures include comorbidity (Charlson comorbidity score (CCI) (29)) and depression (Patient Health Questionnaire (PHQ-9) depression scale (30)), as they can potentially influence executive function, memory, and attention. While sitting, participants will first rest for two minutes, during which, they will be asked to relax with eyes open staring at the instruction monitor (saying “rest”) and to not think about any specific topic (31). Then they will flex and extend the elbow of the right arm as consistently as possible for two minutes, while counting numbers backward by three. We selected counting numbers as the cognitive task because it involves working memory and executive functioning (32). We also showed that counting backward by “three” is difficult enough for aMCI/AD screening (23). To assess motor function, wearable motion sensors are attached to the upper-arm and wrist. We will derive UEF motor score (range: cognitive normal=0; cognitive impairment=1) based on speed and accuracy of motor function performance. Points are assigned based on parameter
comparisons to previously determined ranges for: 1) flexion number; 2) range of motion variability; and 3) flexion variability (timing of flexions) (25, 26). We will use fNIRS, with 46 channels, for measuring brain function. We will assess the complexity of brain function time-series for six brain networks, including default mode (episodic memory (33)), frontoparietal (executive functioning (33)), ventral and dorsal attention (detection of salient stimuli and selective attention (34)), somatomotor, and visual (35). We will use HbO and HbR data to extract complexity measures for resting and dual-task conditions, using entropy analysis. To minimize the duration of testing, we will implement the “sample entropy (SampEn) method”, which is less sensitive to bias for short time series (36). We will use convergent cross mapping (CCM) to calculate the dysregulation of interaction between motor and brain functions. CCM is a nonlinear approach for estimating the interaction between two time series (fNIRS and gyroscope data) based on the state space reconstruction of manifolds (current and past behavior state) (7). With this approach, we will estimate interactions between two time series (i.e., motor and brain function) by quantifying the correspondence between two manifolds. This approach is appropriate for relatively short time series. For statistical analysis, we will evaluate differences in fNIRS SampEn and CCM among the three cognitive groups using ANOVA, adjusted for age, sex, and other confounding variables (e.g., comorbidities and depression). To evaluate the test-retest reliability of UEF parameters between two assessments, we will use intraclass correlation coefficient (ICC) two-way mixed effects F-test models.

Proposed One-Year and Long-Term Outcomes:
Successfully achieving our goals, we will: 1) provide an objective multimodal approach for MCI screening, suitable for hospitalized older adults; and 2) understand the underlying neural mechanism and structural interference across brain networks for dual-tasking among older adults with cognitive impairment, useful for rehabilitation programs. Accomplishing the proposed project will provide the preliminary results for an R21 NIH resubmission to CNN (scored 33rd percentile) and an R01 NIH (long-term plan to submit to ASG). The main concern for R21 was the lack of previous evidence for fNIRS in quantifying brain function during physical activity. Within our recent research, we tested the application of fNIRS for assessing brain function among healthy young participants (39% increase in fNIRS complexity for two-minute dual-task compared to resting). Within the proposed project, we will show differences between fNIRS results between cognitively impaired and healthy older adults.

Year End Progress Summary:
Finishing the proposed project we were able to achieve new discoveries in the field of cognitive impairment assessment using brain function analysis. Here the findings are summarized. Cognitive impairment is an increasingly relevant health concern, as data estimates demonstrate that by 2040 the number of older adults with dementia will surpass nine million in the United States, approximately a 170% increase compared to 2001. Despite this high prevalence, over half of patients with dementia never receive an evaluation, indicating that a quick and objective routine test for screening cognitive decline in older adults is needed. Alzheimer’s disease (AD) is associated with a low value of nonlinear complexity of the brain function, which can be quantified using multiscale entropy analysis. Our proposed solution is an upper extremity function dual-task screening method measured by functional near infrared spectroscopy (fNIRS). The aim of this study was to investigate fNIRS entropy data in a mixed model to better understand its relationship with cognitive function and task condition (resting-state and dual-task). The sample population for this data includes 56 adults living in Arizona with ages ranging from 18-96. Measurements were taken over the frontal (right and left) and parietal (right and left) brain regions. The cognitive status of participants was a significant mixed model factor for the following brain regions: left frontal, right frontal, left parietal and right parietal (p<0.004). The task type was a significant mixed model factor for the following brain regions: right frontal, left parietal and right parietal (p<0.042). The
results of this study indicate potential for the use of fNIRS multiscale entropy analysis as a screening tool for cognitive impairment. More research is necessary to better understand other potential confounding factors as well as validate this approach in a larger sample size. Based on current finding we submitted an abstract to The Alzheimer’s Association International Conference, which be presented in July 2023 in Amsterdam. We also listed the related publications and grants.
Imaging and cognition in rodent models of aging and hypertension. Theodore Trouard, PhD, Gene Alexander, PhD, Carol Barnes, PhD. University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
1. Complete analysis of cross sectional MRI (anatomical and diffusion) carried out on 9 cohorts of rats collected within a study of cognitive aging. 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 analysis of longitudinal MRI (anatomical and diffusion) from cohorts of rats before and after the induction of long term 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).
3. Compare imaging results with alternative analyses carried out in Dr. Alexander’s lab and with behavioral studies carried out in Dr. Barnes’s lab.

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 (R01 AG049464; R01 AG049464). 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.

Preliminary Data, Experimental Design and Methods:
Diffusion-weighted imaging has been carried out in a total of 111 Fisher 344 rats in the Cognitive Aging (CAS) study. They were separated into nine distinct groups (3 ages: young adult, middle and old adult and 3 cognitive performance ratings: low, average and high performance). Diffusion-weighted imaging has been carried out in 50 Fisher 344 rats in the Hypertension (HTN) study at two time points. Diffusion tensor and fiber orientation distribution function (FODF) templates were generated from the entire cohort.

Proposed One-Year and Long-Term Outcomes:
All data for this project has been collected and our goal is to finish up the processing of the data in the summer of 2022. 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. The completed processing and analysis of dMRI data in the rat model of hypertension (Specific Aim 2) will allow comparison of neuroanatomical correlations with behavior and the effects of hypertension.
The data obtained and analysis carried out will support grants that utilize rodent models of aging and Alzheimer’s. Many ongoing studies have already benefitted from the analysis techniques established, and the requested funding will help bring this work to completion and establish pipelines to be use in future grants.
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Year End Progress Summary:
All of the diffusion MRI processing (DTI and FBA) has been completed as proposed (Specific Aims 1 and 2). In addition to the DTI and FBA analysis we have also carried out atlas-based analysis, voxel-based morphometry (VBM) and deformation based morphometry (DBM) on high-resolution structural MRI of the same cohorts of rats. The structural and diffusion results indicated that there is no observable correlation of brain structure with regard to cognitive status. However, there is a significant correlation of changes in brain structure with respect to age. Notably, between 6 and 15 months of age, there is a significant increase in overall brain size, but a decrease in relative cortical volume. These results, for the first time, demonstrate that 6 month old rats are not “fully developed” and that brain size changes cannot be described by a simple increase or decrease in overall brain size.

Imaging results from the Cognitive Aging Study have been compared to cognitive scores on the modified Morris water maze using the corrected integrated path length (CIPL). Aging rats demonstrated an increase in CIPL scores which correspond to a decrease in cognitive performance. There was no change in the structure of the brain that correlated to cognitive performance.

Imaging results from the Hypertension Study have been compared to cognitive scores on the modified Morris water maze using the corrected integrated path length (CIPL). Rats experiencing 10 weeks of hypertension showed severe end organ damage (fibrosis in the heart and kidneys) but no difference in CIPL scores were observed. No structural or microstructural differences were observed between groups either.

These results were presented at Society for Neuroscience [1,2], the 2022 Arizona Alzheimer’s Consortium Scientific Conference [3,4], and the 2023 International Society for Magnetic Resonance in Medicine [5]. Two manuscripts based on the abstracts are in preparation with the goal of submitting for publication this summer.

The activity included in this project has resulted in generation of multiple NIH grants.
**Support for brain MRI acquisition and analysis.** Theodore Trouard, PhD, Andrew Rouse, PhD, Carol Barnes, PhD, Lee Ryan, PhD, Maria Altbach, PhD, Nan-kuei Chen, PhD, Aneta Kielar, PhD, Matthew Grilli, PhD, Steven Rapcsak, MD, Ying-hui Chou, PhD, Craig Weinkauf, PhD. University of Arizona, Arizona Alzheimer’s Consortium.

**Specific Aims:**
The specific aim of this project is to establish a neuroimaging acquisition and analysis core at the University of Arizona in Tucson to be a core service to AAC investigators. This will include partial support of a neuroimaging scientist that will be available to a wide group of investigators focused on aging and Alzheimer’s Disease, as well as an application scientist who will help establish MRI acquisition protocols.

**Background and Significance:**
A significant amount of research at the University of Arizona and across the AAC employs brain MRI. Often, investigators rely on their own laboratories and personnel to develop their projects and build the necessary acquisition and 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.

**Preliminary Data, Experimental Design and Methods:**
This project will partially support two scientists to aid brain MRI research at the University of Arizona in Tucson and the AAC. The scientists will interface with personnel at UArizona as well as the broader AAC community. Regular workshops will be held on implementation of MRI techniques and processing tools that will be open to all AAC investigators and their laboratory personnel. These workshops will be held via Zoom so that participants across the state can participate. The support of these two scientists will also be included into an NIH high end instrumentation (HEI) grant for new 3T MRI at the University of Arizona.

**Proposed One-Year and Long-Term Outcomes:**
Within the year, we will have resubmitted a $2,000,000 NIH HEI grant for a new 3T MRI. The scientist will also have interfaced with many investigators and will have held at least three state-wide workshops on MRI methods.

**Year End Progress Summary:**
This project supported an MRI imaging scientist, Dianne Patterson PhD, at 0.5FTE, and an application scientist, Mr. Kevin Johnson, at 0.2 FTE. They have been instrumental in aiding many AAC researchers design, carry out, and analyze MRI data. Dianne Patterson has held bimonthly workshops on neuroimaging topics and has made recordings of these workshops available online to the AAC community. Their work has been critical in recruitment of new users to the MRI facility and the establishment of a Brain Imaging Center at the University of Arizona. Their contributions helped obtain a favorable and ultimately fundable score on an NIH High-End Instrumentation grant S10 OD032166 “3T MRI scanner for Advanced Brain Imaging.” This grant will bring a state-of-the-art 3T MRI to the University of Arizona in 2023 which will enhance the brain MRI research done by our investigators as well as make them more competitive for federal funding.
Understanding the effects of micro-embolic events in Asymptomatic Extracranial Carotid Artery Disease on neuroinflammation and blood brain barrier integrity. Craig Weinkauf, MD, PhD, Juan Arias, MD, Kevin Johnson, BA, Maria Altbach, PhD. University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
Hypothesis: Subjects with asymptomatic Extracranial Carotid Atherosclerotic Disease (aECAD) and micro-embolic events have increased MRI neuroinflammatory markers and blood-brain barrier dysfunction compared to those with aECAD but without micro-embolic events. We will test this by performing advanced MR-based imaging in 10 aECAD subjects with microembolic and 10 aECAD subjects without microemboli. These experiments greatly complement our current work and provide an opportunity for collecting exciting preliminary data for future grant applications.

Background and Significance:
aECAD is a growing disorder that primarily affects the elderly population. Currently, aECAD is primarily associated with higher incidence of stroke and transient ischemic attack. In addition, there is increasing evidence suggesting that aECAD contributes to cognitive decline and neurodegeneration. This is highly relevant because identifying a subpopulation of patients with asymptomatic ECAD that are at higher risk of developing Alzheimer’s Disease and Related Dementias (ADRD) might prompt earlier interventions to a disease that is only treated for stroke prevention.

Preliminary Data, Experimental Design and Methods:
Our preliminary data shows that among a wide pool of inflammatory molecules, VCAM-1 was significantly upregulated in patients with ECAD. Further analyses revealed that higher VCAM-1 expression was associated with key MRI biomarkers of neurodegeneration linked to ADRD. One of our ongoing studies is projected to recruit 160 patients with ≥ 50% asymptomatic carotid stenosis (hi aECAD), a fact that makes it feasible to screen and recruit a subset of 20 patients with and without micro-embolic events for this proposed study. 10 subjects with hi aECAD and ≥ 2 microemboli during event monitoring will be enrolled as part of the study group. 10 subjects with hi aECAD and 0 microemboli during event monitoring will be part of the control group.

Proposed One-Year and Long-Term Outcomes:
One-year outcomes: Study participants will undergo carotid ultrasound, TCD and contrast-enhanced MRI evaluation, data will be processed and analyzed. We hypothesize that we will find that subjects who have microembolic events will have significantly higher markers of neuroinflammation.
Long-term outcomes: RO1 submission for evaluation of mechanisms of neurodegeneration and cognitive dysfunction in subjects with Asymptomatic Extracranial Carotid Artery Disease.

Year End Progress Summary:
Our team of medical imaging experts developed a study protocol that incorporates carotid ultrasound imaging, state-of-the-art MR perfusion imaging (Figure 1), and cutting-edge transcranial doppler (TCD) robotic evaluation. However, we faced some unexpected challenges, such as delayed IRB approval for contrast studies and poor initial TCD performance. To address these issues, we purchased a different and better with increased automation TCD robotic system that helps the project needs (the AAC grant was re-budgeted for this purpose). This system includes a highly sensitive and automated emboli detection software (Figure 2).
Despite such challenges, 10 participants were enrolled in a 6-month timeframe. To date, no findings speak towards our Specific Aims have been identified. Data analysis will continue in the next 6 months, the results will be used for future publications and grant applications exploring the impact of aECAD on neuroinflammation and blood brain barrier integrity. As we are able to process these data we will be sure to reference AAC grants (current and past) for relevant manuscripts.

Figure 1: Relative cerebral blood flow (rCBF) map from a participant with high asymptomatic Extracranial Carotid Atherosclerotic Disease (aECAD). Images generated by a Dynamic Susceptibility Contrast (DSC)

Figure 2: Embolic event detected on Transcranial doppler (TCD) monitoring in a participant with high right asymptomatic Extracranial Carotid Atherosclerotic Disease (aECAD). M-Mode doppler shows an embolus (top yellow arrow) in the proximal right
Manuel Lymph Drainage Massage (MLDM) treatment for Alzheimer’s Disease: a pre-clinical trial. Marlys Witte, MD, Paulo Pires, PhD, Elizabeth Hutchinson, PhD, Russell Witte, PhD, Janet Funk, MD, University of Arizona, Arizona Alzheimer’s Consortium.

Specific Aims:
SA1: Does manual lymph drainage massage (MLDM) increase cervical lymphatic flow and protein clearance? We will directly measure this by isolation/cannulation/sampling of cervical lymphatics and also indirectly by magnetic resonance imaging (MRI) of interstitial fluid (ISF) movement after cisterna magna injection and photoacoustic imaging/ultrasound (PAI) of cervical lymphatic dynamics.

SA2: Does MLDM reduce Amyloid-β (Aβ) accumulation in the brain with a concomitant increase in Aβ in cervical lymph nodes? Using post-mortem samples, we will measure brain and cervical lymph node Aβ accumulation as well as cervical lymph Aβ clearance from SA1 samples.

SA3: Does MLDM slow the progression of cognitive decline? We will use standard tests of nesting and novel object recognition to evaluate behavioral-cognitive status.

Background and Significance:
Alzheimer’s disease (AD) is a progressive neurodegenerative disease. AD pathogenesis has been attributed to pathological accumulation of Aβ and abnormally hyperphosphorylated tau proteins. Current AD drugs primarily treat cognitive impairment and behavioral manifestations. Attempts to reduce Aβ deposition, preventing production or aggregation, have had little success and recent FDA approved immunotherapies are costly with significant side-effects.

Brain lymphatic dysfunction has recently been implicated in AD. The brain’s unique “glymph” pathway not only regulates extracellular water and ion balance but also transports ISF, including perivascular and cerebrospinal fluid (CSF), containing proteins and other macromolecules into endothelial-lined meningeal lymphatics and thence into contractile valved cervical lymphatics and the deep (dCLVs) and superficial lymph nodes (sCLVs). Obliteration of dCLVs reduces glymph clearance and increases brain Aβ content in APP/PS1 AD mice.

MLDM is currently the gold standard for treatment of head/neck lymphedema and also a useful adjunct in other body parts. MLDM’s gentle circular massage increases lymphatic flow, contractility, and tracer protein clearance. Therefore, MLDM could accelerate removal of toxic accumulations of AD-specific proteins, improving cognition and slowing AD progression.

Preliminary Data, Experimental Design, and Methods:
Two sequential Experiments #1 and 2 will be performed beginning at 2 and 6 months using 5xFAD and wildtype (WT) mice. Mice will receive upper body MLDM (5 min., 3x per week for 8 weeks) with a handheld mini-massager. Sham controls will receive MLDM to the distal hind paws only. Behavioral assessments and imaging (MRI or PAI) will take place pre- and post-treatment. After imaging, CLVs will be cannulated to collect cervical lymph, followed by post-mortem isolation of cervical lymph nodes and brain tissue. Immunoassays, including the quantification of Aβ, and mass spectrometry will be performed on all samples.

