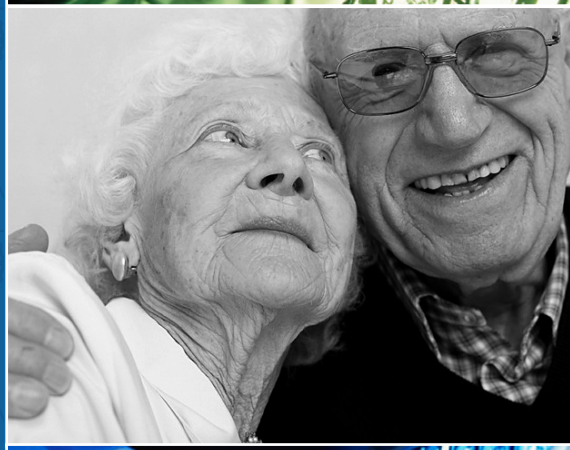
2021 Arizona Alzheimer's Consortium

Scientific Conference Abstracts & Annual Report



Hosted by the University of Arizona
Sept. 9, 2021

ARIZONA
ALZHEIMER'S
CONSORTIUM

Annual Report

July 1, 2020 to June 30, 2021

and

Annual Scientific Conference

September 9, 2021

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Preface

The COVID-19 pandemic has taken an extraordinary toll on all of us. It has changed the way we do our work, educate our children, care for our families, stay socially connected, and conduct our lives. It has caused far too many people to become sick, die, or have residual symptoms, and it has had a major impact on the care and well-being of persons and families who have been struggling with Alzheimer's disease (AD) and other serious health conditions.

Throughout this period, our front-line health workers and researchers have been asked to find ways make an impact, while maintaining the safety of our patients, families, research participants, and each other. It has not been easy. Yet, I am struck by how many people have pulled together, albeit virtually, to care for each other, show the flexibility needed to address our myriad of needs and aspirations, and still make progress. I am moved by many of my colleagues, family members, and friends, who have been impacted by furloughs, unemployment, and innumerable personal challenges, and have still found ways to support and care for others, particularly our heroic frontline workers.

I am also struck by how academic, industry, and government workers have come together and put aside parochial interests to develop, test, and deploy promising antibody cocktails in time for last autumn's surge, and the way that they have worked to develop, test, and extensively deploy life-changing vaccine therapies in record time. Their efforts underscore the value of working together. I cannot wait for the time when all of us are able to put aside our fears, understand that the benefits of COVID-19 vaccination far outweigh the risks, and get vaccinated to help ourselves, our families, our communities, and each other.

Like the rest of the world, the Arizona Alzheimer's Consortium has been impacted by this coronavirus pandemic, and our researchers and clinicians have sought to do their part to help. We have done our best to connect with and support our patients, family caregivers, research participants, and one another. We have worked hard to adapt, learn new technologies, and capitalize on virtual assessments and communications as much as we can, and we have been forced to do far more work from our own homes than we ever imagined. I am amazed by the progress that we continue to make in the fight against AD despite these historic challenges.

When the Consortium's previous Scientific Conference, Public Conference, and Retreat were canceled, we held out hope that our Annual Scientific Conference in 2021 could be held in-person. The rapidly growing number of COVID-19 cases caused by the Delta variant led us to consider canceling our September 9th Scientific Conference due to safety considerations. Recognizing the safety needs of our conference participants, their families, and others with whom they have contact, we have decided to require participants both to confirm in advance that they have been fully vaccinated and to wear masks during the meeting. To address the needs of our colleagues who have not yet been vaccinated, those who are not comfortable attending the meeting in-person despite our precautions, and those who are unable to travel to and spend the entire day in Tucson, we are offering a Zoom link for our oral presentations. We realize there were several options, none of which were ideal, and we ask everyone for their patience and understanding.

We are excited about the chance for our researchers, trainees and students to come together in-person to listen to our distinguished keynote speaker, Dr. Zaven Khachaturian, interact with more than 125 poster and 12 oral presenters, learn from each other, forge new collaborations, and continue to advance the fight against AD. We hope that our colleagues who are not able to attend in-person will value our annual report and Zoom meeting format, and we hope that everyone stays safe and healthy as we all seek to get through this challenging time together. We

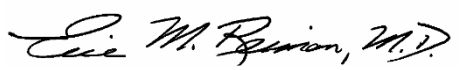
are extremely grateful to our Conference organizers, including our hosts at the University of Arizona, for their flexibility, resourcefulness, and support.

Before COVID-19, the World Health Organization predicted that AD would be the *Worldwide Pandemic of the Twenty-First Century*. AD continues to take extraordinary tolls on cognitively impaired persons and their families, and even greater tolls on those during the COVID-19 pandemic. Due to the growing number of people living to older ages, the number of living persons with cognitive impairment due to AD will triple by 2050 to include 100 million persons with AD dementia, taking an overwhelming financial toll around the world—unless we do something about it right now.

I believe that we can do just that. Based on recent developments, I believe that we have a realistic chance to find and support the availability of effective AD-modifying and prevention therapies within the next five years; furthermore, I believe that we will start to transform care for cognitively impaired persons and their families along the way. We will continue to play leadership roles in these and other important endeavors, working together, right here in Arizona.

I want to personally apologize for the disruption and inconvenience associated with the safety precautions we have invoked for the in-person Scientific Conference. I hope you understand the reasoning behind our decision, and that you find the meeting valuable, whether you participate virtually or in-person. Our hearts go out to those of you who have lost loved ones during this time. We wish you and your families good health and a productive path forward as we try to get through the current pandemic “together.”

Sincerely,



Director, Arizona Alzheimer’s Consortium

Introduction to the Annual Report

Background

The Arizona Alzheimer's Consortium is the nation's leading model of statewide collaboration in Alzheimer's disease (AD) research. It includes more than 150 researchers and staff from seven principal organizations, including Arizona State University, Banner Alzheimer's Institute, Banner Sun Health Research Institute, Barrow Neurological Institute, Mayo Clinic Arizona, the Translational Genomics Research Institute, and the University of Arizona, as well as four affiliated organizations, including the Critical Path Institute, Midwestern University, Northern Arizona University and the University of Arizona College of Medicine, Phoenix. Established in 1998, the Consortium is intended to make a transformational difference in the scientific fight against AD and AD-related diseases (ADRD), to engage Arizona's underserved and understudied Native American and Latino communities, to help address the unmet needs of patients and family caregivers, and to advance the understanding and promotion of healthy cognitive aging. The Consortium's major themes concern the early detection and prevention of AD. Its primary goal is to find effective AD prevention therapies as soon as possible.

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

Eric Reiman, MD, is the Director of the Consortium and the NIA-sponsored AD Research Center (ADRC). Richard Caselli, MD, and Jessica Langbaum, PhD are the ADRC's Associate Directors, and Carol Barnes, PhD, chairs the Consortium's 25-member Internal Scientific Advisory Committee. Mr. David Jerman is Administrative Director of the Consortium's state- and organizational-supported research program, Mrs. Andrea Schmitt is Administrative Director of its ADRC grant. Executives from each of the seven principal organizations serve on the Consortium's Board of Directors. The Consortium's external advisors include Drs. Marilyn Albert, Zaven Khachaturian, Bruce Miller, and Thomas Montine, who are internationally recognized for their contributions and leadership roles in the study of AD and/or related disorders. They conduct annual site visits, review the progress and productivity of both the Consortium and ADRC, and provide formal feedback and recommendations to researchers, NIA, and the state of Arizona.

The Arizona Alzheimer's Consortium capitalizes on the state's strengths in areas such as brain imaging and emerging fluid biomarkers, genomics, computational, mathematical, statistical, and big data analyses of complex data sets, basic, cognitive, and behavioral neurosciences, clinical and experimental therapeutics, and neuropathology research. It has made pioneering contributions to the scientific understanding of AD, including unusually early detection and tracking 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, providing data, biological samples and interested research participants for

researchers inside the state and around the world, and has introduced promising new care models for patients and family caregivers. The Consortium continues to attract new researchers and clinicians and support other biomedical research developments in the state, making Arizona a destination center for the advancement of AD research and care.

State and organizational matching funds continue to provide the “glue” for this geographically distributed research program, the “fuel” needed to launch new research initiatives, and the “scaffolding” needed to reach the Consortium’s over-arching goals. Funds are used to support dozens of research projects each year, almost all of which involve researchers from different scientific disciplines, and about half of which include researchers from different organizations. Arizona is recognized for its courage, its groundbreaking organizational and scientific paradigms, and its ability to make things happen in the fight against AD.

Shared Resources to Advance the Study of AD

Since securing NIA’s first statewide AD Center grant in 2001, Arizona has played a prominent role in the National AD Centers Program, with continuous competitive grant funding as the “Arizona AD Core Center” (ADCC) for the past twenty years. In place of its longstanding grant mechanisms for its AD Centers Program, NIA developed a mechanism to establish new ADRCs, with increased funding, additional research Cores with a growing emphasis on AD biomarkers, and mechanisms to support the development of promising researchers in the scientific fight against AD, including those from under-represented groups, through Developmental Projects and a “Research Education Component” (REC). In September 2020, we submitted a competitive grant to establish a new ADRC that addresses NIA’s updated goals to have an even greater impact on this field. Our new ADRC includes Administrative, multi-site Clinical, Data Management and Statistics (DMS), Biomarker, Neuropathology, and Outreach, Recruitment and Engagement (ORE) Cores and a Research Education Component (REC). For the last twenty years, the ADCC has focused on “the early detection and prevention of AD.” Capitalizing on recent developments, the ADRC will place a special emphasis on “blood-based biomarkers (BBBs) in the diagnosis, preclinical study and prevention of ADRD.”

The Arizona ADRC has six specific aims: 1) To optimize our ADRC cores, to extensively share our data and samples, to forge innovative and impactful multi-institutional, multi-disciplinary collaborations, to capitalize on and support our growing statewide collaborative research program, and to make a profound difference in the fight against AD and ADRD. 2) To capitalize on major state, organizational and philanthropic commitments to augment and leverage our cores, to further address our ADRC goals, and to broaden our impact in addressing 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 Native American communities, to actively support their participation in ADRD research, and to help advance the use of BBBs 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 BBBs to revolutionize ADRD in research, treatment development and clinical care, to inform the study of preclinical AD, and to help provide the best possible chance to find and support the accelerated approval of an AD prevention therapy within the next five years.

Together, our expected ADRC grant, our new NIA grant for the study of cognitively unimpaired persons at six levels of genetic risk based on their APOE genotype, our new Gates Ventures grant, and state, organizational and philanthropic funds will allow our researchers to provide an extraordinary resource of data and biological samples for neuropathological study and diagnostic validation of BBBs for ADRD, including blood samples from several hundred brain donors in the last years of life who have comprehensive neuropathological assessments after they die. These

funds will support our efforts to provide data and biological samples needed to confirm the accuracy of BBBs in Hispanic/Latino and Native American participants using CSF and brain imaging measurements, setting the stage to dramatically increase the use of biomarkers in these and other underrepresented groups. These funds will enable us to provide resources to support studies of preclinical AD and nonpathological aging in our cognitively unimpaired participants at differential genetic and/or biomarker risk, and allow researchers inside Arizona and around the world to incorporate more affordable, scalable, and repeatable BBBs in independently funded studies. Some (but not nearly all) of our shared resources are summarized in the table below:

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

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

Our ADRC grant application, which was found to have numerous strengths and relatively modest and highly addressable limitations, received an excellent impact score. In May, we provided a point-by-point response to each of our Summary Statement Comments, including clarifications and proposed improvements. We expect to receive our Notification of Award for our new ADRC soon, providing $15.7M in total NIA funding through June 30, 2026.