Proposed One-year and Long-term Outcomes:
SA1: MLDM will increase ISF/CLV flow/protein clearance in 5xFAD, possibly also in WTs.
SA2: MLDM will reduce brain Aβ content while increasing it in lymph within dCLVs/sCLVs and in cervical lymph nodes.
SA3: MLDM will slow progression of cognitive decline in 5xFAD mice.
Year End Progress Summary:
SA1: An MRI protocol was developed specifying contrast agent, kinetics, administration route, and reproducibility. Gadolinium (0.4 μL) was injected into the cisterna magna, of wildtype (WT) control mice and, after technical adjustments, they consistently showed prompt (≤10 minutes) visualization of cervical lymph nodes, the exterior outline of the brain (presumably meningeal lymphatic vasculature), and concentration in the ventral surface of the brain consistent with the area above the cribriform plate, and, only later, gradual entry into brain substance; all findings consistent with a direct CSF-lymphatic pathway. Our earlier initial attempts at MRI in 5xxAD mice had been technically unsuccessful. The high resolution PAI protocol is still under refinement in WT control mice in regard to the optimal contrast agent (Evans blue vs indocyanine green aggregates), timing, positioning and injection site (snout vs. intracerebral injection). No pre- or post-MLDM imaging was completed until these protocols are optimized or alternatively, only comparisons of massaged vs. non-massaged mice or acutely massaged mice during imaging will be performed.

SA2: Aβ 40/42 concentration was analyzed by ELISA assay in successive groups of MLDM and non-MLDM treated, 7-8 month-old 5xFAD mice and compared to WT controls. In general, Aβ40 was low or undetectable in the brain and cervical lymph nodes of all 3 subgroups, whereas Aβ42 was substantially but variably elevated (range 878-2035 picograms/mL per 50 μg protein loaded) in both MLDM and non-MLDM treated mice. Similarly, Aβ42 was elevated but variable in dCLVs and sCLVs of MLDM and non-MLDM mice (~¼-⅓ of the brain concentration), reaching significance p<0.05 with higher level (mean 317 vs. 44.5) in MLDM in the first experiment, but only trending in the second experiment (mean 258 vs. 210). Central blood (non-hemolyzed) levels were undetectable for both Aβ40 and Aβ42. ELISA assay for fibrillar protein was technically unsuccessful. Attempts at cervical lymph sampling (and also therefore direct lymphatic cannulation) have not been feasible thus far; supermicrosurgical techniques for access to cervical lymphatics are being established and optimized in our lab.

SA3: Expertise in behavioral testing has recently been acquired and specific tests, both those reviewed prior and additional tests, are being optimized for baseline and post-MLDM treatment testing in our laboratory. These include assessments of cognition and impaired sociability (to address social isolation behavior) seen in AD population and recapitulated in 5xFAD mice. The challenges encountered during the project included the availability of litter-matched and appropriate age-AD mice, both locally and commercially, as well as low fertility for breeding and genetic drift in our own colony. However, these issues have been addressed by obtaining limited commercial availability of aged mice and initiating a new breeding program. To further address these limitations, the use of a rat AD model, TgF344-AD, has been initiated. The use of rats will improve the proposed research as standardization of the MLDM protocol in this model is more feasible. Moreover, the increased size of the deep and superficial cervical nodes will allow for individual, as opposed to pooled analysis in mice, analysis of AD-specific protein in each node. For the same reason, cannulation and lymph collection in rats will be more successful and yield a larger and higher quality sample for analysis by mass spectrometry. Another challenge encountered was the mid-year abrupt departure of the part-time Lymphology Laboratory Director. This interrupted the work flow until a highly qualified PhD-level translational neuroscientist was hired full-time to continue this research. The work above is ongoing and with the use of a local CORE grant and other funds, obtained through the support of this grant from the Arizona Alzheimer’s Disease Consortium, we expect to secure further funding and complete the proposed research investigating MLDM as a new therapy for AD.
β-amyloid regulation of astrocytic fatty acid metabolism. Fei Yin, PhD, Adam Raikes, PhD, Francesca Vitali, PhD. University of Arizona; Arizona Alzheimer’s Consortium.

Specific Aims:
1) Specific Aim 1. To assess β-amyloid-induced astrocytic metabolic reprogramming focusing on fatty acid metabolism
2) Specific Aim 2. To determine region-specific lipid metabolic profile in a mouse model of Alzheimer’s disease (AD)
3) Specific Aim 3. To correlate regional lipid metabolism with myelin integrity in the AD mouse model

Background and Significance:
Brain lipid dyshomeostasis is an early and persistent hallmark of AD, and multiple top AD risk factors are involved in lipid trafficking and lipid metabolism. However, despite abundant correlational evidence, the precise mechanisms by which disrupted lipid metabolism is triggered and how it subsequently contributes to AD pathologies and neurodegeneration, remain elusive.
Astrocytic degradation of fatty acids (FAs) has been recently demonstrated neuroprotective against hyperactivity- or stroke-induced damages. We also reported that APOE-ε4 (ApoE4), the greatest genetic risk factor for late-onset AD, disrupts astrocytic FA β-oxidation (FAO), the process by which FAs are degraded (Qi et al., Cell Rep, 2021; supported by AAC Project 2019-2020). Moreover, our findings demonstrate that astrocytic mitochondria are essential in maintaining brain lipid homeostasis by performing FAO, and its loss induces metabolic, inflammatory, synaptic, and cognitive hallmarks that are reminiscent of AD.
Research proposed herein addresses the knowledge gap of astrocytic lipid metabolism in the AD brain metabolic system and determines whether β-amyloid accumulation has a direct effect on astrocytic FAO, and thereby contributes to the disrupted lipid homeostasis in AD brains.

Preliminary Data, Experimental Design and Methods:
Our preliminary data suggest that FAO capacity is impaired in astrocytes of 5xFAD mouse brains. Primary astrocytes isolated from 4-month-old 5xFAD mice exhibited higher levels of intracellular lipid droplets (LDs) compared to astrocytes isolated from age-matched wildtype (WT) control mice. Further, metabolic characterization of these astrocytes showed that 5xFAD astrocytes had reduced capacity to respire on exogenously supplied free FAs (oleate-BSA). These results suggest that amyloidosis in 5xFAD brains is associated with a deficit in astrocytic FAO capacity and an accumulation of lipids in LDs, which resemble the phenotype of astrocytes with FAO deficiency.

Functional characterizations, gene ontology (GO) enrichment and REVIGO analyses of the brains and astrocyte of 5xFAD mouse will be performed. Both male and female WT and 5xFAD mice will be included in the analyses proposed below. N=10 per group will be used for in vivo studies. In vitro analyses will include cells from 5 mice / group, each with an experimental duplication.

Aim 1. To determine whether β-amyloid can directly reprogram astrocyte metabolism and suppress FAO, WT primary astrocytes will be treated with Aβ1-42. After that, astrocytic capacity to metabolize FA or glucose will be determined by the Seahorse XF Analyzer. In addition, mitochondrial dynamics and LD volumes will be determined after the treatments to correlate mitochondrial phenotype with FAO capacity and lipid accumulation.
Aim 2. The goal of this experiment is to test whether regional diversity in astrocytic response to β-amyloid pathology is related to differential FAO capacity. Acute brain slices from WT or 5xFAD mice will be prepared, and punches of different regions of these slices will be metabolically assessed for FAO and glycolysis. Further, we will obtain lipid profile and enriched lipid metabolic pathways in WT and 5xFAD mice.

Aim 3. As astrocytic lipid synthesis is required for oligodendrocyte-mediated myelination, this Aim will test whether disrupted lipid metabolism across different brain regions is correlated with changes in myelin microstructural integrity. In vivo magnetic resonance imaging (MRI) will be used to identify changes in brain structure and myelin integrity in WT and 5xFAD brains. Regional myelin integrity will then be correlated with the lipid profile as proposed in Aim 2.

Proposed One-Year and Long-Term Outcomes:
Outcomes of the proposed studies will provide insights into the role of astrocytic FAO in AD, especially its direct relationship with amyloid pathology. Results obtained from this study will be used to seek external funding from the National Institute on Aging or private agencies to further explore the role of astrocytes in regulating lipid homeostasis and how a disruption to astrocytic metabolic function contributes to lipid-related abnormalities seen in human AD brains.

Year End Progress Summary:
1. FAO deficit proceeds LD accumulation in a mouse model of AD
Consistent with our preliminary data that reduced FAO capacity was observed in 5xFAD astrocyte, LDs were detected in subiculum of 5xFAD mice, but not other brain regions at 6-month-of-age, with perilipin-2 (Plin2, LD surface marker) protein expression also upregulated in the cortex. Subiculum is also where Aβ deposition first appears in 5xFAD mice. Importantly, a subset of LDs in 5xFAD brains were localized to astrocytes (GFAP+), but none could be localized to neurons (NeuN+) or microglia (IBA-1+). Moreover, compared to WT brains or LD-negative areas, LD-containing areas in 5xFAD brains showed substantially higher GFAP immunoreactivity, corroborating the link between lipid accumulation and astrocyte reactivity.

To investigate whether FAO is impaired in 5xFAD mouse brain, FA-induced respiration was measured with acute hippocampal slices. As seen in 5xFAD astrocyte, 5xFAD slices showed a lower ability to respire on FA compared to WT brains regardless of glucose presence. In parallel with the reduced FAO capacity, 5xFAD astrocytes also had lower expression of the FAO regulator PPARα. Importantly, by tracing BODIPY-C12, we found markedly higher mitochondrial localization of the fluorescent FAs in astrocytes from 4- or 6-month-old 5xFAD mice than those from age-matched WT mice, confirming a mitochondrial FAO deficit. These data collectively reveal that signs of lipid accumulation in 5xFAD brains are spatially in proximity to Aβ pathology and temporally preceded by impaired astrocytic FAO.

2. 5xFAD mouse hippocampi share key transcriptomic signatures on inflammation, synaptic function and lipid metabolism with astrocytic FAO deficit model
To systematically determine to what extent lipid dyshomeostasis in 5xFAD mice resemble that of astrocytic FAO deficit mice (astrocyte-specific Tfam knockout mice; TfamAKO), we compared their hippocampal transcriptome for overlapped genes, pathways, and mechanisms by leveraging a 5xFAD RNA-sequencing dataset (from AD Knowledge Portal). By comparing transcriptomic signatures of these two models at their advance stages (12-month for 5xFAD and 6-month for TfamAKO, each compared to their respective controls), 1,127 overlapping DEGs were identified (hypergeometric test p<0.001). 94% of these common DEGs changed in the same direction (853 upregulated and 206 downregulated) with the fold changes of all shared DEGs highly correlated (r = 0.64; p < 0.00001) between models. Pathway enrichment analysis of these shared DEGs followed by removals of redundant GO terms identified inflammatory response, cytokine
production, synaptic function, and lipid metabolism as common mechanisms perturbed by both 5xFAD and Tfam\textsuperscript{AKO}. Together, outcomes of these transcriptome level comparisons corroborate the phenotypic similarities between these two models and underscore a mechanistic role of astrocytic FAO in amyloidosis-induced lipid dysregulation and neurodegeneration.

3. \textit{β}-amyloid induced astrocytic FAO deficits and LDs accumulation
To determine whether \textit{β}-amyloid can directly trigger astrocytic metabolic reprogramming and suppress FAO, we incubated WT primary astrocyte with oligomeric Aβ (oAβ). oAβ treatment promoted LDs accumulation and substantially increased GFAP intensity and the secretion of inflammation mediator, prostaglandin E2 (PGE2), indicative of higher astrocyte reactivity. Consistently, levels of lipid classes including free FAs (FFA) and triacylglycerol (TAG) were increased in oAβ-treated astrocytes. We next investigated whether LD accumulation in oAβ-treated astrocytes is accompanied by reduced FA degradation. Indeed, blocking carnitine palmitoyltransferase I (CPT1)-mediated long-chain FA transport into the mitochondria using etomoxir induced a smaller oxygen consumption rate (OCR) drop in oAβ-treated astrocytes relative to vehicle-treated astrocytes, suggesting FA catabolism was compromised in oAβ-treated cells. In parallel with reduced FAO capacity, oAβ-treated astrocytes also showed downregulation of key FA degradation genes, including the transcriptional factor \textit{Pparα} and genes controlling mitochondrial FA import and FAO. To further determine whether oAβ disruption of FA metabolism occurs at tissue level, we determined FA metabolizing capacity in oAβ-treated acute hippocampal slices. Consistent with the \textit{in vitro} results, hippocampal slices treated with oAβ showed a reduced oxygen-consumption rate (OCR) in the presence of exogenous FAs (oleate-BSA). These findings suggest that \textit{β}-amyloid-triggered FAO deficit in astrocyte is likely responsible for the LD accumulation and aberrant lipid profiles. These data corroborate the unique role of astrocytic FA degradation in protecting the brain from \textit{β}-amyloid-induced lipid homeostasis and neurodegeneration.


A NIH R01 application will be submitted in July 2023 to determine whether and how altered astrocytic FA degradation modifies AD onset and progression and whether it can be therapeutically targeted.
Cognitive effects of carotid disease and carotid intervention. Wei Zhou, MD, Ted Trouard, PhD, Ying-hui Chou, PhD, Chiu-Hsieh Hsu, PhD, Gloria Guzman, Salil Soman, MD, Thomas Hastukami, MD, PhD, University of Arizona; Surgical Services Southern Arizona VA Health Care System; Washington University; Beth Israel Deaconess Medical Center, Harvard Medical School, 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:
Extracranial carotid atherosclerosis is not only a major cause of ischemic stroke, but also doubles the risk of cognitive impairment. Decreased CBF due to hypoperfusion and frequent SBIs due to repetitive microembolization are two important etiologies of cognitive dysfunction in patients with asymptomatic carotid stenosis. Carotid revascularization is an effective strategy for stroke prevention by eliminating the embolic source and improving perfusion. Although studies have shown an overall cognitive benefit, up to 30% of patients experience procedure-related cognitive deterioration despite an absence of neurologic complication. The mechanisms by which this cognitive decline occurs are poorly understood.

We and others have observed a high incidence of procedure-related SBIs (20-80%) despite an absence of clinical symptoms. Our previous work suggest that SBIs are, in part, responsible for patients experiencing post-intervention cognitive decline and that higher incidence of SBIs in the hemodynamic risk area. However, there is limited information on how CBF and SBI interact and how their interaction affects cognitive function long-term.

Our central hypothesis is that impaired CBF increases the risk of intervention-related SBIs and leads to cognitive deterioration. By understanding the dynamic interaction between CBF, the characteristics of SBIs, and their cognitive effects, we will have a better understanding of cognitive impairment and vascular dementia. The proposal may also change our current clinical practice by identifying a subgroup of patients at risk for SBIs and therefore carotid intervention should be restrained in asymptomatic patients.

Preliminary Data, Experimental Design and Methods:
1. CBF analysis: we analyzed ASL CBF of 16 subjects who underwent carotid interventions. CBF maps were quantified using the one-compartment standard kinetic model and the individual CBF maps were then normalized to the standard MNI template space using Statistical Parametric Maps (SPM). 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).

2. Cognitive measures: For cognitive evaluation, we focused on episodic memory, which was measured by Rey Auditory Verbal Learning Test (RAVLT) with parallel forms. A total of 144 subjects who underwent carotid intervention for severe atherosclerotic disease were evaluated. After normalizing against age-matched Mayo’s older Americans normative studies (MOANS) and group means, Z scores for sum of the trial were generated. As expected, the average preop Z score for our patient cohort was lower (Z=-0.79, SD 1.3, CI: -1 to -0.53) than age-adjusted norm in MOANS (updated AVLT norms for age 56 to 97), 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 scores 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 SBIs contributed to decline in this group of patients.

**Proposed One-Year and Long-Term Outcomes:**
We expect to generate useful preliminary information on CBF changes and correlations between CBF and SBIs at one year. We also expect to identify obstacles in resting state fMRI measures. This preliminary data is critical for our NIH grant application in the 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 the carotid artery.

**Year End Progress Summary:**
We first examined the cognitive performance of 170 consecutive patients who underwent intervention and received neuropsychometric testing pre-intervention, and at 1-, 6-, and 12-month postoperatively. After normalized again age and education-matched control, we observed significant improvement in multiple executive function measures at 1, 6, and 12 months following carotid intervention. We also observed significantly improvement in episodic memory 1 and 6 months following carotid intervention. However, some patients experienced significant decline despite of an improvement in the overall cohort. (Annals of Surgery 2022; 276(3):539-544; PMCID: PMC9387545). We have previously reported that the volume of silent brain infarcts secondary to procedure-related microembolization correlated to significantly memory decline postop (J Vasc Surg. 2017 Mar;65(3):686-694. PMCID: PMC53287950).

Among the aforementioned patients, 58 patients also received baseline MRI with arterial spin labelling (ASL) sequence on a 3T GE scanner. CBF maps were quantified using PCASL. Individual maps were normalized using the Montreal Neurological institute template space using SPM8. We found that baseline ASL CBF is significantly correlated with baseline executive function measured by Trial Making Test (P=0.03) after adjusting for age, gender and BMI.
Understanding the role of Resistin in vascular dysfunction and cognitive impairment. Wei Zhou, MD, Paulo Pires, PhD, Mitchell Lazar, PhD. University of Arizona; Institute for Diabetes, Obesity, and Metabolism; University of Pennsylvania Perelman School of Medicine, Arizona Alzheimer’s Consortium.

Specific Aims:
1) Relate serum resistin level to procedure-related postoperative cognitive decline
2) Characterize human resistin-related arterial stiffness and tissue changes in novel murine models

Background and Significance:
There is an increasing evidence supporting the ability of the central nervous system to incite an inflammatory response to a variety of injuries including ischemia and trauma. Inflammation has been linked to cognitive decline and risk of dementia. Many studies, including ours, have associated postop inflammatory biomarkers to poor cognitive performance long-term. Resistin, an adipokine initially identified in mice, is considered a link between diabetes and obesity. Increasing clinical evidences associate human resistin with insulin resistance, obesity, arterial stiffness, and cardiovascular disease. High plasma resistin level is also associated with neuroinflammatory markers, early cognitive decline, and dementia in many population-based investigations, but the finding is not consistent across all cohorts, and the mechanistic insight of how resistin leads to cognitive impairment is largely unknown.

On the cellular level, resistin induces proinflammatory transformation of macrophages. To understanding the role of human resistin in cardiovascular disease and vascular dementia, we need to overcome the fact that human resistin and mouse resistin are significantly different. Over the last two years, we have successfully bred resistin knockout mice, Retn−/−, a strain that does not express murine resistin; and Retn−/−/BAC-hRetn (Tg), a transgenic strain that lacks murine resistin but expresses human resistin at levels similar to that in humans In collaboration with Lazar lab. In this proposal, we will utilize these novel murine model to study the role of resistin in inflammation, arterial remodeling, and vascular dementia.

Preliminary Data, Experimental Design and Methods:
We treated 23 weeks old Retn−/− and Tg mice with high-fat (HF) diet or regular chow (RC) for 4 weeks. Then middle cerebral arteries (MCA) were isolated and pressure myograph were generated to depict stress/strain curve. HF Diet alone increased compliance in Retn−/− mouse, whereas it decreased compliance in Transgene mice. Furthermore, the extent of the shift in the stress-strain relationship is higher in Retn−/− mice. This preliminary study suggests an interesting interaction between HF and expression of human resistin to decrease compliance in intracranial arteries.

Proposed One-Year and Long-Term Outcomes:
At one year we expect to have preliminary data on the relationship between resistin and cognitive changes, we will expect to have a better understanding of the effects of human resistin on arterial compliance. Our long-term plan is to determine the impact of human resistin on vascular dementia and cognitive impairment using these novel genetically modified mice. We plan to submit a NIH application in the next 18 months.
Year End Progress Summary:
To better understand how human resistin affect atherosclerosis and vascular dementia, and the potential interaction between human resistin and APOE, we developed 2 new double knockout mouse strains with atheroprone Apoe<sup>−/−</sup> background over the last year: Retn<sup>−/−</sup>:Ape<sup>−/−</sup> (DKO) and Retn<sup>−/−</sup>/BAC-hRetn:Ape<sup>−/−</sup> (Tg-DKO). We observed advanced atherosclerotic plaques in older Apoe<sup>−/−</sup> and Tg-DKO mice. Both strains have the presence of resistin with mouse resistin in Apoe<sup>−/−</sup> and human resistin in Tg-DKO. To differentiate the in vivo effect of mouse and human resistin, we examined the brachiocephalic arteries of 12-week old animals, we observed significant higher vascular cell adhesion protein 1 expressions in Tg-DKO compared with Apoe<sup>−/−</sup> mice (P=0.02), suggesting that human resistin play a more significant role in the genesis and progression of atherosclerosis than mouse resistin.
Rod microglia, gut microbiome, vital imaging, and plasma biomarker as tools to investigate mechanisms of AD and TBI. 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 develop gene expression profiles of rod microglia variants. Hypothesis: Rod microglia as a subset of activated microglia have a distinct gene expression profile to determine the variant function and origin.
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 evaluate vascular permeability and function in response to repeated brain injury, as a pathological mechanism for vascular dementia using miniature microscopes in mice.
4) To validate plasma biomarker presence in acute and chronic TBI, and other conditions.

Background and Significance:
[1] Microglia heterogeneity and their differential roles in health and disease are at the forefront of understanding and then treating neurological disease. We have pioneered investigations into the activated rod microglia isoform that has no known gene profile. To leverage the analytical power of single cell gene expression, it is possible to deploy bulk cell sequencing, isolated cell sequencing, or spatial transcriptomics. For this aim, we leverage all approaches to determine feasibility moving forward. The goal is a subset of genes expressed with rod microglia neuropathology to aid future molecular tool development.

[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 inflammation process, which can have multiple systemic effects. Subsequently, 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 measure to track disease processes. Peripheral inflammation and fecal microbiome can be used as disease and therapeutic biomarkers.

[3] Our miniature microscope (miniscope) technology can image fluorescent molecules through a cranial window in mice to observe vascular function, compound bio-availability, and clearance. Using penetrable (fluoro-2-deoxyglucose), diagnostic (fluorescein), and impenetrable (fluoro-dextrans) compounds, the cerebrovascular response to physiological conditions can be monitored through time-lapse imaging. Here we develop foundational understanding for repeated TBI and advance analytical approaches.

[4] Prior aims, partially supported by AAC funding, identified a putative plasma biomarker for TBI. Additional experiments are proposed to validate and verify the target, timing, and sensitivity for clinical translation.

Preliminary Data, Experimental Design and Methods:
[1] To achieve gene expression of rod microglia, initial laser capture microdissection and spatial transcriptomics approaches were unsuccessful. The amount and quality of starting material did permit technical completion of the protocols. To advance the aim, single nucleus RNA
sequencing has been conducted on regions with abundant rod microglia (brain-injured primary sensory cortex) in comparison to unaffected cortex (no rod microglia). Analytical platforms clustered cells to identify microglia, subclustered microglia to identify separate sensory from remote cortex microglia, and subclustered again into a potential rod microglia cluster. The proposed rod microglia have genes associated with cell structure (cytoskeleton, motility), inflammation, and activation (mitochondria, ATP production). These genes are high value targets for in situ hybridization studies.

[2] Neurological disease extends into the periphery, where associated inflammation can affect multiple systems. Our techniques are optimized for estrous cycle determination, immune cell population flow cytometry, and microbiota DNA extraction from feces. Ongoing work includes bacterial DNA sequencing and subsequent metagenomic analysis.

[2] Mixed-sex mice have been subjected to biosample collection (blood, feces, vaginal lavage) before and after diffuse TBI. Blood samples are analyzed by flow cytometry to track leukocytes (monocytes, neutrophils, B and T lymphocytes) as the population distributions (percentage) shift in response to injury, time, and sex. In a supervised analysis, labeled cells are quantified as Cd11b^Ly6c^high monocytes, inflammatory Cd11b^Cd115^ monocytes, and Cd11b^Ly6g^ neutrophils as percentages of the total population. Unsupervised analytical approaches have clustered the data to identify 8 or more cell types that reinforce or extend the supervised analysis. Fecal samples have been processed to amplify and sequence bacterial 16S genomes to assess microbiome diversity and abundance. The diversity of the fecal microbiome serves as a pharmacodynamic endpoint to monitor post-injury inflammation and response to probiotic intervention. Comparisons are made over time, between sexes, and among the flow cytometry and microbiome outcome measures.

[3] Miniature microscopes visualize fluorescent compounds in the vasculature and cortex under a cranial window. During combinations of high-speed and time-lapse imaging, fluorescent compounds are administered to observe vascular morphology and function, with regard to dye-tracer permeability from the vasculature. Administration of closed-head injury with miniscope imaging demonstrated that vascular permeability was minimal, and encouraged more severe injury administration. Image processing algorithms will be developed and refined to quantify vascular responsivity.

[4] A plasma-based biomarker discriminated brain-injured from uninjured animals over time post-injury. Western blot protocols have been optimized for human serum and plasma samples. De-identified human samples from the Banner Sun Health Brain and Body Donation program were obtained to present healthy and aged/diseased conditions. Traditional western blots were run on agarose gels and identified the potential antigen of interest. New studies with brain injury samples are required to determine the specificity from aging and disease.

**Proposed One-Year and Long-Term Outcomes:**
Ms. Giordano is the lead on Aim 1 to conduct gene expression on activated microglia. We anticipated a successful sequencing run, followed by intensive computational analysis. If time permits, validation studies using in situ hybridization and/or pPCR will be conducted. The genomic results will advance tool development, such as transgenic animals, diagnostic tools, and therapeutic interventions. Ms. Rojas is the lead on Aim 2 to track inflammation and microbiome diversity. All biosamples have been collected and effort is applied to sample quality control and preparation for sequencing. Mr. Griffiths is the lead on Aim 3 to analyze data from miniscopes. Cohorts of video imaging continue while analysis techniques align data collection with outcomes.
Mr. Griffiths and Mr. Tallent lead Aim 4 to validate the blood biomarkers. With validation in human samples, invention disclosure and distribution may be possible.

**Year End Progress Summary:**

1. 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 defaulted to bulk single nucleus sequencing because spatial transcriptomics and laser capture microdissection protocols failed to provide quality starting material to complete the protocol. To quantify gene expression from brain regions inhabited by rod microglia, we deployed a more crude approach of regional analysis between the sensory cortex with rod microglia and the entorhinal cortex without rod microglia. As stated above, a dozen genes were identified uniquely to a small subcluster of microglia hypothesized to represent rod microglia. These targets can be pursued for validation and verification. Immediate next steps are validation by in situ hybridization and reanalysis of published single cell gene expression databases to subcluster rod microglia.

   Of note, the National Institute on Aging awarded a 4-year R01 to continue the molecular tool development for antibodies and genes associated with rod microglia. This funding represents a successful transition of AAC funding into NIH funding for a multi-PI team of investigators.

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 has identified 8 or more unique cell type clusters in studies of the estrous cycle, brain injury, and response to probiotic treatment. Concurrently, all fecal samples have been processed and set for microbiome sequencing. An analysis strategy has been defined to determine microbiome diversity and abundance to injury, estrous, and probiotic intervention.

3. Our research team has advanced technical capability to build, modify, implant, and use miniscopes to visualize brain dynamics during behavior. Ongoing work has collected high-speed and time-lapse imaging of fluorescent dextrans (multiple molecular weights) and labeled glucose to evaluate cerebral blood flow and blood brain barrier permeability. These protocols can be deployed to 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 awarded as a successful transition from AAC to federal funding.

4. A pilot project from the Banner Sun Health Brain and Body Donation Program availed 24 blood samples for biomarker analysis. The samples permitted protocol refinement to compare biomarker performance in serum and plasma, where the results were expectedly different, and the biomarker remained viable to identify aging/disease conditions. Significant effort was put towards material transfer agreements and other legal steps, which include permission to evaluate blood from brain-injured patients. Protocols are being finalized for bulk sample analysis.

   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.
2022 Publications and Manuscripts


Crown LM, Gray DT, Schimanski LA, Barnes CAC, Cowen SL. Aged rats exhibit altered behavior-induced oscillatory activity, place cell firing rates, and spatial information content in the CA1 region...


agonist danavorexton improves narcolepsy phenotype in a mouse model and in human patients. 


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


Parra KL, Alexander GE, Raichlen DA, Klimentidis YC, Furlong MA. Exposure to air pollution and risk of incident dementia in the UK Biobank. Environmental Research. 2022; 209, 112895. PMCID: PMC8976829.


van Dyck CH, M.D.1, Chad J. Swanson, Ph.D.2, Paul Aisen, M.D.3, Randall Bateman, M.D.4, Christopher Chen, B.M.B.Ch.5, Michelle Gee, Ph.D.6, Michio Kanekiyo, M.S.2, David Li, Ph.D.2, Larisa Reym derman, Ph.D.2, Sharon Cohen, M.D.7, Lutz Froelich, M.D., Ph.D.8, Sadao Katayama, M.D.9, Marwan Sabbagh, M.D.10, Bruno Vellas, M.D.11, David Watson, Psy.D.12, Shobha Dhadda, Ph.D.2, Michael Irizarry, M.D.2, Lynn D. Kramer, M.D.2, Takeshi Iwatsubo, M.D.13 Lecanemab for Treatment of Early Alzheimer’s Disease, NEJM November 29, 2022 DOI: 10.1056/NEJMoa2212948 Ida Mohebpour; Michael Malek-Ahmadi; Thomas Virden, III; Angela Breitmeyer; Marwan N Sabbagh; Briana Auman; Christine M Belden; Parichita Choudhury; Autumn Arch; Kathryn Davis; Carol Cline; Naudia Moorley; Alireza Atri; Geidy Serrano; Thomas G Beach. Neuropathologic Validation of the Alzheimer’s Questionnaire. Aging Clin Exp Res. 2022 Aug 29. doi: 10.1007/s40520-022-02222-9. Online ahead of print.PMID: 36031683.


2023 Publications and Manuscripts


Chiu SY, Wyman-Chick KA, Ferman TJ, Bayram E, Holden SK, Choudhury P, Armstrong MJ. Sex differences in dementia with Lewy bodies: Focused review of available evidence and future


DeCourt B, Sabbagh MN. The importance of genomics in advancing the treatment of dementia, Lance Neurology 2022 Published online June 10, 2022, https://doi.org/10.1016/S1474-4422(22)00234-4.


Hill PF, de Chastelaine M, Rugg MD. Patterns of retrieval-related cortico-striatal connectivity are stable across the adult lifespan. Cerebral Cortex. 2023. PMID: 36124666.


Adulthood Imparts Cognitive and Brain Changes in Rats: A Focus on Hysterectomy at Short-, Moderate-, and Long-Term Intervals After Surgery. Hormones and Behavior.


Mbs GBY, Wasek B, Bottiglieri T, Malyshova O, Caudill MA, Jadavji NM. Dietary vitamin B12 deficiency impairs motor function and changes neuronal survival and choline metabolism after


Rowe RK, Lifshitz J (2023) Motor, cognitive, anxiety-like, and depressive-like behavior following one or two diffuse TBIs in the mouse. Open Data Commons for Traumatic Brain Injury. OCD-TBI:828, https://doi.org/10.34945/F5BS3R.

Sabbagh MN, DeCourt B. Biomarker-based diagnosis of preclinical Alzheimer disease: time for the clinic?. Nat Rev Neurol (2023). https://doi.org/10.1038/s41582-022-00767-x


Sharp N*, Fani M#, Alrahyan M#, Youngstedt S, Yeom Y, Maxfield M. Effect of Dynamic Lighting Intervention on Sleep Quality, Depression, and Agitation in Older Adults with Dementia in Long-Term Care Facilities: A Clinical Trial. The Gerontologist (50% completed, will be submitted in September 2023).


Silva JF, Polk FD, Savu A, Kath AM, Gee MT, Pires PW. BKCa nitrosylation is associated with cerebral microvascular dysfunction in female 5x-FAD mice. bioRxiv. 2023.06.06.543962; doi: https://doi.org/10.1101/2023.06.06.543962. PMID: 37333104. PMCID: PMC10274786.


2022 – 2023
Current & Pending Grants
## CURRENT & PENDING GRANTS

### 2022-2023 Current Grants

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<td>Creative Health Collaborations Hub</td>
<td>7/1/2020 – 6/30/2022</td>
<td>National Endowment for the Arts</td>
<td>$160,000</td>
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<td>P30 AG072980 (Reiman)</td>
<td>9/5/2021 – 6/30/2026</td>
<td>National Institutes of Health (NIH)</td>
<td>$15,727,544</td>
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<td>Alzheimer’s Disease Core Center</td>
<td>5/15/2016 – 4/30/2024</td>
<td>National Institutes of Health (NIH)</td>
<td>$3,806,602</td>
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<td>EPIC: A Group-based Intervention for Early-stage AD Dyads in Diverse</td>
<td>9/30/2021-8/31/2026</td>
<td>National Institutes of Health (NIH)</td>
<td>$2,111,808</td>
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<td>Cognitive Decline and Dementia Risk in Older African Americans</td>
<td>1/1/2022-12/31/2024</td>
<td>National Institutes of Health (NIH)</td>
<td>$175,000</td>
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<td>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</td>
<td>4/1/2023-3/31/2028</td>
<td>National Institutes of Health (NIH)</td>
<td>$4,737,761</td>
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<td>The Epidemiology of Cognitive Decline in African Americans: Identifying Risk and Protective Factors</td>
<td>7/1/2022-6/30/2027</td>
<td>National Institutes of Health (NIH)</td>
<td>$630,329</td>
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<td>Effects of Combined Aerobic and Resistance Exercise on Sleep, Cognition, and Blood Biomarkers as Surrogate Endpoints for Cognition in Older Adults with Amnestic Mild Cognitive Impairment (aka The CARE Trial)</td>
<td>7/1/2023 – 6/30/2028</td>
<td>National Institutes of Health (NIH)</td>
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<td>Current &amp; Pending Grants</td>
<td>PI/Co-I</td>
<td>Award Period</td>
<td>Total Project Amount</td>
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<td><strong>David W. Coon (Co-I)</strong></td>
<td>FP00034907 (Polh) Arizona State University Foundation (ASUF) / Institute for Mental Health Research CarePRO Virtual LTC: Addressing the Mental Health Concerns of Family Caregivers for People Living with ADRD in Long Term Care</td>
<td>7/1/2023-6/30/2023</td>
<td>$125,000</td>
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<td><strong>Lynch, Michael (Pl)</strong></td>
<td>1922914 National Science Foundation (NSF) EDGE CT: Development of a Molecular Toolkit for Integrative Organismal Research in the Microcrustacean Daphnia pulex</td>
<td>12/1/2019 – 11/30/2023</td>
<td>$1,799,999 Total Project</td>
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<td><strong>Benjamin Readhead (Pl)</strong></td>
<td>1R01AG058469-01A1 Integrated understanding of complex viral network biology in Alzheimer’s Disease</td>
<td>3/2019-2/2024</td>
<td>$405,444 Total Award</td>
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<td><strong>Benjamin Readhead (Co-I)</strong></td>
<td>NIH R01 AG062500 S6K1 as a novel link between aging and Alzheimer’s disease</td>
<td>4/2019-2/2024</td>
<td>$3,040,398 Total</td>
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<td><strong>Benjamin Readhead (Pl)</strong></td>
<td>NIH 1 R01 AG 062514-01 Modulation of Alzheimer’s disease by Herpes simplex virus infection</td>
<td>09/2019-05/2024</td>
<td>$97,882 Total Award</td>
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<td><strong>Benjamin Readhead (Pl)</strong></td>
<td>BAI/Nomis AGR 08/22/18 A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Reg</td>
<td>7/2017-6/2023</td>
<td>$954,215</td>
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<td><strong>Benjamin Readhead (Co-I)</strong></td>
<td>NIH P30 AG072980 Arizona Alzheimer’s Disease Research Center (ADRC)</td>
<td>9/2021-6/2026</td>
<td>$15,727,544 Total Award</td>
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<td><strong>Benjamin Readhead (Pl)</strong></td>
<td>NIH U01 AG061835 Identification of the genetic and transcriptomic networks of cognitive and neuropathological resilience to Alzheimer’s disease associated viruses</td>
<td>9/2018-4/2023</td>
<td>$5,721,083 Total</td>
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523
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<tr>
<th><strong>Current &amp; Pending Grants</strong></th>
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<tr>
<td><strong>Benjamin Readhead (Co-I)</strong></td>
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<tr>
<td>BrightFocus Foundation 1026846</td>
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<tr>
<td>Explainable deep learning approach for consensus and region-specific transcriptional networks in Alzheimer’s disease</td>
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</table>