Productivity, Progress and Impact

The Arizona Alzheimer's Consortium is the leading statewide AD Center in the nation and one of the most productive AD research programs in the world. Since its inception in 1998, its researchers have generated thousands of publications, grants, and contracts, as well as 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. They have helped clarify genetic and non-genetic (e.g., microbial) risk, resilience, and resistance factors and disease mechanisms, offered targets at which to aim new AD treatments, provided new insights about the pathological changes associated with AD and ADRD, and provided targets for the discovery of drug and gene therapies to treat and prevent AD.

2. 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 across six regions that are differentially affected by AD pathology in 100 brain donors with and without AD; Consortium researchers continue to use these and other resources to implicate disease networks, risk factors, and potential drivers at which to aim new AD treatments.

3. They continue to introduce new data-sharing, biological sample-sharing, and collaborative paradigms to assist researchers in Arizona and around the world—including data and samples from their own observational studies and prevention trials, data from a growing number of clinical trials of AD and other disorders through the Critical Path for AD (e.g., CPAD, https://c-

path.org/programs/cpad/), and online memory tests and other information that has been generated in >225,000 participants from across the world via the MindCrowd project (www.mindcrowd.org).

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 have provided invaluable resources of data and volunteers from persons at three levels of genetic risk for AD (i.e., with two, one and no APOE4 alleles) and in Colombian autosomal dominant AD (ADAD)-causing mutation carriers and non-carriers from the world's largest ADAD kindred. They introduced new experimental paradigms, image-analysis techniques, and composite cognitive tests to help in this endeavor. Their work anticipated and advanced the conceptualization of preclinical AD. As noted below, this work continues to inform the design of prevention trials in persons at increased genetic and/or biomarker risk and provides the foundation needed to launch a new era in AD prevention research.

5. 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, playing leading roles in the international study of the aging mind and brain.

6. They have demonstrated leadership in brain imaging and other research studies to detect, track, and study AD and related disorders starting many years before the onset of symptoms, assessing genetic and non-genetic risk factors, and introducing image analysis methods and the use of emerging BBBs to address these goals with improved power. They have likewise led efforts to validate amyloid and other emerging PET methods in persons at the end of life who subsequently donate their brains and support future FDA approval for their use in the clinical setting. They have begun to develop resources and tools to evaluate promising cerebrospinal fluid (CSF) assays, blood tests, and mobile technologies as soon as possible.

7. They and their collaborators continue to play leadership roles in the study of chronic traumatic encephalopathy (CTE) through "DIAGNOSE CTE", a national NINDS-sponsored longitudinal study which aims to characterize clinical, cognitive, PET, CSF, neuropathological, and blood-based biomarker changes in National Football League (NFL) players, college football players, and normal control participants who deny significant participation in contact sports, providing a shared resource of data and biological samples for the field.

8. 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 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.

9. They have begun to show the promise of BBBs in the early detection, tracking, study, and diagnosis of AD and the evaluation of AD-modifying and prevention therapies. These researchers and their collaborators have demonstrated the diagnostic accuracy of plasma ptau217 in persons who provided blood samples at the end of life, donated their brains, and had neuropathological assessments after they died. Additionally, they have begun 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 Native American groups. They believe that BBBs have the potential to transform AD/ADRD research,

treatment development, and clinical care, and galvanize the inclusion of persons from under-served and under-represented groups.

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

11. The Alzheimer’s Prevention Initiative (API) set the stage for a new era in AD prevention research, including the first NIH- and industry supported prevention trials of putative AD-modifying treatments in cognitively unimpaired persons at genetic or biomarker risk. The API established precedent-setting public-private partnerships, data and biological sample sharing commitments, and strategies to support the potential development of surrogate biomarker endpoints in the accelerated evaluation and approval of prevention therapies. Furthermore, the API has resulted in better tests of the amyloid hypothesis that 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, and new prevention trials that provide a realistic chance to find and support the accelerated approval and availability of prevention trials within the next five years.

i) With support from NIA, Genentech/Roche, and philanthropy, the API Autosomal Dominant AD (ADAD) Trial has been evaluating the anti-oligomeric amyloid antibody therapy crenezumab in cognitively unimpaired amyloid-positive and negative members of the world’s largest ADAD kindred in Colombia at a timepoint close to the ADAD mutation carriers’ median age of 44 at mild cognitive impairment (MCI) onset. The trial will be completed in 2022, as baseline data are now available, and trial data and biological samples are to be shared after the trial is over; other trials in this remarkable kindred are planned.

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

iv) With support from NIA and an industry partner (*to be announced*), plans are underway to initiate an API/A4-related prevention trial of an amyloid plaque-reversing antibody treatment in cognitively unimpaired amyloid-positive APOE4 carriers and non-carriers in 2022. AD prevention trials are currently designed to show a slowing in cognitive decline or clinical progression, but if ongoing pivotal trials of the same drug in cognitively impaired persons demonstrated a clinical benefit, it would be possible to conduct an interim analysis after only two years of treatment and to support the accelerated approval of the same treatment in the secondary prevention of AD using the same biomarker endpoints associated with the clinical benefit in the pivotal trial, as well as to confirm a clinical benefit in follow-up assessments. This study would thus have the potential to find and support the accelerated approval of an AD prevention therapy within the next five years, setting the stage to rapidly evaluate and support the accelerated approval of a wide range of prevention therapies and providing an invaluable resource of data and samples for the field.

v) With support from Lilly, Lilly and API together have recently announced a potentially groundbreaking study of the company's amyloid plaque-reducing antibody treatment donanemab in cognitively unimpaired APOE4 carriers and non-carriers using the BBB plasma p-tau217 to identify those persons who are amyloid-positive while enabling trial participants to have virtual assessments without having to travel to a study site, thereby supporting the inclusion of persons from more remote locations and understudied groups to participate in the trial. In a Phase 2 Trial, donanemab was suggested to reverse PET evidence of amyloid-plaque deposition, reduce plasma p-tau concentrations (an indicator of amyloid-related tau pathophysiology), and slow clinical decline. If these findings are confirmed in ongoing clinical trials, the prevention trial will provide a realistic chance to find and support the accelerated approval of an AD prevention therapy within the next five years.

vi) API includes exceptionally large registries and related programs to support enrollment in AD prevention trials and affiliate studies. It includes a Colombian API Registry with nearly 6,000 PSEN1 E280A mutation carriers and non-carriers from the world's largest ADAD kindred, including nearly 1,200 mutation carriers who are virtually certain to develop MCI and dementia due to AD at early ages, the North American Alzheimer's Prevention Registry with >360,000 members (www.endALZnow.org), GeneMatch (a national resource of more than 85,000 members who permit us to determine their APOE genotype for research purposes), genetic risk disclosure and impact assessment programs to help support interest and enrollment in prevention trials, engagement programs to inform participants about relevant prevention trials and other research opportunities, and other emerging methods and strategies to help find and support the approval of an AD prevention therapy as soon as possible. These and related efforts have had a profound impact on researchers, policy makers, and other stakeholders around the world.

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, related disorders and brain aging. They continue to make historic 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.

Emerging Developments, Opportunities and Initiatives

Aducanumab and Other Amyloid Plaque-Reducing Treatments. Two years ago, the field was rocked by disappointing efficacy and safety findings from several trials of anti-amyloid treatments, reminding us that nearly 100% of AD clinical trials had failed since 2002. Since then, the field has seen promising but not yet definitive clinical and biomarker findings from several amyloid plaque-reducing antibody therapies.

While highly controversial, the decision-making and communication process that led the FDA to announce accelerated approval of aducanumab, an intravenous antibody therapy that has been shown to dramatically reverse PET measurements of amyloid plaque deposition, could have a significant impact on AD drug development and care. Biogen's two pivotal trials of aducanumab in amyloid-positive persons with MCI and mild dementia were prematurely discontinued in March 2019 following a futility analysis that suggested that the treatment was unlikely to show a benefit if the trials were completed. Additional data came in following treatment discontinuation, leading Biogen to conclude that it did not take into consideration the possibility that it would take some time after amyloid plaque reduction to show a clinical benefit and to suggest that the drug was

actually effective. One of the prematurely discontinued trials demonstrated efficacy using the trial's prespecified primary clinical endpoint; the other trial did not—but a post hoc analysis suggested a similar clinical response in those persons treated at the highest dose for the longest duration. Working with Biogen to understand these findings, and noting the suggested benefit of two other amyloid plaque-reducing therapies in Phase 2 trials, the FDA granted accelerated approval for aducanumab in the treatment of AD based on its judgment that this and other amyloid plaque-reducing treatments are "reasonably likely" (but not certain) to have a clinical benefit.

Whatever one thinks of FDA's decision, pivotal trials are currently evaluating three other amyloid plaque-reducing antibody treatments (gantenerumab, lecanemab, and donanemab) in amyloid-positive patients with MCI and mild dementia, and results from these more definitive trials will be available in the next two years. If these treatments demonstrate a clinical benefit, it will be a game changer for the field, as it will confirm the role of certain amyloid aggregates in the pathogenesis, treatment, and potential prevention of AD. Trial data, samples, and findings from this work will clarify those biological effects that are associated with a clinical benefit, enable theragnostic biomarkers to inform the development of promising AD-modifying treatments in clinical trials, and accelerate the evaluation and approval of these and eventually other treatments in the prevention of AD using surrogate biomarker endpoints that are reasonably likely to predict a clinical benefit. It could also lead more primary care providers to ask their patients about memory and thinking problems during their annual wellness visits and take proactive steps to better address their medical and non-medical needs.

While we are excited about these opportunities, FDA's decision also raises a number of important questions, which will need to be addressed in the near future. For instance, what are the rules going forward for the approval of AD-modifying treatment in clinical trials? What can be done to ensure that the ongoing pivotal trials are completed and that other AD-modifying drug trials are not compromised by what could become a "standard of care" in those locations in which treatment is available and reimbursed? Which patients are most likely to benefit from aducanumab treatment based on the available evidence? (The recently published "appropriate use criteria" should help address that particular question.) What can be done to support the affordability and widespread availability of these antibody treatments like aducanumab, and the PET and MRI safety assessments that may be needed to support their appropriate use? (This is a question that the Centers for Medicare and Medicaid Services (CMS), other payers, health systems, and policy makers are now trying to address.) Will that include lower prices than Biogen has proposed to charge or discontinuation of treatment after evidence of amyloid plaque reversal? What about the further development and future use of more widely available and less expensive blood tests to characterize persons for the presence or absence of amyloid plaques, mechanisms that do not rely exclusively on the paucity of dementia specialists to consider and provide appropriate care, and the development of less expensive approaches to prevent the return of amyloid plaques?

It will take time for the dust to settle, but we hope that many of the opportunities will be realized, many of the challenges will be addressed, and that there will be many more effective ways to treat, manage, and prevent AD. Meanwhile, the field is excited about ongoing efforts to diversify the portfolio of promising AD-modifying and prevention therapies, including new approaches to the discovery of therapeutic targets, and a growing number of antibody, small molecule, and developing gene therapies, repurposed drugs, and non-drug therapies continue to be developed for the treatment and prevention of AD and age-related cognitive decline that could be put to the test in more informed and successful ways. There is slow but steady progress in the development of treatments that target additional aspects of amyloid and tau pathophysiology, the immune response to amyloid aggregation, APOE, neurodegeneration, and other biological processes inside and outside the brain that may be involved in the predisposition to and protection from AD.

Arizona researchers are playing important roles in several of these endeavors.