| **Sydney Schaefer (PI)** | 07/01/2023-06/30/2024 |
| Edson Initiative for Dementia Care and Solutions, Biodesign Institute, Arizona State University (Schaefer) | $124,740 Total Project |
| Comparing state anxiety between cognitive and motor testing among older adults to advance earlier dementia screening |

| **Sydney Schaefer (co-I)** | 08/15/2022-7/31/2025 |
| NSF 2216344 (Schweighofer) | $199,893 subcontract-ASU |
| National Science Foundation | $707,000 Total Project |
| Personalizing motor learning |

| **Sydney Schaefer (Primary Sponsor)** | 07/01/2023-06/30/2024 |
| F32 AG071110-01A1 (PI: Hooyman) | $211,182 Total Project |
| NIH/NIA | Using an Online Video Game to Predict Functional and Cognitive Decline within the MindCrowd Electronic Cohort |

| **Michael Sierks (PI)** | 09/01/2016 – 06/30/2023 |
| R01 AG054048 (Siers) NIH | $1,761,841 Total Project |
| Protein variants as blood-based biomarkers for diagnosing and staging AD |

| **Michael Sierks (PI)** | 01/30/2022 – 08/31/2024 |
| R43 AG076091 (Siers) NIH via Virtici | $26,993 Total Project |
| A Novel Multiparameter Blood Test for Early Detection of Alzheimer’s Disease |

| **Michael Sierks (PI)** | 09/01/2021 – 08/31/2024 |
| W81XWH2110837 (Siers) NIH via Virtici | $1,295,595 Total Project |
| DOD-ARMD: Army Medical Research Acquisition Activity Targeting Toxic Oligomeric Protein Variants Generated after Traumatic Brain Injury to Decrease Risk of AD |

| **Michael Sierks (Project PI)** | 07/01/2022 – 06/30/2023 |
| CTR057001 (Coon) Arizona Alzheimer’s Consortium (AAC) FY23 | $25,000 Individual Project |
| AAC FY23: Disruption of neuronal proteostasis in early stage Alzheimer’s disease |

| **Michael Sierks (Project PI)** | 07/01/2023 – 06/30/2024 |
| TBD Pending Setup (Coon) Arizona Alzheimer’s Consortium (AAC) FY24 | $29,000 Individual Project |
| AAC FY24: Intracellular Targeting of Toxic Tau Variants as a novel treatment for Alzheimer’s Disease |

<p>| <strong>Michael Sierks (PI)</strong> | 8/1/2022 – 7/31/2024 |
| 1R21AG079095-01 (Siers) NIH | $431,750 Total Project |
| Purification and Characterization of a toxic AD associated intracellularly generated amyloid beta fragment |</p>
<table>
<thead>
<tr>
<th>Project Title</th>
<th>Principal Investigator</th>
<th>Start Date</th>
<th>End Date</th>
<th>Grant Number</th>
<th>Funding Agency</th>
<th>Award Amount</th>
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<tr>
<td>Exploiting sex-dependent brain injury response for nanoparticle therapeutics</td>
<td>Sarah Stabenfeldt (PI)</td>
<td>01/01/2021</td>
<td>11/30/2025</td>
<td>R01 NS116657 (Stabenfeldt/Sirianni) NIH/NINDS</td>
<td>$2,551,485</td>
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<tr>
<td>Linking TBI secondary injuries to FTLD- and ALS-like neurodegeneration</td>
<td>Sarah Stabenfeldt (PI)</td>
<td>08/15/2021</td>
<td>07/31/2023</td>
<td>R03 NS122018 (Stabenfeldt/Bowser) NIH/NINDS</td>
<td>$100,000</td>
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<td>John Templeton Foundation grants</td>
<td>Sarah Stabenfeldt (co-I)</td>
<td>07/01/2021</td>
<td>06/30/2023</td>
<td>62189 (Bennett)</td>
<td>$234,437</td>
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<td>Craftwork as Soulwork: Sanctifying Scientific Practice among Genetics Researchers</td>
<td>Sarah Stabenfeldt (Co-I)</td>
<td>10/01/2022</td>
<td>09/30/2024</td>
<td>W81XWH-22-1-0388 CDMRP (Acharya) DOD – ARMY</td>
<td>$300,000</td>
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<tr>
<td>Developing vaccines for immunological defense from traumatic brain injury</td>
<td>Sarah Stabenfeldt (MPI)</td>
<td>04/01/2023</td>
<td>12/31/2026</td>
<td>R01 AG077768-01 (Lifshitz/Stabenfeldt) NIH/NIA</td>
<td>$2,842,247</td>
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<td>Molecular tool development to identify, isolate, and interrogate rod microglial</td>
<td>Sarah Stabenfeldt (Co-I)</td>
<td>04/01/2023</td>
<td>03/31/2027</td>
<td>1R01HL162809 (Brown) NIH/NHLBI</td>
<td>$2,360,944</td>
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<tr>
<td>Anti-microbial platelet-like-particles to treat internal bleeding and augment subsequent healing</td>
<td>Jessica Verpeut (PI)</td>
<td>06/01/2023</td>
<td>05/31/2024</td>
<td>AGR 5/25/2023 (Verpeut)</td>
<td>$50,000 Total Project</td>
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<tr>
<td>Institute for Mental Health Research grants</td>
<td>Jessica Verpeut (PI)</td>
<td>07/01/2022</td>
<td>06/01/2023</td>
<td>LTR 6/29/22 (Coon)</td>
<td>$350,000 Total Project</td>
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<tr>
<td>Arizona Alzheimer’s Consortium/Arizona Department of Health Services (ADHS) grants</td>
<td>Jessica Verpeut (PI)</td>
<td>06/01/2023</td>
<td>05/31/2024</td>
<td>LTR 6/29/22 (Coon)</td>
<td>$350,000 Total Project</td>
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<tr>
<td>Validating a preclinical Alzheimer’s disease behavioral assessment in the TgF344-AD rat</td>
<td>Yalin Wang (MPI)</td>
<td>8/1/2021</td>
<td>8/31/2025</td>
<td>R01EY032125 (Wang/Lu)</td>
<td>$1,559,565</td>
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<td>Hierarchical Bayesian Analysis of Retinotopic Maps of the Human Visual Cortex with Conformal Geometry</td>
<td>Yalin Wang (PI)</td>
<td>9/15/2021</td>
<td>05/31/2026</td>
<td>R01DE030286 (Lepore)</td>
<td>$230,192.00</td>
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<td>Children’s Hospital Los Angeles grants</td>
<td>Yalin Wang (PI)</td>
<td>9/15/2021</td>
<td>05/31/2026</td>
<td>R01DE030286 (Lepore)</td>
<td>$230,192.00</td>
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<tr>
<td>Early Joint Cranial and Brain Development from Fetal and Pediatric Imaging</td>
<td>Yalin Wang (PI)</td>
<td>8/1/2020</td>
<td>07/31/2023</td>
<td>R21AG065942 (Wang)</td>
<td>$444,976</td>
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<td>Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transport</td>
<td>Yalin Wang (PI)</td>
<td>8/1/2020</td>
<td>07/31/2023</td>
<td>R21AG065942 (Wang)</td>
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<td>Start/End Date</td>
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<tr>
<td>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</td>
<td>Yalin Wang (Co-I)</td>
<td>10/1/2021-9/30/2023</td>
<td>National Science Foundation (NSF)</td>
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<tr>
<td>Are aging outcomes worse for women with autism? Sex differences in the neurocircuitry of symptom camouflaging and its vulnerability to aging</td>
<td>Yalin Wang (Co-I)</td>
<td>9/15/2021-9/14/2023</td>
<td>HHS: National Institute of Health (NIH)</td>
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<tr>
<td>Building IoT: Development of a Patient-specific Thermal and Lighting Environment Control Framework for the Patient's Cognitive Performance and Well-being in the Dementia Care</td>
<td>Nastaran Shishegar/Nina Sharp (PI)</td>
<td></td>
<td>Edson Initiative Seed Grant</td>
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<tr>
<td>Arizona State University Foundation (ASUF)/Women and Philanthropy A New View for Drug Design Against Lyme Arthritis: Imaging Proteins at the Bacterial Outer Surface</td>
<td>Petra Fromme (Co-I)</td>
<td>07/01/2022-12/31/2023</td>
<td>$49,472 Total Project</td>
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<td>MRI: Acquisition of a femtosecond laser system for time-resolved studies using Arizona State University’s (ASU) Compact X-ray Light Source (CXLS)</td>
<td>Petra Fromme (PI)</td>
<td>10/01/2020-09/30/2023</td>
<td>$771,919 Total Project</td>
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<td>Biology with X-ray Lasers</td>
<td>Petra Fromme (PI)</td>
<td>08/01/2013-09/30/2023</td>
<td>$11,739,959 Total Project</td>
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<td>Molecular mechanisms of moisture-driven DAC within polymeric sorbents (MissionDAC)</td>
<td>Petra Fromme (Co-I)</td>
<td>03/15/2023-02/29/2028</td>
<td>$90,800,000 Total Project</td>
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<td>Molecular electro-photosynthesis (MEPS) as a bioelectronic platform for organic synthesis</td>
<td>Petra Fromme (Co-I)</td>
<td>09/01/2022-08/31/2025</td>
<td>$1,651,740 Total Project</td>
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<td>Microbial electro-photosynthesis (MEPS) as a bioelectronic platform for organic synthesis</td>
<td>Petra Fromme (Co-I)</td>
<td>01/01/2023-12/31/2025</td>
<td>$420,996 Total Project</td>
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<td><strong>Petra Fromme (PI)</strong></td>
<td><strong>09/15/2018-09/14/2023</strong></td>
<td><strong>$341,928 Total Project</strong></td>
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<td>DE-SC0019457</td>
<td>DOE: Office of Science (OS)</td>
<td>Collaborative Project: Regulation of Sustained Cyclic Electron Flow (CEF)</td>
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<tr>
<th><strong>Petra Fromme (PI)</strong></th>
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<tr>
<td>5R01GM095583-10</td>
<td>HHS:NIH</td>
<td>Dynamics of membrane proteins unraveled by time-resolved serial crystallography</td>
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<th><strong>Ashley Stokes (PI)</strong></th>
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<tr>
<td>NIH/NINDS R01 NS124575 (Stokes)</td>
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<td>Multi-scale functional connectivity in preclinical models of Parkinson’s disease</td>
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<th><strong>Ashley Stokes (PI)</strong></th>
<th><strong>06/01/2022 – 05/31/2024</strong></th>
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<tr>
<td>NIH/NINDS R21 NS125535</td>
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<td>Investigating the role of cerebral perfusion in demyelination and repair in multiple sclerosis with MRI</td>
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<tr>
<th><strong>Ashley Stokes (PI)</strong></th>
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<tr>
<td>Arizona Biomedical Research Centre RFGA2022-010-26</td>
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<td>Assessment of neurovascular factors implicated in mild cognitive impairment and Alzheimer’s disease</td>
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<tr>
<th><strong>Ashley Stokes (Co-PI)</strong></th>
<th><strong>07/2020 – 06/2023</strong></th>
<th><strong>$50,000 Total Project</strong></th>
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<tr>
<td>Valley Research Partnership P2-5021</td>
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<td>A Highly Specific Inhibitor of Matrix Metalloproteinase-9 Abrogates Tissue Plasminogen Activator Mediated Hemorrhagic Transformation in Experimental Ischemic Stroke</td>
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<thead>
<tr>
<th><strong>Ashley Stokes (Co-I)</strong></th>
<th><strong>07/01/2018 – 06/30/2024</strong></th>
<th><strong>$6,149,580 Total Project</strong></th>
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<tr>
<td>NIH/NIA P30 AG019610-20 (Reiman; Core PI: Alexander)</td>
<td>ARIZONA ALZHEIMER’S DISEASE CORE CENTER (ADCC): Brain Imaging and Fluid Biomarkers (BI-FB) Core (Core G)</td>
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<th><strong>Ashley Stokes (Co-I, Site PI)</strong></th>
<th><strong>04/01/2020 – 03/31/2025</strong></th>
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<tr>
<td>NIH/NCI UG3 CA247606-01 (Quarles)</td>
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<td>Structural and Functional Imaging for Therapy Response Assessment in Brain Cancer</td>
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<th><strong>Ashley Stokes (Co-I, Site PI)</strong></th>
<th><strong>12/01/2022 – 06/30/2026</strong></th>
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<tr>
<td>NIH/NCI R01 CA213158 (Quarles)</td>
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<td>Establishing the validity of brain tumor perfusion imaging</td>
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<th><strong>Nadine Bakkar and Ashley Stokes (Co-PI)</strong></th>
<th><strong>07/01/2022 – 06/30/2023</strong></th>
<th><strong>$157,500 Total Project</strong></th>
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<tbody>
<tr>
<td>AZ Alzheimer’s Consortium / Barrow Neurological Foundation</td>
<td></td>
<td>Imaging and molecular biomarkers of blood-brain and blood-CSF barrier cerebrovascular health in dementias</td>
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<tr>
<th><strong>Ashley Stokes (Co-I)</strong></th>
<th><strong>12/01/2022 – 06/30/2026</strong></th>
<th><strong>$1,200,000 Total Project</strong></th>
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<tr>
<td>U.S. Dept of Veterans Affairs I01RX002691-01A2 (Migrino)</td>
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<td>Mechanistic role of vascular dysfunction in TBI-mediated cognitive dysfunction</td>
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</table>
**CURRENT & PENDING GRANTS**

**Nadine Bakkar (PI)**  
07/01/2022 – 06/30/2023  
Barrow Neurological Foundation  
$110,500 Total Project  
Single nuclear profiling of vascular dysfunction in Amyotrophic lateral sclerosis (ALS)

**Yonas Geda (PI)**  
5/1/2018-11/30/22  
RO1 AG057708 (Geda)  
NIA  
$356,362  
Pathways linking neuropsychiatric symptoms with Alzheimer’s disease neuroimaging biomarkers and the outcome of incident Mild Cognitive Impairment/Dementia.

**Yonas Geda (site PI)**  
07/2019 – 06/2024  
5U01 AG006786-34 (PI:Petersen ) MCR to Dr. Geda  
NIA  
$22,950: 07/2021 – 06/2022  
Alzheimer’s Disease Patient Registry Renewal

**Yonas Geda (Co-I)**  
11/2020 – 03/2026  
R01 AG069453 (PI: Eric Reiman)  
NIA  
$111,475  
APOE in the Predisposition to, Protection From and Prevention of Alzheimer’s disease

**Yonas Geda (Sub-I)**  
6/2022-5/2024  
R01 AG059008 (Sabbagh)  
NIA  
$1,693,093  
MCLENA-1: Clinical Trial for the Assessment of Lenalidomide in Amnestic MCI Patients

**Yonas Geda (Sub-I)**  
6/2022 – 7/2026  
R01 AG073212 (Sabbagh)  
NIH, NIA  
$3,762,033.00  
Repurposing Siponimod for Alzheimer’s Disease

**Rita Sattler (Co-PI)**  
07/01/23-06/30/28  
NIH/NINDS R01NS127108-01 (Kruer)  
$3,350,000  
Genomic analysis of the Multiplex, Autozygous Populations in Cerebral Palsy (MAP CP) cohort: a focused approach to a complex disease

**Rita Sattler (Co-PI)**  
09/01/22-8/31/27  
NIH/NINDS NS120331-01A1 (Zarnescu)  
$3,532,730  
RNA dysregulation in neurodegeneration

**Rita Sattler (Multi-PI)**  
08/01/22-7/31/24  
NIH/NINDS R21 NS128550-01 (Sattler/Van Keuren-Jensen)  
$427,960  
Transcriptomic assessment of pathology in PD with dementia and dementia with lewy bodies using iPSC neurons and brain tissue of the same individual

**Rita Sattler (PI)**  
07/01/22-06/30/23  
Barrow Neurological Foundation  
$135,000  
Role of astrocyte-microglia crosstalk in C9orf72-mediated neuronal cortical degeneration
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<td><strong>Rita Sattler (PI)</strong></td>
<td>09/22/22-08/31/24</td>
<td>NIH/NINDS R21 NS130492-01 (Sattler) $345,567 Mechanisms of A-I RNA editing-mediated nuclear export of TDP-43</td>
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<td><strong>Rita Sattler (PI)</strong></td>
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<td>NIH/NINDS R01 NS120331-01A1 (Sattler/Van Keuren-Jensen) $4,073,311 Microglia contribution to disease pathogenesis in C9orf72 FTD/ALS</td>
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<td>AAC/BNF $114,000 Total Project Detection of Alpha-Synuclein in Neurodegenerative Diseases</td>
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<td>GR-ARPA-BNF-050123-01 (Racette &amp; Sattler Co-Pi's) $9,994,276 Total Project State of AZ/ARPA Alzheimer’s Disease and COVID-19-Related Cognitive Impairment</td>
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<td>Layla Al-Nakkash (PI), Tom Broderick (Co-PI), Minsub Shim (Co-PI)</td>
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<td>Nancy Bae (PI)</td>
<td>AZ Dept of Health Services-Arizona Alzheimer’s Consortium</td>
<td>The Role of Phosphorylation on the Function of the Telomere Protection Protein RAP1</td>
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<td>Teresa Brobeck (PI)</td>
<td>Parkinson Voice Project</td>
<td>MWU Parkinson Voice Project Program Development Grant</td>
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<td>Tom Broderick (PI)</td>
<td>Phoenix VA Healthcare System</td>
<td>Mechanistic Role of Vascular Dysfunction in TBI-mediated Cognitive Dysfunction</td>
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<td>Gerald Call (PI) &amp; Shaleen Korch (Co-PI)</td>
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<td>Identifying Probiotics and the Bacterial Genes that Ameliorate Motor Dysfunction in a Drosophila Parkinson’s disease Model</td>
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<td>Delrae Eckman (PI)</td>
<td>ADHS 17-00007401 (Eckman)</td>
<td>Arizona Department of Health Services through the Arizona Biomedical Research Commission Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4Targeted-Replacement Mice</td>
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<td>Elizabeth Hull (PI) &amp; Kathryn Leyva (Co-I)</td>
<td>AZ Dept of Health Services-Arizona Alzheimer’s Consortium</td>
<td>Progranulin &amp; Lysosomal pH: Implications for Potential New Therapeutic Strategy for Neurodegenerative Diseases</td>
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<td>Elizabeth Hull (PI) &amp; Kathryn Leyva (Co-I)</td>
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<td>Elucidating a mechanistic link between progranulin and lysosomal function in Alzheimer Disease</td>
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<td>Garilyn Jentarra (PI)</td>
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<td>Identification and Culture of Microbes in Brain Tissue from Alzheimer’s Disease Patients and Controls</td>
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<td>Garilyn Jentarra (Co-PI)</td>
<td>7R21AG072561-02 (Gu/Jentarra)</td>
<td>NIH R21 Targeting Whole Body Fatty Acid Metabolism in Alzheimer’s Disease, with Special Interest in Lauric Acid</td>
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<td>Nafisa Jadavji (PI)</td>
<td>AZ Dept of Health Services-Arizona Alzheimer’s Consortium</td>
<td>Dietary Vitamin B12 Deficiency on Ischemic Stroke Outcome in Aged Female and Male Mice</td>
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### CURRENT & PENDING GRANTS

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<tr>
<td>Nafisa Jadavji (PI)</td>
<td>20AIREA35050015 (Jadavji)</td>
<td>American Heart Association Research Enhancement Award Identification of Developmental Factors Involved in Ischemic Stroke Outcomes in Adulthood and Old Age</td>
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<td>Effects of Chronic Intermittent Hypoxia on Cholinergic Modulation of Hypoglossal Motoneurons</td>
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<td>Ann Revill (PI)</td>
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<td>Minsub Shim (PI)</td>
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<td>Cyclooxygenase-2 Signaling in Cell Senescence and its Role in Chemotherapy-induced Long-term Adverse Sequelae</td>
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<td>Tamara Turner (PI)</td>
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<td>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</td>
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<td>Alzheimer’s Prevention Initiative ADAD Colombia Trial</td>
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<td>NIH/NIA via Institute for Molecular Medicine (Agadjanyan/Schneider/Sultzer)</td>
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<td>Safety/Tolerability/Immunogenicity of first-in-human Aβ DNA vaccine, AV-1959D Phase 1 trials in early-stage AD subjects: based on IND18953 cleared by FDA</td>
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<td>A single-center, adaptive, repeated dose, parallel Phase I study to investigate in autosomal-dominant Alzheimer’s disease the pharmacodynamics of RO7269162 following oral administration in presymptomatic PSEN1 E280A mutation carriers and in non-carriers from the same kindred (BP44161)</td>
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<td>Emily Edmonds (Project PI)</td>
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<td>Data-driven Neuropsychological Diagnoses in the Arizona Alzheimer’s Consortium</td>
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<td>Combination anti-amyloid therapy for preclinical Alzheimer’s Disease</td>
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<td>Jessica Langbaum (PI)</td>
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<td>Establishing the science behind Alzheimer’s recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials</td>
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<td>APOE in the Predisposition to, Protection from and Prevention of Alzheimer’s Disease</td>
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<td>Jessica Langbaum (PI)</td>
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<td>Optimizing Research Infrastructure of Registries to Accelerate Participant Recruitment into Alzheimer’s Focused Studies</td>
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<td>Alzheimer’s Association via University of Southern California SG-22-87715-AHEAD (Raman)</td>
<td>ACTC AHEAD Alzheimer’s Association Proposal: Diverse Recruitment Component</td>
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<td>Michael Malek-Ahmadi (Co-I)</td>
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<td>Neurobiology of Mild Cognitive Impairment in the Elderly</td>
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<td>Advanced Imaging and Machine Learning in Alzheimer’s Research</td>
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<td>Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer’s disease</td>
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<td>Longitudinal Molecular Imaging of Neuropathology and Serotonin in Mild Cognitive Impairment</td>
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<td>Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques</td>
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<td>Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation</td>
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<td>NIH via University of Arizona</td>
<td>R01AG062453 (Chou)</td>
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<td>Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer’s disease biomarkers and risk factors</td>
<td>08/15/2022</td>
<td>04/30/2027</td>
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<td>Interleaved TMS-fMRI for Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnestic Mild Cognitive Impairment</td>
<td>05/01/2022</td>
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<td>Next-Generation Thalamic Nuclei Visualization and Segmentation Methods</td>
<td>12/2022</td>
<td>06/2026</td>
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<td>APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease</td>
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<td>Vascular Contributions to Dementia and Amyloid and Tau Lesions in APOE4 Carriers (VCID)</td>
<td>03/01/2020</td>
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<td><strong>Eric Reiman (Co-I)</strong></td>
<td>Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer’s disease</td>
<td>NIH/NIA via Massachusetts General Hospital</td>
<td>R01AG054671 (Quiroz)</td>
<td>09/01/2017</td>
<td>05/31/2023</td>
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<td><strong>Eric Reiman (Co-I)</strong></td>
<td>The Neighborhoods Study: Contextual Disadvantage and Alzheimer’s Disease and Related Dementias</td>
<td>NIH/NIA via University of Wisconsin-Madison</td>
<td>R01AG070883 (Bendlin/Kind)</td>
<td>03/01/2021</td>
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<td>NIH/NIMHH via University of Colorado Denver</td>
<td>U54MD000507 (Manson/Buchwald)</td>
<td>09/22/2017</td>
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<td><strong>Eric Reiman (Co-I)</strong></td>
<td>Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques</td>
<td>NIH/NIA</td>
<td>RF1AG0733424 (Su)</td>
<td>08/01/2022</td>
<td>07/31/2025</td>
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<td><strong>Eric Reiman (Co-I)</strong></td>
<td>Researching COVID To Enhance Recovery (RECOVER) Initiative</td>
<td>NIH/NIA via University of Arizona</td>
<td>OT2HL161847 (Nikolich-Zugich)</td>
<td>05/2021</td>
<td>05/2025</td>
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<td><strong>Eric Reiman (Co-PI)</strong></td>
<td>Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer’s Disease, Parkinson’s Disease and Related Disorders</td>
<td>Gates Ventures via Banner Alzheimer's Foundation</td>
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<td>NIH/NIA</td>
<td>R01AG058468 (Reiman / Aisen / Alexander / Johnson / Langbaum / Sperling)</td>
<td>09/01/2018</td>
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<td>NIH/NINDS via Boston University/Mayo Clinic</td>
<td><strong>U01NS093334 (Stern/Cummings/Reiman/Shenton)</strong></td>
<td>Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course and Risk Factors</td>
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<td>NOMIS Foundation (Reiman/Liang/Beach/Readhead/Dudley)</td>
<td>NOMIS Foundation via Banner Alzheimer’s Foundation</td>
<td>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</td>
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<td><strong>Eric Reiman (PI)</strong></td>
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<td>F. Hoffmann-La Roche Ltd.</td>
<td>A single-center, adaptive, repeated dose, parallel Phase I study to investigate in autosomal-dominant Alzheimer’s disease the pharmacodynamics of RO7269162 following oral administration in presymptomatic PSEN1 E280A mutation carriers and in non-carriers from the same kindred (BP44161)</td>
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<td><strong>Don Saner (Co-I)</strong></td>
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<td><strong>Don Saner (Core Co-Leader)</strong></td>
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<td><strong>CURRENT &amp; PENDING GRANTS</strong></td>
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<td>Enhancements to a Centralized Data Management System for</td>
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<td>the Arizona Alzheimer’s Disease Core Center (ADCC), Brain</td>
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<td>and Body Donation Program (BBDP), and Apolipoprotein E4</td>
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<td><strong>Pierre Tariot (PI)</strong> 04/01/2017-03/31/2024</td>
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<td>(Reiman/Aisen/Alexander/Johnson/Langbaum/Sperling)</td>
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<td>Weston Family Foundation via University of Arizona</td>
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<td>Neuroscience research to catalyze and scale science-based</td>
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<td>approaches to significantly improve health and well-being.</td>
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<td>Approaches for Personalized Diagnostics and Prognostics of</td>
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<td>MCI due to AD</td>
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<td><strong>David Weidman (Co-I)</strong> 07/01/2021-06/30/2026</td>
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<td>Native American Outreach, Recruitment, and Retention Program</td>
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<td>Global Alzheimer’s Platform Trial-Ready Cohort for</td>
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<td>Preclinical/Prodromal Alzheimer’s Disease</td>
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<td><strong>Yi Su (PI)</strong> 08/01/2022-07/30/2025</td>
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<td>Tracer harmonization for amyloid and tau PET imaging using</td>
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<td>statistical and deep learning techniques</td>
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<td>Cardiovascular Genotype and APOE ε4 Carrier Status Interaction Effects on Amyloid Load in Pre-Clinical Alzheimer’s Disease</td>
<td>Yi Su (Co-I)</td>
<td>06/01/2023 – 03/31/2024</td>
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<td>Yi Su (Co-I)</td>
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<td>State of Arizona via Arizona Alzheimer’s Research Consortium Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members</td>
<td>Yi Su (Project PI)</td>
<td>07/01/2022 – 06/30/2023</td>
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<td>State of Arizona via Arizona Alzheimer’s Research Consortium Advanced Imaging and Data Analysis in Alzheimer’s Research</td>
<td>Yi Su (Project PI)</td>
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<td>09/30/2020-03/31/2026</td>
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<td>Yi Su (Core Co-Leader)</td>
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<td>Alzheimer’s Prevention Initiative ADAD Colombia Trial</td>
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<td>API / A4 Alzheimer’s Prevention Trial</td>
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<td>American Indian and Alaska Native Health Disparities</td>
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<td>Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD</td>
<td>Yi Su (Co-I)</td>
<td>01/01/2021-08/31/2023 (NCE)</td>
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<tr>
<td>Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors</td>
<td>Yi Su (Co-I)</td>
<td>NIH/NIA via Boston University U01NS093334 (Stern)</td>
<td>12/01/2020-11/30/2023 (NCE)</td>
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<td>Pre-competitive Analytical Validation of SV2A PET as a Biomarker of Synaptic Density (From Imaging to Autopsy)</td>
<td>Alireza Atri (Co-PI)</td>
<td>Foundation for the National Institutes of Health (Finnema)</td>
<td>09/01/2022-09/01/2026</td>
<td>~$3,000,000 Total Project</td>
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<td>Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson’s Disease and Related Disorders</td>
<td>Alireza Atri (Co-PI)</td>
<td>Gates Ventures via Banner Alzheimer’s Foundation (Reiman)</td>
<td>09/01/2020-08/31/2024</td>
<td>$3,085,720 Total Project</td>
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<td>Alireza Atri (Co-I; BSHRI Site PI)</td>
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<td>A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer’s Disease (DIAN) – Gantenerumab Open Label Study (DIAN-TU-001 Gant OLEX)</td>
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<td>Washington University St. Louis NCT01760005 (Bateman)</td>
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<td>The complex interaction between Alzheimer’s drivers and aging</td>
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<td>Discovering novel mechanisms for aging-related dementia: probing medin and abeta vasculopathy</td>
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### CURRENT & PENDING GRANTS

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<td>Alpha-synuclein aggregate presence in gastrointestinal tract relative to CNS in 200 neuropathologically-evaluated autopsy subjects</td>
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<td>Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma.</td>
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<td>Development of in vivo quantitative stable isotope probing to quantify microbiome dynamics in Alzheimer’s Disease</td>
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<td>Are Minority Health Disparities in MRSA/MSSA Infections Related to Carriage and Social Relationships?</td>
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<td>Discovering in reverse – using isotopic translation of omics to reveal ecological interactions in microbiomes.</td>
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<td>Improving QIIME 2 pathogen identification and developer community tools</td>
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<td>Normal and Pathological Aging (Preclinical Alzheimer's Disease)</td>
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<td>Principal Investigator</td>
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<td>Richard J Caselli (PI)</td>
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<td>APOE in the Predisposition to, Protection from and Prevention of Alzheimer’s Disease</td>
<td>R01AG069453</td>
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<td>Richard J Caselli (PI)</td>
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<td>Richard J Caselli (PI)</td>
<td>05/2022 – 03/2027</td>
<td>Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer’s Disease</td>
<td>P01 AG052350</td>
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<td>Richard J Caselli (co-I)</td>
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<td>John Fryer (significant contributor)</td>
<td>06/2019 – 05/2024</td>
<td>Mitochondrial Sirtuin 3 in Parkinson’s disease</td>
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<td>John Fryer (PI)</td>
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<td>Microglial apoE in neuroinflammation and Alzheimer’s disease</td>
<td>RF1 AG062110</td>
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<td>John Fryer (PI)</td>
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<td>Novel genetic modifiers of C9orf72 and Tau toxicity (MPDPI w/Dr. Petrucelli)</td>
<td>RF1 AG062077-02</td>
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<td>John Fryer (co-I)</td>
<td>12/2016 – 11/2024</td>
<td>Expanding insights into FTD disease mechanisms</td>
<td>R35 NS097273</td>
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<td>John Fryer (co-I)</td>
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<td>ApoE isoform-specific therapy for Alzheimer disease</td>
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### CURRENT & PENDING GRANTS

**Arizona Department of Health Services**  
Normal and Pathological Aging (Preclinical Alzheimer’s Disease)

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<th>Award Amount</th>
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<td>Synergistic Interaction of amyloid-beta and alpha-synuclein in Lewy body Dementia (LBD CWOW)</td>
<td>John Fryer (PI)</td>
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<td>ApoE isoform-specific therapy for Alzheimer disease</td>
<td>John Fryer (PI)</td>
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<td>Pathobiology of Neurodegeneration in C9ORF72 repeat expansion</td>
<td>Dona Locke (PI)</td>
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<td>Quantifying Multiscale Competitive Landscapes of Clonal Diversity in Glioblastoma</td>
<td>Leslie Baxter (co-I)</td>
<td>09/2017 – 08/2023</td>
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**Arizona Department of Health Services**  
Normal and Pathological Aging (Preclinical Alzheimer’s Disease)

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<td>APOE in the Predisposition to, Protection from and Prevention of Alzheimer’s Disease</td>
<td>Dona Locke (co-I)</td>
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<td>Arizona Alzheimer’s Disease Research Center (ADRC)</td>
<td>Oana Dumitrascu (co-I)</td>
<td>09/2021 – 08/2023</td>
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**Arizona Department of Health Services**  
Normal and Pathological Aging (Preclinical Alzheimer’s Disease)

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<td>Arizona Alzheimer’s Disease Research Center (ADRC)</td>
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<td>Arizona Alzheimer’s Disease Research Center (ADRC)</td>
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# CURRENT & PENDING GRANTS