Blood tests. In addition to the possibility of having the first definitively established AD-modifying treatments within the next two years, the field is also excited about emerging BBBs of amyloid plaque deposition (e.g., plasma amyloid-β42/40 [Aβ42/40]), Aβ-mediated tau pathophysiology and the diagnosis of AD (e.g., plasma ptau217, 231 or 181), the neuronal injury and neurodegenerative changes observed in persons with AD and a wide range of neurological disorders (e.g., plasma or serum NfL), and other pathophysiological features of AD (e.g., plasma GFAP, an indicator of astrogliosis). More work is needed to refine, test, and compare these BBBs to clarify their role in AD research, treatment development, and clinical care. Still more work is needed to find BBBs for ADRD, including indicators of alpha-synuclein/Lewy Body pathophysiology, TDP-43, and cerebrovascular disease. Like AD-modifying drugs, blood tests could have transformational effects in AD research, treatment, development, and care. As previously noted, Arizona researchers will continue to play major roles in the effort to fulfill the promise of BBBs in AD research, treatment development, and clinical care, and to extend their value to research participants, patients, and families from under-represented groups.

Brain Aging Research. Arizona researchers continue to play leadership roles in the study of the normal aging brain and the promotion of cognitive health at older ages. This effort is reflected by the University of Arizona's McKnight Research Institute, a wide range of studies in unimpaired older and younger adults, non-human primates, laboratory rodents, and other models, as well as studies of aging in the MindCrowd Program, promising drug development efforts, and a large U19 grant, entitled "Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human LifeSpan" that has been reviewed by NIA and is under consideration for funding.

Dramatically increasing the value of our cohorts. While we follow several important research cohorts in our longitudinal studies and prevention trials, the value of our cohorts would be dramatically increased by the incorporation of biomarkers, CSF, and blood samples to characterize amyloid, tau, neurodegenerative and cerebrovascular disease burden, and, when available, ADRC (e.g., alpha-synuclein and TDP-43) pathologies. As illustrated above, we have invested in several initiatives to address this challenge and have the greatest possible impact.

Increasing the study of our under-represented Native American and Hispanic 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 Native American 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 >40,000 persons, including >14,000 and 2,000 Hispanic and Native American participants, respectively. We plan to develop and maintain an active cohort of at least 75 Native American and 100 Hispanic research participants in our ADRC multi-site Clinical Core.

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

investigators, including those from diverse backgrounds within the new ADRC's REC, and provide support for their participation in relevant conferences and retreats. We will further develop these research education and training programs over the next year.

New programs, researchers, physicians and leaders. We are pleased to report the opening of Banner Alzheimer's Institute (BAI) Tucson in 2020, extending BAI's comprehensive care model, offering clinical trials and working in partnership with UA to advance AD, Lewy Body Dementia (LBD) and aging research in well characterized research participants. We are thrilled to announce the arrival of Jeffery Kordower, PhD, a leader in neurodegenerative disease research, as Founding Director of the Arizona State University (ASU)-Banner Neurodegenerative Disease Research Center (NDRC) in March 2021, setting the stage for dramatic growth and new translational research discoveries in the coming years. We continue to benefit from major research and clinical recruitments, and the organizational and philanthropic investments needed to support them, at most of our organizations.

Coping with COVID-19. As noted in the Preface, the COVID-19 crisis has had a major impact on our clinical and research programs, the way in which we interact with our patients and research participants, and just about everything else in our lives. Like other researchers, clinicians, and organizations around the world, we continue to find ways to adapt and learn from the current crisis and to advance the fight against AD, ADRD, and cognitive aging.

Looking Ahead

We and our colleagues will continue to develop new scientific and clinical initiatives and advance our existing programs, as well as attract, diversify, and support the development of great researchers and clinicians, while securing the state, organizational, philanthropic and federal investments needed to fulfill our ambitious goals. We will continue to play pioneering roles in the unusually early detection, tracking, and study of AD, as well as the development of AD-modifying, symptomatic, and prevention therapies. Along with the study and treatment of cognitive aging, we will pursue the development and innovative use of 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 BBB and other biomarkers, particularly regarding their use in early and late phase trials, and the push-pull relationships between research applications and methodological development and between brain omics and other observational studies in human subjects and basic science studies in experimental models, along with the development of extensively shared resources from our different programs to have the greatest possible impact.

While there are no guarantees, we and our colleagues in the field have an opportunity to demonstrate the efficacy of amyloid plaque-reducing antibody therapies, provide compelling support for a role of amyloid in the development, treatment, and prevention of AD, and find those theragnostic biomarker endpoints that are associated with a clinical benefit. We have a chance to use those biomarkers to further inform, accelerate, and support the successful development of new treatments in non-clinical and early phase trials, accelerate the evaluation of AD-modifying and prevention therapies, and clarify the mechanisms by which lifestyle interventions and repurposed drugs exert their cognitive-health promoting effects. Indeed, we have a realistic chance to find and support the accelerated approval of AD prevention therapies *within the next five years*.

We have a chance to further develop, test, and compare promising BBBs for AD and ADRD, and to use them in innovative ways, transforming AD research, treatment development, and care, while emphasizing the inclusion of research participants, patients and families from understudied and underrepresented groups. We have a chance to capitalize on multi-omics measurements in the post-mortem human brain, electronic health records and other big data, BBB

endophenotypes, artificial intelligence, machine learning, and other big data analysis methods, as well as complementary experimental studies to clarify AD/ADRD networks, drivers, and risk and protective factors and to provide targets for the discovery and development of new AD-modifying drug treatments. We have a chance to develop new gene therapies and the mechanism needed to deliver them to the right brain cells within the next five years, and put promising gene-silencing antisense oligonucleotide and RNAi treatments to the test in informative early phase treatments along the way. We will continue to see a diversification in AD-modifying treatments, including those that target APOE, and we will have rapid ways to clarify their potential value in early phase trials.

We will have the chance to diversify AD research studies, clinical trials, researchers, and clinicians, and capitalize on this diversity in highly impactful ways. We will have the chance to generate invaluable resources of data, including antemortem and postmortem biological samples as well as interested research participants, and to forge new collaborations in support of these and other goals. Through its leadership and collaborative efforts, shared resources, methods and findings, Arizona researchers are poised to play major role in these and other endeavors.

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

Arizona Alzheimer's Consortium

22nd Annual Conference – Thursday September 9, 2021

University of Arizona (Host Institution)

Student Union

1303 E. University Blvd.

Tucson, AZ 85719

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

WELCOME 9:30 – 9:40AM
Elizabeth "Betsy" Cantwell, Ph.D.
Senior Vice President, Research Innovation and Impact
University of Arizona

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

LEON THAL MEMORIAL LECTURE 10:00 – 11:15AM
Is the rising storm of Alzheimer' disease stoppable?
Zaven S. Khachaturian, Ph.D.
President, Prevent Alzheimer's Disease by 2020, Inc. [PAD 2020]
Editor-in-Chief, Alzheimer's Dementia: Journal of the Alzheimer's Association
Senior Science Advisor to the Alzheimer's Association
Adjunct Professor of Psychiatry and Neuroscience, Johns Hopkins University School of Medicine

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

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

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

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

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

Arizona Alzheimer's Consortium

Oral Research Presentations

SESSION I Moderator: Carol Barnes, PhD

11:15 – 11:26 AM **A novel tau-based rhesus monkey model of Alzheimer's pathogenesis.** Jeffrey Kordower. Arizona State University; University of California Davis; University of Florida, Arizona Alzheimer's Consortium.

11:27 – 11:38 AM **APOE4 disrupts neuron-astrocyte coupling of lipid metabolism.** Fei Yin. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

11:39 – 11:50 AM **Improved comparability between measurements of mean cortical amyloid plaque burden derived from different PET tracers using multiple regions-of-interest and machine learning.** Kewei Chen. Banner Alzheimer's Institute; Washington University, St. Louis; Arizona State University; Arizona Alzheimer's Consortium.

11:51 – 12:02 PM **The Critical Path for Alzheimer's Disease (CPAD) Consortium – A platform for pre-competitive data sharing, standardization, and analysis to support quantitative tools for AD drug development**. Sudhir Sivakumaran. Critical Path Institute; Arizona Alzheimer's Consortium.

12:03 – 12:14 PM **Mapping of SARS-CoV-2 brain invasion and histopathology in COVID-19 disease.** Geidy Serrano. Banner Sun Health Research Institute; Stanford University; Mayo Clinic Florida; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

12:15 – 12:26 PM **Observational and interventional studies of the contribution of the gut microbiota mice modeling Alzheimer's disease pathologies.** Emily Cope. Northern Arizona University; Arizona Alzheimer's Consortium.

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Oral Research Presentations

SESSION II Moderator: Lee Ryan, PhD

3:00 – 3:11 PM **Dysregulation of homologs retinoblastoma binding protein (RBBP) 4 and 7 in the context of Alzheimer's disease.** Jessica Judd. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

3:12 – 3:23 PM **Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk.** Craig Weinkauf. University of Arizona; University of Arizona College of Medicine; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

3:24 – 3:35 PM **Ultrasound-assisted lumbar puncture in Alzheimer's disease and related dementias research: A pilot study**. Danielle Goldfarb. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Banner University Medical Center; Harvard Medical School; Brigham and Women's Hospital; Arizona Alzheimer's Consortium.

3:36 – 3:47 PM **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 Van Keuren-Jensen. Translational Genomics Research Institute; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

3:48 – 3:59 PM **The immediate early gene EGR3 influences expression of Alzheimer's disease gene TREM2.** Amelia Gallitano. University of Arizona; Arizona State University; Syracuse University; Arizona Alzheimer's Consortium.

4:00 – 4:11 PM **The MindCrowd project: Progress, collaboration, and electronic cohort recruitment in the time of COVID-19.** Matthew Huentelman. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium

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Poster Presentations

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1. **THE TELOMERE PROTECTIVE PROTEIN RAP1 AND AN ISOFORM OF GLIAL FIBRILLARY ACID PROTEIN AFFECT GAMMA SECRETASE ACTIVITY IN A YEAST SYSTEM.** Abel KN, Strash G, Carpenter R, Bae NS, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

2. **NANOLIPOSOMAL TREATMENT REDUCES STROKE INJURY FOLLOWING MIDDLE CEREBRAL ARTERY OCCLUSION IN MICE.** Ahmad S, Kindelin A, Truran S, Karamanova N, Lozoya M, Griffiths DR, Weissig V, Lifshitz J, Ducruet AF, Migrino RQ. Barrow Neurological Institute; Phoenix VA; Midwestern University; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

3. **AAC TOOLS WEBSITE.** Amador RR, Bauer R, Parizek D, Saner D. Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.

4. **DATA MANAGEMENT AND STATISTICAL CORE.** Amador RR, Bauer R, Parizek D, Saner D. Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.

5. **ARIZONA'S DEMENTIA CAPABLE SYSTEM – TARGETING THREE UNDERSERVED GROUPS.** Angulo A, Cortés M, Carbajal B, Carbajal L, Cordova L, Weatherall Z, Gómez-Morales A, Glinka A, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

6. **THE EFFECT OF AGING AND NEUROLOGICAL DISORDERS ON MUSCLE FIBER SIZE IN THE PSOAS MUSCLE: A PILOT STUDY.** Arce R, Serrano GE, Russell A, Vargas D, Intorcia A, Walker J, Glass M, Oliver J, Papa J, Nelson C, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

7. **EXTRACRANIAL CAROTID ATHEROSCLEROSIS IS ASSOCIATED WITH INCREASED NEUROFIBRILLARY TANGLE ACCUMULATION.** Arias JC, Edwards M, Vitali F, Nagae L, Beach TG, Serrano GE, Weinkauf CC. University of Arizona; University of Arizona College of Medicine; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

8. **STUDIES ON THE TELOMERE PROTECTION PROTEIN RAP1 AS A NEURONAL TRANSCRIPTION FACTOR.** Bae NS, Virdi S, Abel KN, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

9. **EXPLORING THE UTILITY OF TMS MOTOR RESPONSE FOR PREDICTING RESPONSIVENESS TO TMS BASED INTERVENTIONS IN MILD COGNITIVE IMPAIRMENT.** Baham JM, Sundman MH, Chen AYC, Chou YH. University of Arizona; Arizona Alzheimer's Consortium.