### Sleep for Stroke Management and Recovery Trial (Sleep SMART)

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<td>Meredith Wicklund (neurologist)</td>
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<td>06/2026</td>
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<td>Bryan Woodruff (co-I)</td>
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<td>Bryan Woodruff (co-I)</td>
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<td>Matthew Huentelman (co-I)</td>
<td>R01 AG067781 / Rogalski</td>
<td>05/01/2020</td>
<td>01/31/2025</td>
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<td>NIH/ Northwestern University</td>
<td>Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer’s disease</td>
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<td>Matthew Huentelman (co-I)</td>
<td>UG30D023313/ Deoni, D’Sa, Hbbins, &amp; Mullesr</td>
<td>09/21/2016</td>
<td>08/31/2023</td>
<td>$825,338</td>
<td>NIH/ Rhode Island Hospital</td>
<td>The Developing Brain: Influences and Outcomes</td>
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<td>Matthew Huentelman (co-I)</td>
<td>W81XWH1910534/ Schwedt</td>
<td>09/01/2019</td>
<td>08/31/2023</td>
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<td>DoD-CDMRP/ Mayo Clinic, AZ</td>
<td>A multidisciplinary translational approach to investigate the mechanisms, predictors and prevention of persistent post traumatic headache.</td>
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<td>U19 AG073153/ Rogalski/Geula</td>
<td>Study to uncover pathways to exceptional cognitive resilience in aging (SUPERAging)</td>
<td>Matthew Huentelman</td>
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<td>NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease</td>
<td>Matthew Huentelman</td>
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<td>Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan</td>
<td>Matthew Huentelman</td>
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<td>Arizona Alzheimer’s Disease Core Center</td>
<td>Matthew Huentelman</td>
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<td>Co-I</td>
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<td>R03AG073906/Piras</td>
<td>Genomic determinants of sleep traits as risk and protective factors for Alzheimer's disease</td>
<td>Matthew Huentelman</td>
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<td>R01HL153112/Hale</td>
<td>Targeting Resident Cardiac Fibroblast Subpopulations for Protection Against Fibrosis</td>
<td>Matthew Huentelman</td>
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<td>R01AG068098/ Grilli</td>
<td>Tracking autobiographical thoughts: a smartphone-based approach to identify cognitive correlates of Alzheimer’s disease biomarkers and risk factors in clinically normal older adults.</td>
<td>Matthew Huentelman</td>
<td>08/15/2022</td>
<td>04/30/2027</td>
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<td>$199,369</td>
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<tr>
<td>R01AG077444/ Rogalski</td>
<td>Asymmetric neurodegeneration and language in primary progressive aphasia</td>
<td>Matthew Huentelman</td>
<td>06/15/2022</td>
<td>03/31/2027</td>
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<td>NA/Huentelman</td>
<td>Determining the Genetic Factors Related to Exceptional Age-related Memory</td>
<td>Matthew Huentelman</td>
<td>07/01/2022</td>
<td>12/31/2024</td>
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<td>Improving Brain Performance to Combat Alzheimer's</td>
<td>Matthew Huentelman</td>
<td>07/01/2022 – 12/31/2024</td>
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<td>Identifying Genetic Risk Factors of Alzheimer's</td>
<td>Kendall Jensen</td>
<td>09/01/2019 – 08/31/2023</td>
<td>$466,532</td>
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<td>Development and application of a scalable workflow for immunoaffinity isolation and molecular analysis of exRNA carrier subclasses.</td>
<td>Kendall Jensen</td>
<td>09/16/2019 – 06/30/2023</td>
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<td>Molecular dissection and imaging of extracellular vesicles to define their origin and targets</td>
<td>Kendall Jensen</td>
<td>03/01/2021 – 03/31/2024</td>
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<td>Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD</td>
<td>Kendall Jensen</td>
<td>01/15/2022 – 11/30/2026</td>
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<td>The essentiality of serine and glycine for skeletal muscle regeneration in aging</td>
<td>Kendall Jensen</td>
<td>09/2021-03/2024</td>
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<td>Astrocyte regulation of cortical neurodegeneration in C9orf72 FTD/ALS</td>
<td>Kendall Jensen</td>
<td>01/2022 -01/2024</td>
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<td>Correlation of exRNA cargo from brain-enriched extracellular vesicles in blood with single nuclei sequencing from brain.</td>
<td>Kendall Jensen</td>
<td>03/2022 – 02/2024</td>
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<td>The essentiality of serine and glycine for skeletal muscle regeneration in aging</td>
<td>Kendall Jensen</td>
<td>07/2020 – 06/2023</td>
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## CURRENT & PENDING GRANTS

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  
**Kendall Jensen (PI)**  
CP20/ Jensen  
Foundation  
04/2022 – 03/2024  
$912,250

Natural Killer Cell-Derived Extracellular Vesicles as Therapeutic and Prognostic Tools in Non-Small Cell Lung Cancer  
**Kendall Jensen (multi-PI)**  
R21NS128550/ Sattler & Jensen  
NIH/ St Joseph’s Hospital and Medical Center  
08/2022 – 07/2024  
$207,630

Transcriptomic assessment of pathology in PD with dementia and dementia with Lewy Bodies using iPSC neurons and brain tissue of the same individuals  
**Kendall Jensen (co-I)**  
R01DK133847/ Das  
NIH/ Massachusetts General Hospital  
09/2022 – 07/2026  
$650,121

Characterization of beta-cell-specific extracellular vesicle cargo as functional biomarkers for type 1 DM disease (TEDDY)  
**Kendall Jensen (co-I)**  
R21NS128550/ Sattler  
NIH/ St Joseph’s Hospital and Medical Center  
09/2022 – 08/2024  
$18,554

Mechanisms of A-I RNA editing-mediated nuclear export of TDP-43  
**Kendall Jensen (co-I)**  
CTR051001/ Eric Reiman  
07/01/2022-06/30/2023  
$116,000

Validation of single nuclei sequencing in Alzheimer’s disease across multiple cell types  
**Kendall Jensen (co-I)**  
021821/ Cookson  
Michael J Fox Foundation/NIH/NIA  
04/2023 – 03/2025  
$368,840

Single-cell transcriptomics and proteomics profiling of the immune cells in the blood and cerebrospinal fluid of Parkinson’s disease patients with the LRRK2 mutation.  
**Kendall Jensen (co-I)**  
MJF-0251971/Ajami  
Michael J Fox Foundation/ Oregon Health & Science University  
02/16/2023–02/15/2025  
$496,975

FOUNDIN- microglial phenotypes from PPMI lines  
**Kendall Jensen (multi-PI)**  
1R24NS132738-01 / Jensen & Eitan & Dong  
NIH  
06/01/2023 – 05/31/2024  
$2,250,030

A Large-scale Extracellular Vesicle RNA-seq Resource for Parkinsons Disease  
**Kendall Jensen (co-I)**  
1U19CA264512/ Portnow  
NIH/ City of Hope  
09/01/2022 -08/31/2023  
$10,000
### CURRENT & PENDING GRANTS

CPP2: Extracellular vesicle cargo from biofluids as neuro-pharmacodynamic reporter in glioblastoma

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<tr>
<th>Raffaella Soldi (Research Scientist)</th>
<th>04/2021 – 03/2024</th>
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<tr>
<td>Foundation/ Tgen/ Altin &amp; Sharma</td>
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<tr>
<td>Enhancing the efficacy of tumor-infiltrating lymphocyte (TIL) therapy by enriching tumor neoantigen specificity</td>
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Raffaella Soldi (Research Scientist)  
ACOHCOH2720A014/Sharma  
City of Hope National Medical Center/Tgen  
Gene Surgery: Small-molecule inhibitor of CDK7

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<tr>
<th>Raffaella Soldi (Research Scientist)</th>
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<td>ACOHCOH2720A018/ Priceman &amp; Sharma</td>
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<td>City of Hope Board of Governor’s/ Tgen</td>
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<tr>
<td>Multi-targeted CAR-Engineered TILs for Treatment of Advanced Pancreatic Cancer</td>
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Raffaella Soldi (Project Co-PI)  
CTR057001/Reiman/Sharma & Soldi  
Arizona Department of Health Services/Banner  
A CRISPR knockout negative screen to identify genes that lead to enhancement of efficacy of antibodies targeting amyloid beta (Aβ) in Alzheimer's disease

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<th>Sunil Sharma (PI)</th>
<th>09/2018 – 09/2023</th>
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<tr>
<td>W81XWH1810617 / Sharma &amp; Welm</td>
<td>$3,386,423</td>
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<td>DOD</td>
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<td>RON kinase as a multi-faceted therapeutic target for metastatic breast cancer</td>
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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

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<tr>
<th>Sunil Sharma (PI)</th>
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<tr>
<td>ACOHCOH2720A014/ Sharma</td>
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| City of Hope National Medical Center  
Gene Surgery: Small-molecule inhibitor of CDK7 |

Sunil Sharma (co-I)  
ATFDG012440A008/ Trent  
Discount Tire  
Enhancing the efficacy of tumor-infiltrating lymphocyte (TIL) therapy by enriching tumor neoantigen specificity

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| City of Hope Board of Governor’s  
Multi-targeted CAR-Engineered TILs for Treatment of Advanced Pancreatic Cancer |

Sunil Sharma (PI)  
R44 CA278144 / Kaadige & Sharma  
NIH  
Development of a potent and selective oral ENPP1 inhibitor for oncology  
09/2022 – 08/2024
## CURRENT & PENDING GRANTS

<table>
<thead>
<tr>
<th>Grant Holder</th>
<th>Grant Details</th>
<th>Funding Amount</th>
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<tbody>
<tr>
<td><strong>Craig Weinkauf (PI)</strong></td>
<td>1R01AG070987 (Weinkauf) NIH/NIA Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer’s Disease Risk</td>
<td>08/15/2021-05/31/2026 $4,900,000 Total Project</td>
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<tr>
<td><strong>Elizabeth Hutchinson (MPI)</strong></td>
<td>R01 943783 (Frank/Hutchinson/Bondi) NIH/NIA Joint Estimation Diffusion Imaging (JEDI) for Improved Tissue Characterization and Neural Connectivity in Aging and Alzheimer’s Disease</td>
<td>06/01/2023-05/30/2028 Total costs: $7,691,496 UA total costs: $2,022,918</td>
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<tr>
<td><strong>Elizabeth Hutchinson (Co-I)</strong></td>
<td>R01 AG073230 (Federal, PI:Pires) NIH/NIA Role of Endothelial K+ Channels in Age-Related Dementia</td>
<td>07/01/2022-06/30/2027 $23,750 Total Subaward</td>
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<tr>
<td><strong>Elizabeth Hutchinson (PI)</strong></td>
<td>(Hutchinson/Trouard/Barnes) Arizona Alzheimer’s Consortium Microstructural MRI mapping of hippocampal and brain stem substructures in the bonnet macaque brain during aging</td>
<td>07/01/2023-06/30/2024 $30,000 Total Project</td>
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<tr>
<td><strong>Fei Yin (PI)</strong></td>
<td>RF1 AG068175 (Yin) NIH/NIA ApoE Regulation of Neuron-Astrocyte Metabolic Coupling in Alzheimer’s Disease</td>
<td>05/15/2021-04/30/2024 $1,131,312 Total Project</td>
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<tr>
<td><strong>Fei Yin (Project Leader)</strong></td>
<td>P01 AG026572 (Brinton) NIH/NIA Perimenopause in Brain Aging and Alzheimer’s Disease Project 1: Metabolic Mechanisms of Perimenopausal Neuroimmune Transformation: Therapeutic Targets and Windows</td>
<td>04/01/2021-05/31/2026 $15,168,816 Total $1,712,931 Project 1</td>
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<tr>
<td><strong>Fei Yin (Core Leader)</strong></td>
<td>P01 AG026572 (Brinton) NIH/NIA Perimenopause in Brain Aging and Alzheimer’s Disease Analytic Core</td>
<td>04/01/2021-05/31/2026 $15,168,816 Total $2,282,929 Analytic Core</td>
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<td><strong>Fei Yin (Co-I)</strong></td>
<td>R21 AG072561 (Gu) NIH/NIA via FIU Targeting Whole-body Fatty Acid Metabolism in Alzheimer’s Disease, with Special Interest in Lauric acid</td>
<td>04/15/2022-05/31/2024 $76,750 Total Project</td>
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<td><strong>Fei Yin (Co-I)</strong></td>
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<td><strong>$6,006,958 Total Project</strong></td>
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<td>R01 AG057931 (Brinon/Mosconi/Chang)</td>
<td>NIH/NIA</td>
<td>Sex Differences in the Molecular Determinants of Alzheimer’s Disease Risk: Prodromal Endophenotype</td>
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<tr>
<th><strong>Fei Yin (Co-I)</strong></th>
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<tr>
<td>R37 AG053589 (Brinton)</td>
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<td>Aging and Estrogenic Control of the Bioenergetic System in Brain</td>
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<th><strong>Fei Yin (Co-I)</strong></th>
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<tr>
<td>RF1 AG057931 (Kaddurah-Daouk/Brinton/Kastenmuller/Chang)</td>
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<td>Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment</td>
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<th><strong>Fei Yin (Co-I)</strong></th>
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<tr>
<td>U01 AG076450 (Thatcher)</td>
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<td>Nonlipogenic ABCA1 inducers for ADRD</td>
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<tr>
<th><strong>Gene E. Alexander (MPI)</strong></th>
<th><strong>08/01/2019-04/30/2024</strong></th>
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<tr>
<td>R01 AG064587 (MPIs: Alexander, Bowers, Woods)</td>
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<td>Revitalizing Cognition in Older Adults at Risk for Alzheimer’s Disease with Near-Infrared Photobiomodulation</td>
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<tr>
<th><strong>Gene E. Alexander (Core Leader)</strong></th>
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<tr>
<td>3P30AG019610-19S1 (PI: Reiman, Core Leader: Alexander)</td>
<td>NIA</td>
<td>Brain Imaging and Fluid Biomarkers Core</td>
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<td>P30AG072980 (PI: Reiman, Core Leader: Alexander)</td>
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<td>R01AG072445 (MPIs: Raichlen, Alexander, Klimentidis)</td>
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<td>Inactivity, Sedentary Behavior, and the Risk for Alzheimer’s Disease in Middle Aged to Older Adults</td>
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<th><strong>Gene E. Alexander (MPI)</strong></th>
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<td>R56AG067200 (MPIs: Alexander, Raichlen)</td>
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<td>Physical Activity Predictors of Cognitive and Brain Health in the Risk for Alzheimer’s Disease.</td>
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<tr>
<td>Augmenting Cognitive Training in Older Adults</td>
<td>Gene E. Alexander (PI UA Sub)</td>
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<tr>
<td>A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults</td>
<td>Gene E. Alexander (MPI)</td>
<td>McKnight Brain Research Foundation</td>
<td>05/01/2018-04/30/2024 NCE $120,000 Total Project</td>
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<td>Transcutaneous Vagal Nerve Stimulation and Cognitive Training to Enhance</td>
<td>Gene E. Alexander (PI UA Sub)</td>
<td>McKnight Brain Research Foundation</td>
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<td>Behavioral and Neuroimaging Network Biomarkers of Brain Aging and Alzheimer’s Disease</td>
<td>Gene E. Alexander (PI)</td>
<td>State of Arizona</td>
<td>07/01/2023-06/30/2024 $27,806 Total Project</td>
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<td>Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults</td>
<td>Gene E. Alexander (Co-I)</td>
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<td>09/01/2019-08/31/2024 $1,765,250 Total Project</td>
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<td>Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation</td>
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<td>Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer’s Disease Risk</td>
<td>Gene E. Alexander (Co-I)</td>
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<td>Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer’s disease biomarkers and risk factors in clinically normal older adults</td>
<td>Gene E. Alexander (Co-I)</td>
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<td>07/01/2022-06/30/2027 $4,600,829 Total Project</td>
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<td><strong>Judith Su (PI)</strong></td>
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<td>NIH/NIGMS</td>
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<tr>
<td>Label-free single molecule detection for basic science and translational medicine</td>
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<td>Defense Threat Reduction Agency</td>
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<td>Sensitive, Selective, and Affordable Chemical Threat Sensing</td>
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<td>Using Frequency Locked Microtoroid Optical Resonators</td>
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<td>NSF CAREER: Bioinspired optical sniffer based on microtoroid resonators and science and technology convergence</td>
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<tr>
<td>Measuring Binding Affinities of Ligands to Taste Receptors</td>
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<td>Using Microtoroid Optical Resonators</td>
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<td>University of Arizona Center of Excellence</td>
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<td>Non-addictive opioid therapeutic development – a pilot study</td>
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<td><strong>Kaveh Laksari (PI)</strong></td>
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<tr>
<td>Enhanced Clinical Diagnosis through imaging and Modeling: A Machine Learning Data Fusion Framework</td>
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<td><strong>Lee Ryan (Project Lead)</strong></td>
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<td>U19 AG065169 (Barnes)</td>
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<td>Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan</td>
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<td>Lee Ryan</td>
<td>NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults (Initiative: Researching COVid to Enhance Recovery (RECOVER) Initiative)</td>
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<td>Lee Ryan</td>
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<td>Lee Ryan</td>
<td>Evaluating Neurofilament Light Protein (NFL) as a Marker of Neuronal Damage in Older and Middle-Aged Adult Survivors of SARS-CoV2</td>
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<td>Marlys H. Witte, MD</td>
<td>Investigation of glymphatic/lymphatic flow in Alzheimers mouse models using novel, non-invasive imaging modalities.</td>
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<td>Marlys H. Witte, MD</td>
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<td>Matt Grilli</td>
<td>Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer’s disease biomarkers and risk factors in clinically normal older adults</td>
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<td>Genetically Informed Studies of Social Connectedness and Health</td>
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<td>Precision and binding as two dimensions of medial temporal lobe amnesia</td>
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<td>Accelerated treatment for co-occurring insomnia, nightmares, and PTSD</td>
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<td>Development of High-Speed and Quantitative Neuro MRI Technologies for Challenging Patient Populations</td>
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<td>Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan</td>
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<td>Interleaved TMS-fMRI for Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnestic Mild Cognitive Impairment</td>
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<td>Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation</td>
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<td>Nan-kuei Chen (Co-I)</td>
<td>4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents</td>
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<td>Nan-kuei Chen (Co-I)</td>
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<td>Nan-kuei Chen (Co-I)</td>
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<td>Nima Toosizadeh (PI)</td>
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<td>Nima Toosizadeh (PI)</td>
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<td>Paul Hill (PI)</td>
<td>A noninvasive assay of entorhinal grid coding in mild cognitive impairment</td>
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<td>Paul Hill (Co-I)</td>
<td>A neurocomputational model of age-related differences in navigation</td>
<td>Paul Hill (Co-I)</td>
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<td>Paulo W. Pires (Co-PI)</td>
<td>Role of Endothelial K+ Channels in Age-Related Dementia</td>
<td>Paulo W. Pires (Co-PI)</td>
<td>NIH/NIA via Loma Linda University</td>
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<td>Paulo W. Pires (PI)</td>
<td>Improving glymphatic and microvascular function in Alzheimer’s disease</td>
<td>Paulo W. Pires (PI)</td>
<td>Alzheimer’s Association</td>
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<td>Paulo W. Pires (Co-I)</td>
<td>Investigating The Role Of Blood Flow In Heat Stress Hypophagia And Hypogalactia</td>
<td>Paulo W. Pires (Co-I)</td>
<td>USDA/NIFA</td>
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<td>Paulo W. Pires (Co-I)</td>
<td>Nonlipogenic ABCA1 inducers for ADRD</td>
<td>Paulo W. Pires (Co-I)</td>
<td>NIH/NIA AD Supplement</td>
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<td>R43 OD034043-01A1 (Gibson/Cowen)</td>
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<td>NIH/SBIR Development of in-cage health monitoring system for laboratory animals.</td>
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<td>5 R01 AG031581 (Barnes)</td>
<td>05/15/2023- 04/30/2028</td>
<td>NIH/NIA Frontal and Temporal Lobe Interactions in Rat Models of Normative Aging and Alzheimer’s Disease</td>
<td>$3,266,421</td>
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<td>P30 NIH-NIDA 3042524 (Porreca is lead)</td>
<td>07/01/2021-06/31/2026</td>
<td>NIH/NIDA Core Center of Excellence in Addiction Studies My role: Direct pilot program to fund research leading to NIDA applications</td>
<td>$6,422,364</td>
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<td>R01NS123424-01 (Cowen/Heien/Lewis)</td>
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<td>NIH BRAIN Initiative Control of the time course of dopamine release through optimized electrical brain stimulation.</td>
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<td>NIH/NINDS NS123512-01 (Miller/Cowen)</td>
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<td>NIH/NINDS NS123512-01 (Miller/Cowen) Alpha-synuclein driven cellular changes and vocal dysfunction in Parkinson’s Disease</td>
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<td>5R01NS122805-03 (Falk)</td>
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<td>Mechanisms of low-dose ketamine treatment for Parkinson’s disease</td>
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<td>S10 OD032166 (Trouard)</td>
<td>03/15/2023-03/14/2024</td>
<td>NIH/NIA via University of Arizona 3T MRI scanner for Advanced Brain Imaging</td>
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<td>R43 AG067894(Trouard)</td>
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<td>NIH/NIA via University of Arizona Targeted ultrasound contrast agents for the disruption of Alzheimer’s plaques</td>
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<td>R41 NS124450 (Morrison)</td>
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<td>NIH/NIA via University of Arizona NanO2 as a Cerebroprotectant in a tMCAO Stroke Model in Mice</td>
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<td><strong>Theodore P. Trouard (Co-I)</strong>&lt;br&gt;U19 AG065169 (Barnes)&lt;br&gt;NIH/NIA via University of Arizona&lt;br&gt;Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan</td>
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<td><strong>Theodore P. Trouard (PI)</strong>&lt;br&gt;S10 OD032166 (Trouard)&lt;br&gt;NH via University of Arizona&lt;br&gt;3T MRI scanner for Advanced Brain Imaging</td>
<td>03/15/2023</td>
<td>03/14/2024</td>
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<td><strong>Wei Zhou (MPI)</strong>&lt;br&gt;U01 DK119094 NIH/NIDDK (Gurtner/Zhou)&lt;br&gt;The University of Arizona Wound Care Center Clinical Research Unit</td>
<td>02/22/2023</td>
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<td><strong>Wei Zhou (Site-PI)</strong>&lt;br&gt;U01NS080168 Mayo Clinic (sub-NIH/NINDS)&lt;br&gt;Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)</td>
<td>03/01/2017</td>
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<td><strong>Wei Zhou (Site-PI)</strong>&lt;br&gt;R01NS097876 Mayo Clinic (sub-NIH/NINDS)&lt;br&gt;Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial – Hemodynamics (CREST-H)</td>
<td>05/15/2017</td>
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<td><strong>Ying-hui Chou (PI)</strong>&lt;br&gt;R01 AG062543 (Chou)&lt;br&gt;NIH/NIA&lt;br&gt;Enhancement of hippocampal plasticity using repetitive transcranial magnetic stimulation</td>
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<td>Interleaved TBS-fMRI for Spaced Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnestic Mild Cognitive Impairment</td>
<td>Ying-hui Chou (PI)</td>
<td>R21 AG077153 (Chou)</td>
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<td>Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults</td>
<td>Ying-hui Chou (Co-I)</td>
<td>R01 AG061888 (Wilson)</td>
<td>01/01/2020</td>
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<td>4D Transcranial acoustoelectric imaging for high resolution functional mapping of neuronal currents</td>
<td>Ying-hui Chou (Co-I)</td>
<td>U01 EB028662 (Witte)</td>
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<td>Brain Injury Rehabilitation Modality, Regulation, &amp; Structural Plasticity</td>
<td>Jonathan Lifshitz (PI)</td>
<td>VA Merit I01 RX002472</td>
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<td>Developing and Testing a Novel Virtual Cognitive Rehabilitation Program to Alleviate Persistent Cognitive Dysfunction Following Traumatic Brain Injury</td>
<td>Jonathan Lifshitz (PI)</td>
<td>VA Merit I01 RX002472</td>
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<td>Mechanistic role of vascular dysfunction in TBI-mediated cognitive dysfunction</td>
<td>Raymond Migrino and Jonathan Lifshitz (dual PI)</td>
<td>VA Merit I01002691</td>
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<td>Sleep, inflammation and therapeutic efficacy of NTS-104 in diffuse TBI</td>
<td>Jonathan Lifshitz (PI)</td>
<td>NCL-TBI-2021-011</td>
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<td>Miniscope in vivo imaging of cumulative traumatic brain injury</td>
<td>Jonathan Lifshitz (PI)</td>
<td>R21 NS131877</td>
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<td>Sleep, inflammation and therapeutic efficacy of NTS-104 in diffuse TBI</td>
<td>Jonathan Lifshitz and Sarah Stabenfeldt (dual PI)</td>
<td>R01 AG077768</td>
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## CURRENT & PENDING GRANTS