10. **ALZHEIMER'S DISEASE NEUROPATHOLOGICAL COMORBIDITIES ARE COMMON IN THE YOUNGER-OLD.** Beach TG, Malek-Ahmadi M. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

11. **NEUROPATHOLOGICAL DIAGNOSES OF SUBJECTS AUTOPSIED IN THE PHASE 3 CLINICOPATHOLOGICAL STUDY OF FLORTAUCIPIR F18 PET IMAGING.** Beach TG, Montine TJ, Serrano GE, Sue LI, Intorcia AJ, Walker J, Glass M, Fleisher AS, Pontecorvo MJ, Devous Sr. MD, Lu M, Mintun MA, on behalf of the A16 study investigators. Banner Sun Health Research Institute; Stanford University School of Medicine; Avid Radiopharmaceuticals; Arizona Alzheimer's Consortium.

12. **LONGITUDINAL ASSESSMENT OF INTRAVOXEL INCOHERENT MOTION DIFFUSION-WEIGHTED MRI (IVIM-DWI) METRICS IN ALZHEIMER'S DISEASE.** Bergamino M, Steffes L, Burke A, Baxter L, Caselli RJ, Sabbagh MN, Walsh RR, Stokes AM. Barrow Neurological Institute; Mayo Clinic Arizona; Lou Ruvo Center for Brain Health, Cleveland Clinic; Arizona Alzheimer's Consortium.

13. **PATIENT-BASED POSTMORTEM FIBROBLAST BANKING FOR AGE-RELATED NEURODEGENERATIVE DISEASE RESEARCH.** Beh ST, Frisch C, Brafman DA, Churko J, Serrano G, Beach TG, Lue L-F. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

14. **IMPROVED COGNITION AND PRESERVED HIPPOCAMPAL FRACTIONAL ANISOTROPY IN SUBJECTS UNDERGOING CAROTID ENDARTERECTOMY.** Bernstein A, Guzman G, Arias J, Bruck D, Berman S, Leon L, Nagae L, Pacanowski J, Zhou W, Goshima K, Tan T-W, Taylor Z, Altbach M, Trouard T, Weinkauf C. University of Arizona; Arizona Alzheimer's Consortium.

15. **ACCELERATING DIFFUSION TENSOR IMAGING OF THE RAT BRAIN USING DEEP LEARNING.** Bilgin A, Do L, Martin P, Lockhart E, Bernstein AS, Ugonna C, Dieckhaus L, Comrie C, Hutchinson E, Chen N, Alexander GE, Barnes CA, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

16. **THE NUCLEAR PORE COMPLEX AND NUCLEOCYTOPLASMIC TRANSPORT: NEURONS AND GLIA IMPLICATED IN ALZHEIMER'S DISEASE.** Brokaw DL, Goras M, Tran M, Delvaux E, Coleman PD. Arizona State University; Arizona Alzheimer's Consortium.

17. **IMPROVED COMPARABILITY BETWEEN MEASUREMENTS OF MEAN CORTICAL AMYLOID PLAQUE BURDEN DERIVED FROM DIFFERENT PET TRACERS USING MULTIPLE REGIONS-OF-INTEREST AND MACHINE LEARNING.** Chen K, Ghisays V, Luo J, Chen Y, Lee W, Benzinger TLS, Wu T, Reiman EM, Su Y. Banner Alzheimer's Institute; Washington University, St. Louis; Arizona State University; Arizona Alzheimer's Consortium.

18. **INCREASED SPATIAL EXTENT OF CEREBRAL TAU PET ELEVATIONS IN FORMER NFL AND COLLEGE FOOTBALL PLAYERS FROM THE DIAGNOSE CTE RESEARCH PROJECT.** Chen K, Reiman EM, Luo J, Protas H, Cummings JL, Shenton ME, Stern RA, Su Y for the DIAGNOSE CTE Research Project. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Boston University School of Medicine; Brigham and Women's Hospital; University of Nevada, Las Vegas; Arizona Alzheimer's Consortium.

19. **SUCCESSFUL RECRUITMENT OF EARLY-STAGE ADRD PARTICIPANTS THROUGH COMMUNITY PARTNERSHIPS AND HIPAA-COMPLIANT FAX REFERRAL PROCESS.** Cortes M, Angulo A, Carll P, Glinka A, Stotler K, Gonzalez-Pyles MS, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

20. **DECREASED DYNAMIC RANGE OF HIPPOCAMPAL CA1 GAMMA IN AGED RATS.** Crown LM, Gray DT, Schimanski LA, Barnes CA, Cowen SL. University of Arizona; Arizona Alzheimer's Consortium.

21. **ADULTHOOD DIETARY CHOLINE DEFICIENCY; A RISK FACTOR FOR OBESITY, IMPAIRED GLUCOSE TOLERANCE, CARDIAC PATHOLOGY AND SUBSEQUENT ALZHEIMER'S DISEASE.** Decker A, Winslow W, Blackwood E, Bilal A, Mcdonough I, Winstone J, Tallino S, Dave N, Glembotski C, Velazquez R. Arizona State University; University of Arizona College of Medicine – Phoenix; Arizona Alzheimer's Consortium.

22. **AN MRI MICROSCOPY TOOLKIT FOR TRACKING MICROSTRUCTURAL CHANGES LINKED TO AGING.** Dieckhaus L, Barnes CA, McDermott K,Gray DT, Hutchinson E. University of Arizona; Arizona Alzheimer's Consortium.

23. **QUANTITATIVE AND VOLUMETRIC AND DIFFUSION WEIGHTED MRI ANALYSIS OF RODENT BRAINS AS A FUNCTION OF AGE AND COGNITION.** Do L, Zempare MA, Bernstein AS, Bharadwaj P, Ugonna C, Chen N, Alexander GE, Barnes CA, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

24. **CSF AMYLOID-BETA, TAU, NEURODEGENERATIVE, AND INFLAMMATORY BIOMARKERS IN COGNITIVELY UNIMPAIRED LATE MIDDLE-AGED & OLDER ADULT APOE ε4 HOMOZYGOTES, HETEROZYGOTES, & NON-CARRIERS FROM THE ARIZONA APOE COHORT.** Ghisays V, Jansen WJ, Chen Y, Protas H, Malek-Ahmadi M, Luo J, Lee W, Chen K, Su Y, Caselli RJ, Zetterberg H, Blennow K, Reiman EM. Banner Alzheimer's Institute; Mayo Clinic Arizona; Sahlgrenska University Hospital, Mölndal, Sweden; University of Gothenburg, Sweden; Arizona Alzheimer's Consortium.

25. **PLASMA AB42/40 RATIOS IN COGNITIVELY UNIMPAIRED LATE MIDDLE-AGED & OLDER ADULT APOE E4 HOMOZYGOTES, HETEROZYGOTES, & NON-CARRIERS.** Ghisays V, Jansen WJ, DeMarco K, Boker C, Chen K, Chen Y, Luo J, Protas H, West T, Meyer M, Kirmess K, Verghese P, Hu H, Yarasheski K, Caselli RJ, Su Y, Reiman EM. Banner Alzheimer's Institute; C2N Diagnostics; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

26. **ULTRASOUND-ASSISTED LUMBAR PUNCTURE IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS RESEARCH: A PILOT STUDY.** Goldfarb D, Viramontes D, Callan M, Liebsack C, Goddard M, Reade M, Malek-Ahmadi MH, Weidman D, Tsai PH, Wu T, Grimsman J, Atri A. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Banner University Medical Center; Harvard Medical School; Brigham and Women's Hospital; Arizona Alzheimer's Consortium.

27. **AUDITORY AND VISUAL SYSTEM FUNCTION AND WHITE MATTER CONDITION IS DIFFERENTIALLY IMPACTED BY NORMATIVE AGING IN MACAQUES.** Gray DT, De La Peña NM, Umapathy L, Burke SN, Engle JR, Trouard TP, Barnes CA. University of Arizona; University of Florida, Gainesville; Arizona Alzheimer's Consortium.

28. **ASSOCIATION BETWEEN CEREBROVASCULAR FUNCTION AND CHRONIC COGNITIVE DYSFUNCTION FOLLOWING MILD-MODERATE TRAUMATIC BRAIN INJURY IN RATS AND LACK OF A MODULATING INFLUENCE BY DIABETES.** Griffiths DR, Fuentes A, Law LM, Bell L, Karamanova N, Truran S, Emerson H, Turner G, Quarles CC, Reaven P, Migrino RQ, Lifshitz J. University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute; Phoenix VA; Arizona Alzheimer's Consortium.

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

30. **REMOTE, UNSUPERVISED FUNCTIONAL MOTOR TASK EVALUATION IN OLDER ADULTS ACROSS THE UNITED STATES USING THE MINDCROWD ELECTRONIC COHORT.** Hooyman A, Talboom J, DeBoth MD, Ryan L, Huentelman M, Schaefer SY. Arizona State University; The Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

31. **THE MINDCROWD PROJECT: PROGRESS, COLLABORATION, AND ELECTRONIC COHORT RECRUITMENT IN THE TIME OF COVID-19.** Huentelman MJ, Talboom JS, Schmidt AM, De Both MD, Naymik MA, Lewis CR, Hay M, Barnes CA, Glisky E, Ryan L. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

32. **INVESTIGATION OF THE STRUCTURE AND ACTIVITY OF TAU PROTEIN AGGREGATE FORMATION.** Huseby CJ, Ranaweera E, Mossman KC, Lowry D, Serrano GE, Hansen DT, Coleman PD, Fromme P. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

33. **SYSTEMATIC ANALYSIS OF BLOOD TRANSCRIPT BIOMARKERS IDENTIFIES SIMILARITIES AND DIFFERENCES ACROSS NEURODEGENERATIVE DISEASES INCLUDING ALZHEIMER'S DISEASE.** Huseby CJ, Delvaux E, Brokaw D, Coleman PD. Arizona State University; Arizona Alzheimer's Consortium.

34. **ROBUST NEUROPSYCHOLOGICAL NORM DEVELOPMENT BASED ON COGNITIVELY NORMAL OLDER ADULTS: EXAMINING TRUE NEUROCOGNITIVE NORMALITY.** James EJ, Malek-Ahmadi MH, Moorley N, Evans B, Auman B, Beach TG, and the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND). Banner Sun Health Research Institute; Banner Alzheimer's Institute; Midwestern University; Arizona Alzheimer's Consortium.

35. **INTESTINAL MICROBIOTA DYSBIOSIS IN TRANSGENIC ALZHEIMER'S DISEASE MOUSE MODELS.** Jentarra G, Jones D, Dodiya H, Chu P, Gonzalez F, Vallejo J, Huang V, Potter P, Jones TB. Midwestern University; University of Chicago; Arizona Alzheimer's Consortium.