**Molecular Tool Development to Identify, Isolate, and Interrogate the Rod Microglia Phenotype in Neurological Disease and Injury**

**Jonathan Lifshitz (PI)**  
VA Merit I01 RX004536  
U.S. Dept. of Veterans Affairs  
Psychoplastogens to make the injured brain receptive to cognitive rehabilitation during the chronic period of TBI  

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**Heather Bimonte-Nelson (PI)**  
NIA  
R01 AG028084 (renewal)  
Variations in hormones during menopause: effects on cognitive and brain aging  

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**Heather Bimonte-Nelson (co-I)**  
NIH  
R21 Grant, R21DA055879  
Contributions of Progestins Independently and Interactively with Contraceptive Estrogen to Nicotine Use  

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**Heather Bimonte-Nelson (co-I)**  
R01 NS116657  
Exploiting sex-dependent brain injury response for nanoparticle therapeutics  

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**Heather Bimonte-Nelson (associate director)**  
NIA (NIH) T32AG044402  
Postdoctoral T32 Training Grant  
Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease  

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### Pending Grants

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<td>HHS: National Institutes of Health (NIH)&lt;br&gt;Effects of Combined Aerobic and Resistance Exercise on Memory and Relevant Underlying Mechanisms in Older Adults with Mild Cognitive Impairment</td>
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<td><strong>David W. Coon (Co-I)</strong>&lt;br&gt;FP00037685</td>
<td>7/1/2023-6/30/2024</td>
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<td>Arizona State University Roybal Center for Older Adults Living Alone with Cognitive Decline: Technology-Enabled Behavioral and Lifestyle Change to Delay Alzheimer’s Disease and Improve Quality of Life</td>
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<td><strong>David W. Coon (Co-I)</strong>&lt;br&gt;FP00038788</td>
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<td>DOD-ARMY: Army Medical Research Acquisition Activity (USAMRAA)&lt;br&gt;A novel therapeutic approach to restore neuronal proteostasis after traumatic brain injury</td>
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<td><strong>Mastroeni, Diego (PI)</strong>&lt;br&gt;FP00027932_Res1</td>
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<td><strong>Sierks, Michael (PI)</strong>&lt;br&gt;FP00029567_Res1</td>
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<td>HHS: National Institutes of Health (NIH)&lt;br&gt;Novel Nanobodies Target Earliest Pathogenic Tau Variants in Neuronal Cells</td>
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<td>HHS: National Institutes of Health (NIH)&lt;br&gt;Disruption of neuronal proteostasis as a tool to identify better therapeutic targets for AD</td>
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<td><strong>Sierks, Michael (PI)</strong>&lt;br&gt;FP00034325</td>
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<td>Sierks, Michael (PI)</td>
<td>Selective identification of TDP-43 variants implicated in LATE AD pathology</td>
<td>7/1/2023 - 6/30/2028</td>
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<td>Sierks, Michael (PI)</td>
<td>Structural analysis of FTD related TDP-43 variants isolated from human brain tissue</td>
<td>7/1/2023 - 6/30/2028</td>
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<td>Hayes, Mark (PI)</td>
<td>Developing Tool for Investigating Small Complex Bioparticle Populations</td>
<td>2/1/2023 - 11/30/2026</td>
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<td>Sierks, Michael (PI)</td>
<td>Identifying sex-dependent pathological differences in early stage Alzheimer’s disease</td>
<td>9/1/2023 - 8/31/2028</td>
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<td>Lucas, Alexandra (PI)</td>
<td>Serp-1 Protease Inhibitor Therapeutic Treatment for SARS-CoV-2 Acute Respiratory Distress Syndrome and Long COVID</td>
<td>8/1/2023 - 7/31/2025</td>
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<td>Lake, Douglas (PI)</td>
<td>Identification of Natural Substrates of QSOX1</td>
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<td>Huseby, Carol (PI)</td>
<td>Region specific Tau protein aggregate structures in novel non-human primate model of Alzheimer’s disease</td>
<td>4/1/2024 - 3/31/2026</td>
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<td>Sierks, Michael (PI)</td>
<td>Development of LATE AD biomarkers and therapeutic targets</td>
<td>4/1/2024 - 3/31/2029</td>
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<td>Edward Ofori (PI)</td>
<td>Motor reserve markers of preclinical Alzheimer’s disease</td>
<td>12/01/2023-11/31/2028</td>
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<td>Benjamin Readhead (PI)</td>
<td>Identifying Gene Targets and Cell Types in the Infectious Etiology of Alzheimer’s Disease</td>
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<td><strong>Benjamin Readhead (Co-I)</strong></td>
<td>9/2023</td>
<td>8/2025</td>
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<td>Unraveling the Message in cell-free layers</td>
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<td><strong>Sydney Schaefer (PI)</strong></td>
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<td>Measuring Expectancy Effects of Transcranial Direct Current Stimulation on Motor Learning</td>
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<td><strong>Sydney Schaefer (PI)</strong></td>
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<td>Validating the quick Behavioral Exam to Advance Neuropsychological Screening (qBEANS) motor learning test for preclinical Alzheimer's disease</td>
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<td><strong>Sydney Schaefer (PI)</strong></td>
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<td>Developing a motor learning test as an equitable approach to screening Hispanic/Latino older adults for preclinical Alzheimer's disease</td>
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<td><strong>Sydney Schaefer (co-I)</strong></td>
<td>08/01/2023</td>
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<td>Neurosessments: Developing a quick, objective motor test to prompt cognitive testing in primary care</td>
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<td><strong>Sydney Schaefer (co-I)</strong></td>
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<td>Neurosessments: Developing a quick, equitable at-home screening tool for preclinical AD</td>
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<td><strong>Michael Sierks (PI)</strong></td>
<td>9/1/2023</td>
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<td>Identifying sex-dependent pathological differences in early stage Alzheimer's disease</td>
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<td><strong>Michael Sierks (PI)</strong></td>
<td>7/1/2023</td>
<td>6/30/2026</td>
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<td>Developing a personalized blood based diagnostic assay for early detection of ALS</td>
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<td><strong>Michael Sierks (PI)</strong></td>
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<tr>
<td>A Novel Antibody that Promotes Neuroprotection and Neurogenesis for Alzheimer's Disease</td>
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### CURRENT & PENDING GRANTS