36. **ADENOSINE TRIPHOSPHATE BINDING CASSETTE SUBFAMILY C MEMBER 1 (ABCC1): A POTENTIAL THERAPEUTIC TARGET FOR THE TREATMENT OF ALZHEIMER'S DISEASE.** Jepsen WM, De Both M, Siniard AL, Ramsey K, Piras IS, Naymik M, Henderson A, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium. (Accepted Abstract)

37. **DO YOU KNOW WHO I AM? A PERSON CENTERED CARE INTERVENTION IN AN ACUTE CARE SETTING.** Johnson K. Honor Health Thompson Peak Medical Center.

38. **DYSREGULATION OF HOMOLOGS RETINOBLASTOMA BINDING PROTEIN (RBBP) 4 AND 7 IN THE CONTEXT OF ALZHEIMER'S DISEASE.** Judd JM, Piras IS, Dave N, Mastroeni D, Huentelman MJ, Velazquez R. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

39. **AMYLOIDOGENIC MEDIN INDUCES ENDOTHELIAL CELL PROTHROMBOTIC ACTIVATION.** Karamanova N, Truran S, Davies H, Madine J, Migrino RQ. Phoenix VA Health Care System; University of Liverpool; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

40. **COMPLEMENT C3A RECEPTOR (C3AR) DEFICIENCY IS NEUROPROTECTIVE IN MOUSE VCID MODEL.** Kindelin A, Nadeem M, Bhatia K, Preul MC, Waters MF, Ducruet AF, Ahmad S. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

41. **LARGE-SCALE BIOMANUFACTURING: PURIFICATION AND CRYOPRESERVATION OF NEURAL CELL TYPES.** Knittel J, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

42. **A NOVEL TAU-BASED RHESUS MONKEY MODEL OF ALZHEIMER'S PATHOGENESIS.** Kordower JH, Beckman D, Chakrabarty P, Donis-Cox K, Morrison JH. Arizona State University; University of California Davis; University of Florida, Arizona Alzheimer's Consortium.

43. **COMPENSATORY AND LIFESTYLE-BASED BRAIN HEALTH PROGRAM FOR SUBJECTIVE COGNITIVE DECLINE: SELF-IMPLEMENTATION VERSUS COACHING.** Locke D, Liou H, Shah A, Buckner S, Stonnington C. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

44. **PLASMA NFL IS ASSOCIATED WITH APOE E4 ALLELIC DOSE, HIPPOCAMPAL ATROPHY AND ALZHEIMER'S-RELATED CEREBRAL HYPOMETABOLISM IN COGNITIVELY UNIMPAIRED LATE-MIDDLE-AGED AND OLDER ADULTS.** Malek-Ahmadi M, Su Y, Devadas V, Luo J, Ghisays V, Protas H, Chen K, Blennow K, Zetterberg H, Caselli RJ, Reiman EM. Banner Alzheimer's Institute; University of Gothenburg; Mayo Clinic Arizona; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

45. **AMYLOID BETA PROTECTS ELDERLY MICE FROM SUCCUMBING TO INFECTION WITH THE NEUROTROPIC PARASITE TOXOPLASMA GONDII.** McGovern KE, Koshy AA. University of Arizona; Arizona Alzheimer's Consortium.

46. **THE IMMEDIATE EARLY GENE EGR3 INFLUENCES EXPRESSION OF ALZHEIMER'S DISEASE GENE TREM2.** Ozols AB, Marballi KK, Meyers KT, Beck KL, Shrourou FY, Hossain AB, Morrison HW, Gallitano AL. University of Arizona; Arizona State University; Syracuse University; Arizona Alzheimer's Consortium.

47. **MEMORY AND THE HIPPOCAMPAL SYSTEM IN AGING ADULTS WITH AUTISM SPECTRUM DISORDER: LONGITUDINAL VERSUS CROSS-SECTIONAL FINDINGS.** Pagni BA, Walsh MJM, Sullivan G, Ofori E, Alvar J, Chen K, Braden BB. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

48. **ASSOCIATIONS BETWEEN DIFFERENT FDG PET INDICES AND CLINICAL RATINGS IN COGNITIVELY UNIMPAIRED OLDER ADULTS.** Protas HD, Chen K, Chen Y, Luo J, Raichle M, Morris JC, Benzinger T, Goyal M, Vlassenko A, Reiman EM, Su Y. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona State University; Washington University School of Medicine; Arizona Alzheimer's Consortium.

49. **PHYSICAL ACTIVITY IS ASSOCIATED WITH INCREASED RESTING-STATE FCMRI IN NETWORKS PREDICTIVE OF COGNITIVE DECLINE IN CLINICALLY UNIMPAIRED OLDER ADULTS.** Pruzin JJ, Klein H, Rabin JS, Schultz AP, Kirn DR, Yang H-S, Buckley RF, Chou H-C, Scott MR, Properzi M, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP. Massachusetts General Hospital, Harvard Medical School; Banner Alzheimer's Institute; Sunnybrook Health Sciences Centre, Toronto; University of Toronto; Brigham and Women's Hospital; University of Melbourne; Arizona Alzheimer's Consortium.

50. **APOE4 DISRUPTS NEURON-TO-ASTROCYTE LIPID CLEARANCE.** Qi G, Mi Y, Shi X, Gu H, Brinton RD, Yin F. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

51. **AMYLOID-B PLAQUES IN THE OLFACTORY BULB IN RELATION TO THE PATHOLOGIC PROGRESSION OF THAL AMYLOID STAGE IN ALZHEIMER'S DISEASE.** Serrano GE, Russell A, Vargas D, Intorcia A, Walker J, Glass M, Arce R, Oliver J, Papa J, Nelson C, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

52. **MAPPING OF SARS-COV-2 BRAIN INVASION AND HISTOPATHOLOGY IN COVID-19 DISEASE.** Serrano GE, Walker JE, Arce R, Glass MJ, Vargas D, Sue LI, Intorcia AJ, Nelson CM, Oliver J, Papa J, Russell A, Suszczewicz KE, Borja CI, Sahoo MK, Zhang H, Solis D, Montine TJ, Zehnder JL, Pinsky BA, Dickson DW, Deture M, Bonfitto A, Huentelman M, Piras I, Beach TG. Banner Sun Health Research Institute; Stanford University; Mayo Clinic Florida; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

53. **WHOLE SOMA DISSOCIATED SUSPENSION ANALYSIS IN HUMAN BRAIN NEURODEGENERATIVE DISEASE: A PILOT STUDY.** Serrano G, Walker J, Intorcia A, Glass M, Arce R, Piras I, Talboom J, Oliver J, Nelson C, Papa J, Cutler B, Sue L, Lue L-F, Huentelman M, Beach TG. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

54. **A 3D INTERACTIVE REPRESENTATION OF LOCUS COERULEUS NUCLEUS MORPHOLOGY IN AGED MACAQUE MONKEYS.** Sinakevitch I, Deer C, McDermott K, Khattab S, Gray DT, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

55. **THE CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM – A PLATFORM FOR PRE-COMPETITIVE DATA SHARING, STANDARDIZATION, AND ANALYSIS TO SUPPORT QUANTITATIVE TOOLS FOR AD DRUG DEVELOPMENT.** Sivakumaran S, Cui Z, Burton J, Priest E, Lau C, White H, Romero K, Karten Y. Critical Path Institute; Arizona Alzheimer's Consortium.

56. **POSTMORTEM INTERHEMISPHERIC DIFFERENCES IN THE DISTRIBUTION PATTERN OF AD-TYPE TAUOPATHY.** Tremblay C, Serrano GE, Sue L, Intorcia A, Walker J, Arce R, Nelson C, Vargas D, Suszczewicz K, Cline M, Borja C, Hemmingsen S, Qiji S, Fleisher AS, Pontecorvo MJ, Montine TJ, Beach TG. Banner Sun Health Research Institute; Avid Radiopharmaceuticals; Stanford University; Arizona Alzheimer's Consortium.

57. **CHRONIC PIAL CEREBRAL ARTERIAL FUNCTION AND COGNITIVE FUNCTION FOLLOWING MILD-MODERATE TRAUMATIC BRAIN INJURY IN RATS.** Truran S, Karamanova N, Young C, Griffiths D, Law LM, Emerson H, Gonzales R, Reaven PD, Quarles CC, Lifshitz J, Migrino R. Phoenix VA Health Care System; Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

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59. **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.** Van Keuren-Jensen K, Alsop E, Antone J, Readhead B, Wang Q, Beach TG, Serrano GE, Liang W, Dudley J, Reiman EM. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

60. **ALZHEIMER'S DISEASE PREVENTION WITHIN REACH BY 2025: TARGETED-RISK-AD-PREVENTION (TRAP) STRATEGY.** Vitali F, Branigan GL, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

61. **ASYMPTOMATIC CAROTID ATHEROSCLEROSIS IS ASSOCIATED WITH INCREASED ALZHEIMER'S AND NON-ALZHEIMER'S DEMENTIA RISK.** Vitali F, Branigan GL, Arias JC, Nagae L, Reiman EM, Brinton RD, Weinkauf C. University of Arizona; University of Arizona College of Medicine; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

62. **MEASURING UP: A COMPARISON OF TAPESTATION 4200 AND BIOANALYZER 2100 AS MEASUREMENT TOOLS FOR RNA QUALITY.** Walker JE, Serrano G, Arce R, Oliver J, Intorcia A, Glass M, Nelson C, Vargas D, Suszczewicz K, Cline M, Borja C, Hemmingsen S, Qiji S, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

63. **DEVELOPING UNIVARIATE NEURODEGENERATION BIOMARKERS WITH LOW-RANK AND SPARSE SUBSPACE DECOMPOSITION.** Wang G, Wu J, Su Y, Caselli RJ, Reiman EM, Wang Y. Ludong University; Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

64. **DEEP LEARNING IDENTIFIES BRAIN TRANSCRIPTOMIC SIGNATURES ASSOCIATED WITH THE NEUROPATHOLOGICAL AND CLINICAL SEVERITY OF ALZHEIMER'S DISEASE.** Wang Q, Readhead B, Chen K, Su Y, Reiman EM, Dudley, JT. Arizona State University; Banner Alzheimer's Institute; Icahn School of Medicine at Mount Sinai; Arizona Alzheimer's Consortium.

65. **EFFECTS OF AEROBIC EXERCISE ON COGNITION AND IMAGING BIOMARKERS IN OLDER ADULTS WITH ALZHEIMER'S DISEASE DEMENTIA.** Yu F, Zhang L, Nelson N, Mathiason M, Salisbury D, Gunter J, Jones D, Botha H, Jack C. Arizona State University; University of Minnesota; University of Saint Thomas; Mayo Clinic Rochester.

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68. **EVALUATING THE IMPACT OF ALZHEIMER'S DISEASE RISK FACTORS ON REAL-WORLD AUTOBIOGRAPHICAL THOUGHT – A MIND WINDOW STUDY.** Andrews EA, Grilli MD, Abraham FF, Mason DL, Raffaelli Q, Mehl MR, Allen JJB, Andrews-Hanna JR. University of Arizona; Arizona Alzheimer's Consortium.

69. **AGE IMPACTS THE BURDEN THAT REFERENCE MEMORY IMPARTS ON AN INCREASING WORKING MEMORY LOAD.** Bernaud VE, Hiroi R, Poisson ML, Castaneda AJ, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

70. **A LONGITUDINAL STUDY OF THE UNIQUE GUT MICROBIOTA OF 3XTG-AD MICE MODELING KEY AD PATHOLOGIES.** Borsom EM, Keefe CR, Hirsch AH, Orsini GM, Conn K, Jaramillo SA, Testo G, Palma Avila M, Bolyen E, Dillon MR, Lee K, Caporaso JG, Cope EK. Northern Arizona University; Arizona Alzheimer's Consortium.

71. **INFLUENCE OF FECAL MICROBIOTA TRANSPLANTATION ON GUT MICROBIOTA COMPOSITION AND NEUROINFLAMMATION OF 3XTG-AD MICE.** Borsom EM, Keefe CR, Hirsch AH, Orsini GM, Conn K, Jaramillo SA, Bolyen E, Dillon MR, Lee K, Caporaso JG, Cope EK. Northern Arizona University; Arizona Alzheimer's Consortium.

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73. **AGE-RELATED DIFFERENCES IN RESTING-STATE COGNITION: AN ADAPTED THINK-ALOUD PARADIGM.** Burns H, Griffith C, Cegavske C, Andrews E, Nye P, Vega-Reid J, Strojek D, Spillman A, Raffaelli Q, Wilcox R, Ryan L, Grilli M, Andrews-Hanna J. University of Arizona; Arizona Alzheimer's Consortium.

74. **METFORMIN IR VS XR: A RETROSPECTIVE OBSERVATIONAL STUDY ON AD PROTECTION.** Butler R, Hallquist A, Torrandell G, Rodgers KE. University of Arizona; Arizona Alzheimer's Consortium.

75. **STRUCTURAL STUDY OF REGULATED INTRAMEMBRANE PROTEOLYSIS OF THE P75NTR BY γ-SECRETASE.** Chan KY, Poh YP, Chiu PL. Arizona State University

76. **UTILIZING TRACTOGRAPHY-GUIDED THETA BURST STIMULATION TO IMPROVE MEMORY PERFORMANCE IN MILD COGNITIVE IMPAIRMENT.** Chen AY, That VT, Ugonna C, Liu Y, Nadel L, Chou Y. University of Arizona; Arizona Alzheimer's Consortium.

77. **TOWARD MICROSTRUCTURAL MR MARKERS IN ALZHEIMER'S: A POST-MORTEM STUDY.** Comrie CJ, Ahsan Z, Beach TG, Serrano GE, Hutchinson EH. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

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79. **AMYLOID-B ANALYSIS FROM MICRODISSECTED HUMAN BRAIN CELLS USING MICROFLUIDICS AND MASS SPECTROMETRY.** Cruz Villarreal J, Egatz-Gomez A, Noutsios GT, Sandrin TR, Coleman PD, Ros A. Arizona State University; Arizona Alzheimer's Consortium.

80. **FIBRILLIN-1 DEFICIENCY ACCELERATES CEREBROVASCULAR AGING, LEAVING THE BRAIN MORE VULNERABLE TO TBI.** Curry T, Bromberg CE, Saber M, Rowe RK, Gonzales R, Esfandiarei M, Currier Thomas T. University of Arizona College of Medicine-Phoenix; Midwestern University; Barrow Neurological Institute at Phoenix Children's Hospital; University of Colorado Boulder; Arizona Alzheimer's Consortium.

81. **IDENTIFICATION OF RETINOBLASTOMA BINDING PROTEIN 7 (RBBP7) AS A MEDIATOR AGAINST TAU ACETYLATION AND SUBSEQUENT NEURONAL LOSS IN ALZHEIMER'S DISEASE AND RELATED TAUOPATHIES.** Dave N, Vural A, Piras IS, Winslow W, Surendra L, Winstone JK, Beach TG, Huentelman MJ, Velazquez R. Arizona State University; Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

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86. **LEGAL IMPLICATIONS OF USING ARTIFICIAL INTELLIGENCE TO PREDICT PRE-SYMPTOMATIC ALZHEIMER'S RISK.** Ghaith S, Marchant GE, Lindor RA. Mayo Clinic; Arizona State University.

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88. **TDP-43 EXPRESSION IN DEMENTIA-RELEVANT CIRCUITS CAUSES AXONAL DEGENERATION AND BEHAVIORAL DEFICITS IN DROSOPHILA.** Godfrey RK, Bjork RT, Williams C, Hala'ufia G, Cowell HB, Lehmkuhl EM, Alsop E, Jensen K, Zarnescu DC. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

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90. **MISLOCALIZED EXPRESSION OF THE NUCLEAR PORE COMPLEX PROTEINS NUP153, -93, AND -214 IN ALZHEIMER'S DISEASE BRAINS.** Goras M, Brokaw D, Delvaux E, Nolz JD, Mastroeni D, Coleman P. Arizona State University; Arizona Alzheimer's Consortium.

91. **AGE-RELATED DIFFERENCES IN THE EFFECTS OF AN SSRI ON COGNITION IN FEMALE RATS.** Hanson TC, Hiroi R, Koebele SV, Bernaud VE, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

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93. **METABOLIC PROFILING OF NEOCORTICAL TISSUE DISCRIMINATES ALZHEIMER'S DISEASE FROM MILD COGNITIVE IMPAIRMENT, HIGH PATHOLOGY CONTROLS, AND NORMAL CONTROLS.** Jasbi P, Shi X, Chu P, Elliott N, Hudson H, Jones D, Serrano G, Chow B, Beach T, Liu L, Jentarra G, Gu H. Arizona State University; Yale School of Medicine; Midwestern University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

94. **NEUROIMAGING CORRELATES OF FINE MOTOR FUNCTION DURING FINGER TAPPING IN HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT COHORTS: A SAGE-FMRI STUDY.** Keeling EG, Prigatano GP, Stokes AM. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

95. **IMPLEMENTATION OF MULTI-CONTRAST, MULTI-ECHO SAGE-FMRI IN AGING AND ALZHEIMER'S DISEASE.** Keeling EG, Bergamino M, Burke AD, Steffes L, Stokes AM. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

96. **USING DIFFUSION TENSOR IMAGING TO IDENTIFY WHITE MATTER CORRELATES OF MOTOR ACQUISITION AND VISUOSPATIAL PROCESSES IN COGNITIVELY-INTACT OLDER ADULTS.** Lingo VanGilder J, Bergamino M, Hooyman A, Beeman SC, Schaefer SY. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

97. **SYNTHESIS OF HIGH AFFINITY DYRK1A PROTACS TOWARDS TREATMENT OF ALZHEIMER'S DISEASE AND SARS-COV-2.** Maddern S, Schofield K, Chavez T, Shaw A, Hulme C. University of Arizona; Arizona Alzheimer's Consortium.

98. **THE RELATIONSHIP BETWEEN HIPPOCAMPAL VOLUME AND MEDIAL TEMPORAL LOBE WHITE MATTER TRACT INTEGRITY IN OLDER ADULTS.** Matijevic S, Haaheim L, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

99. **AGE-ASSOCIATED ALTERATIONS IN LOCUS COERULEUS NEURONAL, GLIAL CELL, AND VASCULAR ELEMENTS IN COGNITIVELY ASSESSED AGED MACAQUE MONKEYS.** McDermott K, Sinakevitch I, Gray DT, Khattab S, Pyon WS, Barnes CA. University of Arizona; University of Florida, Gainesville; Arizona Alzheimer's Consortium.

100. **LONELINESS AND AGING: MANIFESTATIONS OF LONELINESS IN EVERYDAY CONVERSATIONS AMONG OLDER ADULTS.** McVeigh KM, Mehl MR, Wank AA, Polsinelli AJ, Moseley S, Glisky EL, Grilli MD. University of Arizona; Indiana University; Minnesota Epilepsy Group, St. Paul, MN; Arizona Alzheimer's Consortium.

101. **STRUCTURAL AND FUNCTIONAL ANALYSIS OF P47 COFACTOR BINDING ON THE P97 DISEASE MUTANT.** Nandi P, Li S, Coulumbres RC, Wang F, Williams DR, Malyutin AG, Poh Y, Chou TF, Chiu PL. Arizona State University; California Institute of Technology.

102. **NEGATIVE CORRELATIONS BETWEEN GLOBAL MEAN-CORTICAL AND REGIONAL HIPPOCAMPAL AMYLOID-B PLAQUE BURDEN BASED ON PIB AND FLORBETAPIR PET MEASUREMENTS.** Narnur P, Corkill B, Chen Y, Luo J, Lee W, Reiman EM, Su Y, Chen K. University of Arizona; University of Arizona College of Medicine Phoenix; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium

103. **ENOTYPIC EFFECT ON MICROBIOME DEVELOPMENT AND COLONIZATION IN A DROSOPHILA MELANOGASTER MODEL OF PARKINSON'S DISEASE.** Olson SC, Call GB. Midwestern University; Arizona Alzheimer's Consortium.

104. **INVESTIGATING HOW UTILIZING DETAILS AND HOLISTIC PIECES OF INFORMATION DIFFER BETWEEN YOUNGER AND OLDER E4 CARRIERS AND NONCARRIERS.** Palmer JM, Grilli MD, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

105. **PROGESTOGENS IMPACT COGNITION DURING THE TRANSITION TO MENOPAUSE IN THE RAT: DISSOCIATION OF PROGESTOGEN- AND MEMORY-TYPE.** Peña VL, Koebele SV, Northup-Smith S, Woner VE, Melikian R, Patel S, Bulen HL, Ladwig D, Dyer CA, Mayer LP, Bimonte-Nelson HA. Arizona State University; FYXX Foundation; Arizona Alzheimer's Consortium

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107. **EVALUATION OF PHOSPHO-TAU PATHOLOGY IN THE HIPPOCAMPUS AT 6 MONTHS FOLLOWING EXPERIMENTAL TRAUMATIC BRAIN INJURY IN RATS.** Rajaboina B, Mian E, Hair C, Baun J, Zurhellen C, Adelson PD, Thomas TC. Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona-COM-Phoenix; Arizona State University; NeuroScience Associates, Knoxville, TN; U.S. Department of Veterans Affair, Arizona; Arizona Alzheimer's Consortium.

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109. **THE DEVELOPMENT OF A HIGHLY SELECTIVE, WELL-TOLERATED AND ORALLY BIOAVAILABLE INHIBITOR OF DYRK1A FOR TREATMENT OF ALZHEIMER'S DISEASE.** Rokey S, Foley C, Velasquez R, Dunckley T, Shaw A, Meechoovet B, Hulme C. University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

110. **CHARACTERIZATION OF SPATIAL WORKING AND REFERENCE MEMORY ACROSS THE ADULT LIFESPAN IN A TRANSGENIC RAT MODEL OF ALZHEIMER'S DISEASE.** Ruhland AM, Bulen HL, Bernaud VE, Peña VL, Koebele SV, Northup-Smith SN, Opachich Z, Manzo AA, Valenzuela Sanchez M, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

111. **SEX, AGE, AND REGION-DEPENDENT CHANGES IN ASTROCYTE ACTIVATION IN A BEHAVIORALLY RELEVANT CIRCUIT FOLLOWING EXPERIMENTAL TBI IN RAT.** Sabetta Z, Condon A, Krishna G, Adelson PD, Thomas TC. University of Arizona; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; Arizona State University; University of Bath, England; Arizona Alzheimer's Consortium.

112. **NOVEL FRAGMENTS TARGETING DYRK1A AS PLATFORM CHEMOTYPES FOR AD DRUG DISCOVERY.** Schofield K, Chavez T, Gokhale V, Shaw A, Hulme C. University of Arizona; Arizona Alzheimer's Consortium.

113. **DEEP RESIDUAL INCEPTION ENCODED-DECODER NETWORK FOR AMYLOID PET HARMONIZATION.** Shah J, Ghisays V, Luo J, Chen Y, Lee W, Li B, Benzinger TLS, Reiman EM, Chen K, Su Y, Wu T. Arizona State University; Mayo Clinic; Banner Alzheimer's Institute; Washington University in St Louis; Arizona Alzheimer's Consortium.