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<tr>
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<th>Funding Agency</th>
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<td>Michael Sierks (PI)</td>
<td>4/1/2024 - 3/31/2029</td>
<td>A novel therapeutic to promote neurogenesis and restore neuronal proteostasis after traumatic brain injury</td>
<td>HHS: National Institutes of Health (NIH)</td>
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<td>Michael Sierks (PI)</td>
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<td>Sleep fragmentation disrupts proteostasis and contributes to cognitive decline in Lewy Body Dementia and Parkinson’s disease</td>
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<td>Sarah Stabenfeldt (Co-I)</td>
<td>07/01/2023-06/30/2026</td>
<td>Multivalent protein-DNA nanostructures as synthetic blocking antibodies</td>
<td>NIH/NIGMS</td>
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<td>Sarah Stabenfeldt (MPI)</td>
<td>09/01/2023-08/31/2028</td>
<td>Developing vaccines for immunological defense from traumatic brain injury</td>
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<td>Jessica Verpeut (Co-I)</td>
<td>07/01/2023 – 06/31/2024</td>
<td>Validating a preclinical Alzheimer's disease behavioral assessment in the TgF344-AD rat</td>
<td>Arizona Alzheimer’s Coalition/Arizona Department of Health Services (ADHS)</td>
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<td>Jessica Verpeut (Subcontract PI)</td>
<td>07/01/2023 – 06/31/2024</td>
<td>Role of Egr1 in promoting resilience to in utero exposure to inflammation</td>
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<td>Jessica Verpeut (PI)</td>
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<td>Yalin Wang (Project PI)</td>
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<td>Arizona Alzheimer's Consortium (Coon) State of Arizona</td>
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<td>Nastaran Shishegar (Nina Sharp; co-PI)</td>
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<td>Petra Fromme (MPI)</td>
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<td>Integrated Postdoctoral Training in Alzheimer’s and related disorders and Structural Biology</td>
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<td>Development of in cell microcrystal electron diffraction (MicroED)</td>
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<td><strong>Petra Fromme (Co-I)</strong></td>
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<td>Region specific Tau protein aggregate structures in novel non-human primate</td>
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<td>model of Alzheimer’s disease</td>
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<td>Proteolytic modifications, tau protein peptide misfolding, and Alzheimer’s</td>
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<td><strong>Carol Huseby (PI)</strong></td>
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<td>model of Alzheimer’s disease</td>
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<td><strong>Nadine Bakkar (Co-PI) / Ashley Stokes (Co-PI)</strong></td>
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<td>Longitudinal Neuroimaging and Molecular Biomarkers of Cerebrovascular Health</td>
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<td>in ALS</td>
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<td><strong>Yonas Geda (PI)</strong></td>
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<td>Pathways linking neuropsychiatric symptoms with Alzheimer’s disease</td>
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<td>neuroimaging biomarkers and the outcome of incident Mild Cognitive Impairment</td>
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<td>Yonas Geda (Co-PI)</td>
<td>10/1/2023-9/30/2024</td>
<td>STRIDE: an advanced indoor radar sensing and artificial intelligence system for gait estimation to assess the risk of Alzheimer’s Diseases</td>
<td>NIH PA-22-178</td>
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<td>Rita Sattler (PI)</td>
<td>08/01/23-07/31/26</td>
<td>Muscular Dystrophy Association (Sattler) Mechanisms of A-I RNA editing-mediated nuclear export of TDP-43</td>
<td>$300,000</td>
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<td>Manfredsson PI</td>
<td>04/01/24-03/31/26</td>
<td>The role of TDP-43 associated cryptic exon inclusion in KALRN on C9orf72-mediated cortical neurodegeneration</td>
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<td>Enhancing ACMSD Activity as a Novel Gene Therapy for ALS</td>
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<td>Neuroprotective oxytocin receptor signaling in mixed AD dementia</td>
<td>No Number NIH Subaward from Henry Ford Health + Michigan State University</td>
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<td>Layla Al-Nakkash (PI), Minsub Shim (Co-PI), Thomas Broderick (Co-PI)</td>
<td>01/01/2024-12/31/2024</td>
<td>Assessing the effect of intermittent fasting on mice fed a western diet: mechanisms to mitigate the diabetic phenotype</td>
<td>Diabetes Action Research and Education Foundation</td>
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<td>Samantha Day (PI)</td>
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<td>Epigenetic changes in type 2 diabetes progression among a longitudinally studied cohort of American Indians</td>
<td>NIH R01</td>
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<td>Ann Revill (PI)</td>
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<td>Molecular and anatomical hallmarks associated with intermittent hypoxia and aging insights into respiratory dysfunctions associated with Alzheimer's disease</td>
<td>AZ Dept of Health Services-Arizona Alzheimer's Consortium</td>
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<td>Insights into resisting neuroanatomical aging from long-lived giant tortoises</td>
<td>Heather Smith (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium</td>
<td>07/01/2023-06/30/2024</td>
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<td>Validation &amp; Development of Nanoliposomes for Neuroprotection in Stroke</td>
<td>Volkmar Weissig (Co-PI) Arizona Biomedical Research Commission (through AZ Veterans Research and Education Foundation)</td>
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<td>The Aging Autistic Brain: Multi-modal imaging to predict accelerated memory decline</td>
<td>Leslie Baxter (subaward) FP00122779-A1 NIH</td>
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<td>Phase 1 Clinical Study of CAP-1902 in Patients with Mild Cognitive Impairment</td>
<td>Robert Alexander (Co-I) Alzheimer's Drug Discovery Foundation via University of Arizona (Rodgers)</td>
<td>07/2023-06/2025</td>
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<td>CAP-1902: Early clinical development and supporting toxicology studies</td>
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<td>Evaluate the Safety, Tolerability, and Immunogenicity of Adjuvanted Preventive Tau Vaccine, AV-1980R/A, in Cognitively Unimpaired Preclinical AD Participants</td>
<td>Robert Alexander (PI) NIH via Institute for Molecular Medicine R01AG080549 (Agadjanyan/Schneider/Tosun-Turgut/Alexander)</td>
<td>04/01/2024 – 03/31/2029</td>
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<td>Heterogeneity of subtle cognitive decline phenotypes in community-dwelling older adults</td>
<td>Emily Edmonds (Co-I) NIH/NIA via UC San Diego (Thomas)</td>
<td>07/01/2023 – 06/30/2028</td>
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<td>Characterizing Empirically Derived Cognitive Subgroups in the National Alzheimer's Coordinating Center</td>
<td>Emily Edmonds (Project PI) Arizona DHS via Arizona Alzheimer's Consortium</td>
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<td>Informing the size of primary and secondary Alzheimer's disease prevention trials using different biomarker and clinical endpoints in the world’s largest autosomal dominant Alzheimer’s Disease kindred</td>
<td>Valentina Ghisays (Project PI) NIH via ASU / Arizona ADRC</td>
<td>07/01/2023 – 06/30/2025</td>
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<td>Validation of the Multidomain Assessment of Cognition (MDAC)</td>
<td>Michelle James (Co-I) NIH /NIA R03AG086086</td>
<td>12/01/2023 – 11/30/2025</td>
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<td>Early detection of Alzheimer’s disease using ATN: amyloid and tau PET, blood biomarkers, and structural MRI in urban American Indians</td>
<td>Jessica Langbaum (Co-I) NIH via Washington State University (Suchy-Dicey)</td>
<td>12/01/2023 – 11/30/2028</td>
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<td>Targeting Stress to Reduce Risk of ADRD through a Novel Body-Mind Intervention</td>
<td>Jessica Langbaum (Co-I) NIH via Arizona State University (Tang)</td>
<td>04/2024 – 04/2029</td>
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<td>Alzheimer’s Prevention Initiative ADAD Colombia Trial Program</td>
<td>Jessica Langbaum (PI) NIH/NIA R01AG086363 (Alexander/Reiman/Langbaum/Lopera)</td>
<td>04/2024-03/31/2029</td>
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<td>Neuropathological Consequences in Unimpaired Subjects and Subjects with Alzheimer's and Related Dementias after Recovery from SARS-CoV-2 Infection</td>
<td>Michael Malek-Ahmadi (Co-I) NIH/NIA R01AG084661 (Beach)</td>
<td>09/01/2023-08/31/2028</td>
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<td>Validation of the Multidomain Assessment of Cognition (MDAC)</td>
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<td>Developing behavior-based screening tools for preclinical Alzheimer’s disease</td>
<td>Michael Malek-Ahmadi (Co-I) NIH via ASU (Schaefer)</td>
<td>04/01/2024 – 03/31/2029</td>
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<td>Molecular Imaging of Neuropathology and Serotonin in APOE4 Carriers</td>
<td>Hillary Protas (Co-I) NIH/NIA via Johns Hopkins University (Smith)</td>
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<td>The Aging Autistic Brain: Multi-modal imaging to predict accelerated memory decline</td>
<td>Hillary Protas (Co-I)</td>
<td>NIH/NIA via ASU (Braden)</td>
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<td>Effects of Combined Aerobic and Resistance Exercise on Memory and Relevant Underlying Mechanisms in Older Adults with Mild Cognitive Impairment</td>
<td>Jeremy Pruzin (Co-I)</td>
<td>NIH via ASU (Yu)</td>
<td>09/01/2023 – 08/31/2028</td>
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<td>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</td>
<td>Jeremy Pruzin (Co-I)</td>
<td>NIH via ASU R01AG076566 (Yu)</td>
<td>04/01/2023 – 03/31/2028</td>
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<td>Probing Synaptic Plasticity of Precuneus with Transcranial Magnetic Stimulation in Preclinical and Prodromal Alzheimer’s Disease</td>
<td>Steven Rapcsak (Co-I)</td>
<td>NIH via University of Arizona (Chou)</td>
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<td>Early detection of Alzheimer’s disease using ATN: amyloid and tau PET, blood biomarkers, and structural MRI in urban American Indians</td>
<td>Eric Reiman (Co-I)</td>
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<td>12/01/2023 – 11/30/2028</td>
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<td>Alzheimer’s Prevention Initiative ADAD Colombia Trial Program</td>
<td>Eric Reiman (PI)</td>
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<td>04/01/2024-03/31/2029</td>
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<td>Alzheimer’s Prevention Initiative ADAD Colombia Trial Program</td>
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<td>The Colombia-Boston (COLBOS) biomarker study of autosomal dominant Alzheimer’s disease</td>
<td>Yi Su (Co-I)</td>
<td>NIH via the General Hospital Corporation dba Massachusetts General Hospital (Quiroz)</td>
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<td>Early detection of Alzheimer’s disease using ATN: amyloid and tau PET, blood biomarkers, and structural MRI in urban American Indians</td>
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<td>Yi Su (Co-I)</td>
<td>NIH via ASU R01AG076566 (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</td>
<td>04/01/2023 – 03/31/2028</td>
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<td>Yi Su (Co-I)</td>
<td>NIH via ASU (Yu) Effects of Combined Aerobic and Resistance Exercise on Memory and Relevant Underlying Mechanisms in Older Adults with Mild Cognitive Impairment</td>
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<td>Alireza Atri (Co-I)</td>
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<td>Alireza Atri (Site PI)</td>
<td>NIH via University of Southern California (Aisen) Alzheimer’s Clinical Trial Consortium</td>
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<td>Alireza Atri (Co-I)</td>
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<td>Arizona Alzheimer’s Consortium via Arizona DHS (Choudhury)</td>
<td>Trajectories of clinical symptoms and associations with pathology in Lewy body spectrum disorders</td>
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<td>Neuropathological Consequences in Unimpaired Subjects and Subjects with Alzheimer’s and Related Dementias after Recovery from SARS-CoV-2 Infection</td>
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<td><strong>Thomas Beach</strong> (Site-PI)</td>
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<td>NIH R01 via UC Irvine (Mukherjee)</td>
<td>Novel Tau-Targeted Radiohalogenated Agents for Alzheimer’s Disease</td>
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<td>NIH via TGEN (Huentleman/Serrano)</td>
<td>Drug repositioning for Alzheimer’s disease using genomic data from multiple brain regions</td>
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<td><strong>Thomas Beach</strong> (Co-I)</td>
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<td>NIH via ASU (LaBaer/Readhead)</td>
<td>Multiscale networks of the brain microbiome, adaptive immunity, and host transcriptomics in Alzheimer’s disease</td>
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<td><strong>Thomas Beach</strong> (Co-I)</td>
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<td>Dementia in Lewy Body Diseases</td>
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<td>Understanding and reversing vascular aging-related dementia through medin signaling</td>
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<td>Structural analysis of FTD related TDP-43 variants isolated from human brain tissue</td>
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<td>Sex related protein pathology differences in Alzheimer's disease</td>
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<td>Neurogenetics of Aging Vocalizations and Implications for Neurodegenerative Diseases</td>
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<td>Neuropathological Consequences in Unimpaired Subjects and Subjects with Alzheimer’s and Related Dementias after Recovery from SARS-CoV-2 Infection</td>
<td>Geidy Serrano (Co-PI)</td>
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<td>Novel Tau-Targeted Radiohalogenated Agents for Alzheimer’s Disease</td>
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### CURRENT & PENDING GRANTS

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<th><strong>Geidy Serrano (PI)</strong></th>
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<th><strong>Geidy Serrano (Project PI)</strong></th>
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<th><strong>Geidy Serrano (Co-PI)</strong></th>
<th><strong>Greg Caporaso (co-I)</strong></th>
<th><strong>Emily Cope (Subaward PI)</strong></th>
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<tr>
<td>Sex Differences in Alzheimer’s Disease: Synaptic Loss and Histopathology</td>
<td>Single Cell Transcriptomics and Epigenetics of Alzheimer’s Disease Brain</td>
<td>Patient-based postmortem fibroblast banking for translational research</td>
<td>A Human Brain Single-Cell Suspension Resource</td>
<td>Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking</td>
<td>Drug repositioning for Alzheimer’s disease using genomic data from multiple brain regions</td>
<td>Planning grant for an international digital pathology resource from patients with Parkinson’s disease and controls</td>
<td>Multiscale networks of the brain microbiome, adaptive immunity, and host transcriptomics in Alzheimer’s disease</td>
<td>Integrating Multi-Omics and 3D Models to Develop Non-Invasive Diagnostics for Adenomyosis.</td>
<td>The role of detergents in the pathogenesis of eosinophilic esophagitis</td>
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<td>Neuronal Rbbp7 as a mediator against tau pathology in Alzheimer’s disease</td>
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<td>Assessing the cumulative risk of early life exposures on child physical health and neurodevelopment</td>
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<td>Development of a web-based cognitive testing approach for longitudinal use in adults without dementia.</td>
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<td>University of Southern California</td>
<td>$250,000</td>
<td>Identification and development of TREM2 agonists to prevent Alzheimer's disease.</td>
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<td>Matthew Huentelman (PI)</td>
<td>04/01/2023 -03/31/2029</td>
<td>NIH</td>
<td>$4,588,244</td>
<td>Mobile labs for scalable remote neuroassessment to increase access and diversity in clinical trials of Alzheimer’s disease.</td>
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<td>Matthew Huentelman (co-I)</td>
<td>05/01/2024-04/30/2029</td>
<td>NIH/NYU</td>
<td>$417,236</td>
<td>Drug repositioning for Alzheimer's disease using genomic data from multiple brain regions.</td>
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<td>Matthew Huentelman (co-I)</td>
<td>04/01/2024 – 03/31/2029</td>
<td>NIH/Mayo Clinic, AZ</td>
<td>$116,667</td>
<td>Rapid Accessible Phenoscreening of Infants (RAPHI).</td>
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| Kendall Jensen (multi-PI) | 09/01/2019 – 08/31/2023 | NIH/Northern California Institute for Research and Education | $569,069 | Purification of exRNA by Immuno-capture and Sorting using Microfluidic.
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<td>Default Mode Network dysfunction in Down Syndrome</td>
<td>Kendall Jensen (co-I)</td>
<td>04/21/2024 – 05/31/2026</td>
<td>RF1AG081286/ Mufson &amp; Perez</td>
<td>NIH /Barro Neurological Institute, SJHMC</td>
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<td>Integrative Imaging and Multi-omic Analysis of Spatial Transcriptomics</td>
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<td>HuBMAP Administrative Supplement 1</td>
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<td>04/2023 – 03/2024</td>
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<td>NIH/ University of California, San Diego (UCSD)</td>
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<td>Using Peripheral Microglial Exosomes to predict brain inflammation in the human Parkinson’s brain</td>
<td>Kendall Jensen (co-I)</td>
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<td>Comparative single cell atlas of blood-brain and blood-CSF barriers in ALS-FTD</td>
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<td>NIH/ St. Joseph’s Hospital and Medical Center</td>
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<td>RNA modulates TDP-43 pathological interactions and function in ALS and dementia</td>
<td>Kendall Jensen (co-I)</td>
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<td>Strategies to Augment Ketosis (STAK) Mild Traumatic Brain Injury (mTBI)</td>
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<td>DoD/Florida Institute of Human and Machine Cognition</td>
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<td>Plasma neuron-derived extracellular vesicles coupled with measurement of TDP43-associated RNA for ALS diagnostic.</td>
<td>Kendall Jensen (co-I)</td>
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<td>Leandro P. Rizzuto Foundation/ Neurodex</td>
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<td>Best practice to determine management of suspicious lung nodule with minimal patient risk</td>
<td>Kendall Jensen (co-I)</td>
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<td>Kendall Jensen (co-I)</td>
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<td>AZ DHS/Arizona Alzheimer’s Consortium/Banner Health</td>
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<td>FY2024: Arizona's Alzheimer's Consortium Grants: Analysis of single nuclei sequencing in Parkinson’s disease with dementia, Frontotemporal dementia, and Alzheimer’s disease across multiple cell types in the frontal cortex</td>
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<td>Raffaella Soldi (co-I)</td>
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<td>Non-genetic mechanisms of drug resistance in KRAS mutant lung cancer</td>
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<td>Raffaella Soldi (co-I)</td>
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<td>Clinical Trial Application of snapTIL, personalized, neoantigen infiltrating tumor lymphocytes to treat pancreatic cancer</td>
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<td>Sunil Sharma (co-I)</td>
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<td>CTR057001 / Sharma &amp; Soldi</td>
<td>Arizona Department of Health Services/ Arizona Alzheimer’s Consortium/Banner</td>
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<td>A CRISPR knockout negative screen to identify genes that lead to enhancement of efficacy of antibodies targeting amyloid beta (Aβ) in Alzheimer’s disease</td>
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<tr>
<td>Sunil Sharma (Project 3 PI)</td>
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<td>Sunil Sharma (PI)</td>
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<td>Clinical Trial Application of snapTIL, personalized, neoantigen infiltrating tumor lymphocytes to treat pancreatic cancer</td>
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<td>Elizabeth Hutchinson (Co-I)</td>
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<td>Maturation of social and non-social reward processing in the adolescent amygdala and orbitofrontal cortex</td>
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<td>Elizabeth Hutchinson (PI)</td>
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<td>Cerebrospinal fluid transport dysfunction during Alzheimer's disease pathogenesis in the TgF344AD rat brain</td>
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### CURRENT & PENDING GRANTS

<table>
<thead>
<tr>
<th><strong>Elizabeth Hutchinson (Co-I)</strong></th>
<th><strong>Fei Yin (MPI)</strong></th>
<th><strong>Judith Su (multi-PI)</strong></th>
<th><strong>Kaveh Laksari (PI)</strong></th>
<th><strong>Lee Ryan (PI)</strong></th>
<th><strong>Matt Grilli (MPI)</strong></th>
<th><strong>Matt Grilli (Co-I)</strong></th>
<th><strong>Paul Hill (Co-I)</strong></th>
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<tr>
<td><strong>R21 (Sawyer)</strong></td>
<td><strong>U01 AG085179 (Brinton/Vitali/Mosconi/Yin)</strong></td>
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<td><strong>R21 AG081558 (Ekstrom)</strong></td>
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<td><strong>Arizona Department of Health Services via AAC</strong></td>
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<tr>
<td><strong>Advancing Polarization-Sensitive Imaging Toward Intraoperative Guidance for Treatment of Focal Cortical Dysplasia Related Epilepsy</strong></td>
<td><strong>Alzheimer’s On-Ramp Risk Factors Paving the Way to AD-Off-Ramp Therapeutics</strong></td>
<td><strong>Prediction and Experimental Validation of the Ligand Binding and G Protein Signaling of Human Bitter Taste Receptors Related to Cardiometabolic and Inflammatory Diseases</strong></td>
<td><strong>Dynamic cerebrovascular morphology changes in acute ischemic stroke</strong></td>
<td><strong>Psychosocial stress and diurnal cortisol profiles: Examining biological pathways of cognitive health disparities among older adult Latinos and non-Hispanic Whites</strong></td>
<td><strong>Neural correlates of age-related alterations in imaginative thinking</strong></td>
<td><strong>A neurocomputational model of age-related differences in navigation</strong></td>
<td><strong>Determining the efficacy of a navigation intervention to remedy orientation deficits.</strong></td>
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<td><strong>04/01/2024-03/31/2026</strong></td>
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<td>AHS/ABRC</td>
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<td>Developing and validating digital biomarkers of spatial disorientation and early-stage Alzheimer’s disease.</td>
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<th><strong>Paulo W. Pires (MPI)</strong></th>
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<td>The interplay among endothelial cell (EC) autophagy, EC metabolism, and cerebrovascular resilience in the context of aging</td>
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<th><strong>Stephen Cowen (Co-I)</strong></th>
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<td>Uncovering Early Parkinson’s Mechanisms Via A-Synuclein Driven Vocal Dysfunction</td>
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<td>Understanding the divergent impact of human resistin on atherosclerosis and obesity</td>
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<td>Maximizing the Efficacy of Theta Burst Stimulation to Delay Cognitive Decline in Individuals with Prodromal Alzheimer’s Disease</td>
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<td>A comprehensive investigation into the complex relationship between migraine and major cardiovascular/cerebrovascular events (MACE): a multimodal machine-learning approach</td>
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<td>Brain White Matter Hyperintensities in Migraine: A Multi-modal Imaging Project to assess Disease Pathology - A1 Resubmit</td>
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<td>Retinal Imaging Application in Preclinical Alzheimer’s Disease: A Longitudinal Study</td>
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### CURRENT & PENDING GRANTS

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<td>NIH/NICHD</td>
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<td>Jonathan Lifshitz</td>
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<td>U.S. Dept. of Veterans Affairs</td>
<td>Analytical Modeling of Acquired Neurological Injury with Rich Experimental Data Sets</td>
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<td>Jonathan Lifshitz</td>
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<td>Department of Defense</td>
<td>VCR – Virtual cognitive rehabilitation using a virtual reality spatial navigation application for Veterans with a history of TBI</td>
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