114. **PREVENTION OF WEIGHT GAIN AND EXPRESSION OF KEY MARKERS OF ALZHEIMER'S DISEASE IN HIGH FAT-HIGH SUCROSE-FED MALE MICE WITH GENISTEIN AND/OR EXERCISE.** Shah J, Kubinski A, St Aubin C, Banayat T, Broderick TL, Shim M, Al-Nakkash L. Midwestern University; Arizona Alzheimer's Consortium.

115. **AGE-RELATED REGIONAL NETWORK COVARIANCE PATTERN OF GRAY TO WHITE MATTER CONTRAST IN HEALTHY MIDDLE-AGED TO OLDER ADULTS.** Smith SG, Bharadwaj PK, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

116. **INTERACTION OF WMH VOLUME AND SEX DIFFERENCES ON HEART RATE RESPONSE TO AEROBIC EXERCISE IN HEALTHY MIDDLE-AGED TO OLDER ADULTS.** Song H, Raichlen DA, Klimentidis YC, Bharadwaj PK, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

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118. **BODY MASS INDEX-RELATED REGIONAL COVARIANCE PATTERNS OF WHITE MATTER MICROSTRUCTURE IN HEALTHY OLDER ADULTS.** Van Etten EJ, Bharadwa PK, Raichlen DA, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

119. **INFILTRATION OF PERIPHERAL IMMUNE CELLS IN HUMAN BRAIN DURING MID-LIFE.** Van Rossum H, Mishra A, Delatorre N, Padilla-Rodriguez M, Shang Y, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

120. **CLOSER CORRELATIONS BETWEEN FLORBETAPIR PET MEASUREMENTS OF AMYLOID PLAQUE BURDEN USING A CEREBRAL WHITE MATTER REFERENCE REGION AND ALZHEIMER'S DISEASE-RELATED HYPOMETABOLISM**. Wang MS, Bi TB, Jing NY, Ausdemore JC, Kramer HL, Chen Y, Luo J, Weiner MW, Landau SM, Jagust WJ, Su Y, Reiman EM, Chen K. University of Arizona, College of Medicine – Phoenix; Emory University; Square, Inc.; University of Southern California; Creighton University; Banner Alzheimer's Institute; San Francisco Veterans Affairs Medical Center; University of California, San Francisco; University of California Berkeley; Lawrence Berkeley National Laboratory; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

121. **A DROSOPHILA MODEL OF FTD BASED ON C9ORF72 HEXANUCLEOTIDE REPEAT EXPANSIONS.** Williams C, Godfrey K, Cowell H, Hala'ufia G, Zarnescu D. University of Arizona; Arizona Alzheimer's Consortium.

122. **GLYPHOSATE INFILTRATES THE BRAIN AND MAY BE A RISK FACTOR FOR ALZHEIMER'S DISEASE.** Winstone J, Pathak KV, Sharma S, Donnay M, White J, Huentelman M, Pirrotte P, Velazquez R. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

123. **FEDERATED MORPHOMETRY FEATURE SELECTION FOR HIPPOCAMPAL MORPHOMETRY ASSOCIATED BETA-AMYLOID AND TAU PATHOLOGY.** Wu J, Dong Q, Zhang J, Su Y, Wu T, Reiman EM, Ye J, Lepore N, Chen K, Thompson PM, Wang Y. Arizona State University; Beijing Institute of Technology; Banner Alzheimer's Institute; Children's Hospital Los Angeles; University of Michigan; University of Southern California; Arizona Alzheimer's Consortium.

124. **PREDICTING BRAIN AMYLOID USING MULTIVARIATE MORPHOMETRY, SPARSE CODING AND CORRENTROPY.** Wu J, Dong Q, Gui J, Zhang J, Su Y, Chen K, Ye J, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Beijing Institute of Technology; Banner Alzheimer's Institute; Mayo Clinic Arizona; University of Michigan; Arizona Alzheimer's Consortium.

125. **PREDICTION OF BRAIN AMYLOID BURDENS WITH SIGNED DISTANCE FIELD-BASED GEOMETRIC DEEP LEARNING.** Yang Z, Su Y, Chen K, Thompson PM, Reiman EM, Wang Y. Arizona State University; Banner Alzheimer's Institute; University of Southern California; Arizona Alzheimer's Consortium.

126. **EFFECTS OF CHRONIC, HIGH-DOSE MINOCYCLINE TREATMENT ON COGNITIVE PERFORMANCE IN AGING RATS.** Young KF, Zempare MA, Dalmendray AL, Gregolynskyj A, Chawla MK, Guzowski JF, Barnes CA. University of Arizona; University of California at Irvine; Arizona Alzheimer's Consortium.

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Oral Presentation
Abstracts

A NOVEL TAU-BASED RHESUS MONKEY MODEL OF ALZHEIMER'S PATHOGENESIS.

Kordower JH, Beckman D, Chakrabarty P, Donis-Cox K, Morrison JH. Arizona State University; University of California Davis; University of Florida, Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a devastating condition with no effective treatments, with promising findings in rodents failing to translate into successful therapies for patients.

Methods: Targeting the vulnerable entorhinal cortex (ERC), rhesus monkeys received two injections of an adeno-associated virus expressing a double tau mutation (AAV-P301L/S320F) in the left hemisphere, and control AAV-green fluorescent protein in the right ERC. Noninjected aged-matched monkeys served as additional controls.

Results: Within 3 months we observed evidence of misfolded tau propagation, similar to what is hypothesized to occur in humans. Viral delivery of human 4R-tau also coaptates monkey 3R-tau via permissive templating. Tau spreading is accompanied by robust neuroinflammatory response driven by TREM2+ microglia, with biomarkers of inflammation and neuronal loss in the cerebrospinal fluid and plasma. At six months, the model evolved to include neuronal loss in the subiculum and hippocampal subfields, the progression of AT8 pretangle pathology to thioflavin S neurofibrillary tangle formation, and permissive templating across the entorhinal cortex connectome to include retrospenial cortex, contralateral entorhinal cortex and multiple neocortical regions. The tauopathy was easily discerned in vivo using tau PET ligands.

Conclusions: These results highlight the initial stages of tau seeding and propagation in a primate model, a more powerful translational approach for the development of new therapies for AD.

APOE4 DISRUPTS NEURON-ASTROCYTE COUPLING OF LIPID METABOLISM. Qi G, Mi Y, Shi X, Gu H, Brinton RD, Yin F. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Apolipoprotein E (ApoE) is a lipid-binding protein that transports lipids across organs in the periphery, and between different cell types in the brain. As the greatest genetic risk factor for late-onset Alzheimer's disease (AD), the ε4 variant of ApoE (ApoE4) is known to not only impair amyloid-β clearance and promote its aggregation, but also perturb lipid homeostasis and energy metabolism in the brain. While accumulating evidence revealed inter-cellular coordination of lipid transport and clearance between neuron and astrocyte, the mechanistic role of ApoE4 in these processes as it relates to AD etiology is poorly understood. Moreover, since ApoE4 disrupts mitochondrial function, a central player in both lipid synthesis and degradation, the question arises as to whether and how ApoE regulation of lipid metabolism is mechanistically connected with the distinctive properties between neuronal- and astrocytic mitochondria.

Methods: Here, using individual- and co-culture models of primary neurons and astrocytes, and hippocampal slices from the humanized ApoE3 or ApoE4 knockin mice, we investigated the role of ApoE4 in regulating key mechanisms controlling neuron-astrocyte coupling of lipid metabolism, from neuronal storage of fatty acids (FAs) in lipid droplets (LDs), to the mobilization of neuronal LDs and transport of FAs to astrocytes, and eventually to the oxidative degradation of FAs in astrocytes. In addition, by generating novel mouse models that combine ApoE polymorphism with deficits in astrocytic FA degradation, we tested whether ApoE4 modifies AD-related phenotypes by perturbing lipid homeostasis in the brain.

Results: Compared to ApoE3 controls, ApoE4 decreases the sequestration of neurotoxic FAs in neuronal LDs, elevates free FA levels and impairs mitochondrial- and neuronal dysfunction. Neuronal LDs are eliminated upon astrocyte exposure and lipids within are transferred to astrocytes together with ApoE, with ApoE4 in either neurons or astrocytes diminishing the transport efficiency. In ApoE4 astrocytes, increased mitochondrial fragmentation underlies a metabolic shift towards enhanced glucose metabolism and reduced FA β-oxidation, which subsequently elicits lipid accumulation in astrocytes and the hippocampus. Importantly, diminished capacity of ApoE4 astrocytes in eliminating neuronal lipids and degrading FAs underlies their compromised metabolic- and synaptic support to neurons. Finally, we show that AD-related metabolic, inflammatory, and neurodegenerative abnormalities induced by astrocytic FA metabolic dysfunction was further exacerbated by ApoE4.

Conclusions: Collectively, our findings reveal a disruptive role of ApoE4 in regulating brain lipid metabolism and bioenergetic equilibrium coupled across neurons and astrocytes, and they suggest that ApoE4 brains are more vulnerable to disrupted lipid metabolism. Such a previously unappreciated mechanism could underlie the accelerated lipid dysregulation, worsened energy deficits and increased AD risk for those who carry the ApoE4 allele(s).

IMPROVED COMPARABILITY BETWEEN MEASUREMENTS OF MEAN CORTICAL AMYLOID PLAQUE BURDEN DERIVED FROM DIFFERENT PET TRACERS USING MULTIPLE REGIONS-OF-INTEREST AND MACHINE LEARNING. Chen K, Ghisays V, Luo J, Chen Y, Lee W, Benzinger TLS, Wu T, Reiman EM, Su Y. Banner Alzheimer's Institute; Washington University, St. Louis; Arizona State University; Arizona Alzheimer's Consortium.

Background: The conversion of standard uptake value ratios (SUVRs) to Centiloid units using previously described methods has partially but not completely improved the ability to compare measurements of mean cortical amyloid plaque burden, classify positive versus negative amyloid PET scans, assess changes over time, and evaluate amyloid-modifying treatment effects using different radiotracers. Here, we demonstrate improved harmonization between PiB and florbetapir (FBP) PET measurements of mean cortical SUVRs (mcSUVRs) using multiple regions-of-interest (ROIs) and machine learning algorithms.

Methods: PiB and FBP PET image pairs from 91 subjects in the Open Access Series of Imaging Studies (https://www.oasis-brains.org/) were used as the training set to optimize the algorithms to generate each subject's pseudo-PiB mcSUVR measurements from his or her FBP multi-ROI SUVRs . PiB and FBP image pairs from 46 subjects in the Avid-related Centiloid Project (www.gaain.org/centiloid-project) were then used as the test set to compare Pearson's correlation coefficients (r) between the pseudo and actual PiB mcSUVR measurements using our approach to that used in the Centiloid method. SUVRs with cerebellar reference were extracted from multi-ROIs using FreeSurfer with partial volume correction. Pseudo mcSUVRs were generated using ensemble regression, partial least square regression (PLSR) and artificial neural network (ANN) separately, and their correlations with the actual PiB mcSUVR were compared to the PiB-FBP correlation on Centiloid in both training and test sets.

Results: In the training set, the Centiloid based PiB-FBP correlation was r=0.904. An ANN with 7/6 neurons in the 1st/2nd hidden layers improved it to 0.987 ($p \leq 8.3e-12$) and PLSR to 0.973 ($p \leq 3.8e-5$). In the independent test set, ANN improved r to 0.981 from 0.927 ($p \leq 6.6e-4$) and PLSR to 0.964 ($p=0.011$). Ensemble regression did not improve r.

Conclusions: The ANN and PLSR algorithms mapping multi-ROI FBP SUVRs to PiB mcSUVR appear to increase the comparability between measurements of mean cortical amyloid plaque burden using different PET tracers. Additional studies are needed to demonstrate the generalizability to other amyloid PET tracers, clarify its comparability in distinguishing between positive and negative amyloid PET scans, demonstrate its value in longitudinal studies and clinical trials, and extend our approaches to different tau PET ligands.

THE CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM – A PLATFORM FOR PRE-COMPETITIVE DATA SHARING, STANDARDIZATION, AND ANALYSIS TO SUPPORT QUANTITATIVE TOOLS FOR AD DRUG DEVELOPMENT. Sivakumaran S, Cui Z, Burton J, Priest E, Lau C, White H, Romero K, Karten Y. Critical Path Institute; Arizona Alzheimer's Consortium.

Background: The primary objective of the pre-competitive Critical Path for Alzheimer's Disease (CPAD) consortium is to promote, support, and manage pre-competitive data and knowledge sharing from Alzheimer disease (AD) drug development stakeholders. Since the launch of the Industry Data Sharing Initiative, CPAD has acquired fluid and imaging biomarker-rich data sources for development of novel tools to quantify disease progression across the AD continuum. CPAD leverages these data to address drug development challenges in AD by developing regulatory-grade modeling and simulation tools that can convert these data into knowledge to improve strategies in ongoing or future drug development programs.

Methods: Patient-level data from contemporary Phase2/Phase3 AD clinical trials and observational studies are being acquired through formal data contribution agreements within CPAD, curated, mapped to CDISC standards, and integrated for analysis. The integrated data is being transformed to analysis ready subsets for development of a comprehensive set of disease progression models across the continuum of the disease. Models will characterize the time course of clinically relevant measures (ADAS-Cog, CDR-SB, other clinical assessment scales and biomarkers). Covariates including demographics, time from and to diagnosis, genetic status (APOE4), co-morbidities and medication use will be assessed using non-linear mixed effects methods. Monte Carlo simulations will be performed to compare the statistical power by sample size in trials with and without enrichment using relevant covariates.

Results: The CPAD clinical trial repository currently contains 42 studies with 21,078 individual anonymized patient records. CPAD has acquired contemporary AD clinical trial datasets focused on early stages of the disease, providing a rich source of key amyloid, tau and neurodegeneration biomarkers, assessed through magnetic resonance and positron emission tomography neuroimaging and through analysis of biofluids (plasma and cerebrospinal fluid). Model selection based on the log-likelihood ratio and goodness-of-fit plots will be used to select the model structure that most adequately describes the integrated database. Covariate analyses will be performed to identify variables that constitute relevant predictors of baseline severity and disease progression rates. Trial simulations for a therapeutic effect using standard drug effect models for symptomatic and disease-modifying effects will be conducted to estimate an optimal sample size when trials are enriched with a clinically relevant covariate.

Conclusions: The precompetitive end-to-end data acquisition and analysis efforts in CPAD are providing sponsors with regulatory grade tools to optimize AD trial design. This will provide confidence for the industry drug development teams to adapt these tools into their respective research and drug development efforts to accelerate and advance therapeutic innovation in AD.

MAPPING OF SARS-COV-2 BRAIN INVASION AND HISTOPATHOLOGY IN COVID-19 DISEASE. Serrano GE, Walker JE, Arce R, Glass MJ, Vargas D, Sue LI, Intorcia AJ, Nelson CM, Oliver J, Papa J, Russell A, Suszczewicz KE, Borja CI, Sahoo MK, Zhang H, Solis D, Montine TJ, Zehnder JL, Pinsky BA, Dickson DW, Deture M, Bonfitto A, Huentelman M, Piras I, Beach TG. Banner Sun Health Research Institute; Stanford University; Mayo Clinic Florida; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The coronavirus SARS-CoV-2 (SCV2) causes acute respiratory distress, termed COVID-19 disease, with substantial morbidity and mortality. As SCV2 is related to previously-studied coronaviruses that have been shown to have the capability for brain invasion, it seems likely that SCV2 may be able to do so as well. To date, although there have been many clinical and autopsy-based reports that describe a broad range of SCV2-associated neurological conditions, it is unclear what fraction of these have been due to direct CNS invasion versus indirect effects caused by systemic reactions to critical illness. Still critically lacking is a comprehensive tissue-based survey of the CNS presence and specific neuropathology of SCV2 in humans.

Methods: We conducted an extensive neuroanatomical survey of RT-PCR-detected SCV2 in 16 brain regions from 20 subjects who died of COVID-19 disease. Targeted areas were those with cranial nerve nuclei, including the olfactory bulb, medullary dorsal motor nucleus of the vagus nerve and the pontine trigeminal nerve nuclei, as well as areas possibly exposed to hematogenous entry, including the choroid plexus, leptomeninges, median eminence of the hypothalamus and area postrema of the medulla. Subjects ranged in age from 38 to 97 (mean 77) with 9 females and 11 males.

Results: Most subjects had typical age-related neuropathological findings. Two subjects had severe neuropathology, one with a large acute cerebral infarction and one with hemorrhagic encephalitis, that was unequivocally related to their COVID-19 disease while most of the 18 other subjects had non-specific histopathology including focal β-amyloid precursor protein white matter immunoreactivity and sparse perivascular mononuclear cell cuffing. Four subjects (20%) had SCV2 RNA in one or more brain regions including the olfactory bulb, amygdala, entorhinal area, temporal and frontal neocortex, dorsal medulla and leptomeninges. The subject with encephalitis was SCV2-positive in a histopathologically-affected area, the entorhinal cortex, while the subject with the large acute cerebral infarct was SCV2-negative in all brain regions.

Conclusions: Like other human coronaviruses, SCV2 can inflict acute neuropathology in susceptible patients. Much remains to be understood, including what viral and host factors influence SCV2 brain invasion and whether it is cleared from the brain subsequent to the acute illness.

OBSERVATIONAL AND INTERVENTIONAL STUDIES OF THE CONTRIBUTION OF THE GUT MICROBIOTA MICE MODELING ALZHEIMER'S DISEASE PATHOLOGIES. Borsom EM, Keefe CR, Hirsch AH, Orsini GM, Conn K, Jaramillo SA, Bolyen E, Dillon MR, Lee K, Caporaso JG, Cope EK. Northern Arizona University; Arizona Alzheimer's Consortium.

Background: The collective microbes and their genomes that inhabit the gastrointestinal tract, known as the gut microbiome, contribute to a myriad of host functions. The gut microbiome communicates bidirectionally with the brain via immune, neural, metabolic, and endocrine pathways, known collectively as the gut-brain axis. The gut-brain axis is suspected to contribute to the development of Alzheimer's disease (AD). We hypothesize that altered gut microbiota composition contributes to the development of AD pathologies and neuroinflammation. Further, we hypothesize that manipulation of the gut microbiota can alter development of AD pathologies and neuroinflammation via the gut microbiota-brain axis.

Methods: To determine whether the gut microbiota precedes or associates with AD pathologies, we performed a longitudinal study of the fecal, cecum, and ileum microbiome in 3xTg-AD mice modeling amyloidosis, tauopathy, and neuroinflammation associated with AD. Fecal samples were collected fortnightly from 4 to 52 weeks of age (n=57 3xTg-AD mice, n=71 wild-type, n=3198 fecal samples, n=369 ileum, colon, and cecum). To further elucidate the role of the gut-brain axis in AD, we performed fecal microbiota transplants (FMT) from 3xTg-AD mice that have developed amyloidosis and tauopathy (52-64 weeks), to young 3xTg-AD (n=5) or wild-type mice (n=10). Phosphate buffered saline (PBS) was gavaged into 3xTg-AD (n=5) and wild-type mice (n=10) as a control. For FMT, a fecal slurry from aged 3xTg-AD mice was prepared and given to experimental mice via oral gavage. At 8 weeks, mice were gavaged with FMT or PBS for 5 consecutive days, followed by fortnightly maintenance transplants for 24 weeks. The V4 region of the 16S rRNA gene was sequenced on the Illumina MiSeq. Data were analyzed using QIIME 2. Reverse transcriptase qPCR was used to assess microgliosis, astrocytosis, and Th1/Th2 inflammation in the hippocampus and colon.

Results: Our results show altered microbial communities in 3xTg-AD mice when compared to wild-type (p=0.001, pairwise PERMANOVA at 4, 24, and 50 weeks).Using q2-longitudinal, we determined Bacteroides and Turicibacter relative abundance increased over time while Lactobacillus abundance did not significantly change over time in 3xTg-AD mice (r-squared: 0.80; p=1.744259e-76). Gene expression of GFAP (astrogliosis marker) was increased in the colon of 3xTg-AD mice at 24 weeks compared to 52 weeks (p=0.009, Mann-Whitney,) and the hippocampus of 3xTg-AD mice at 52 weeks compared to 52 week WT mice (p=0.015, Mann-Whitney). In the interventional arm, FMT changed microbiome composition compared to control (PBS-treated) mice. *Bacteroides* were increased in 3xTg-AD and wild-type mice receiving FMT.

Conclusions: We have identified changes in the gut microbiota and immune response that may be predictive of the development of AD pathologies. Future studies using a multi-omic approach will assess strain-level features and functions of the gut microbiota in AD. These studies will contribute to our understanding of how features of the gut microbiota may contribute to AD development.

DYSREGULATION OF HOMOLOGS RETINOBLASTOMA BINDING PROTEIN (RBBP) 4 AND 7 IN THE CONTEXT OF ALZHEIMER'S DISEASE. Judd JM, Piras IS, Dave N, Mastroeni D, Huentelman MJ, Velazquez R. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Recently, we identified the retinoblastoma binding protein 7 (Rbbp7) as a mediator against tau pathology observed in Alzheimer's disease (AD) and related tauopathies. Indeed, in human post-mortem brain tissue, AD patients have significantly lower Rbbp7 mRNA expression in the middle temporal gyrus (mtg) compared to age-matched controls and Rbbp7 mRNA expression is negatively correlated with Braak staging (a measure of pathological tau inclusions). We also found evidence that rescuing Rbbp7 levels in mouse models of tauopathies reduces tau acetylation and phosphorylation, key steps leading to tau tangle pathology. Notably, Rbbp7 and Rbbp4 share 92% homology and are expressed in many shared complexes, including complexes implicated in diseased aging and neurodegeneration. Interestingly, decreases in Rbbp4 in the entorhinal cortex has been implicated in normal cognitive aging in both humans and rodent models. Given this homology, in the present study, we examined Rbbp4 mRNA expression levels in various regions of AD post-mortem brain tissue and its changes relative to Rbbp7.

Methods: We used two cohorts of post-mortem brain tissue obtained from the Arizona Study of Aging and Neurodegenerative Disorders/Brain and Body Donation Program. The first cohort included a total of 56 brain samples of young (n = 21, M = 35.4yrs), aged (n = 18, M = 80.7yrs) and AD (n = 17, M = 86.7yrs) patients. The brain area examined for the first cohort included the entorhinal (ent) cortex. The second cohort included a total of 187 brain samples (n = 89 AD, M = 84.66yrs; n = 98 age-matched controls, CTL, M = 84.98yrs) and the brain area examined included the mtg (Broadmann area 21). Subject age, gender, and postmortem autopsy intervals were not significantly different per groups. Rbbp4 mRNA expression was measured by microarray for both the ent cortex and mtg. In the mtg, Rbbp4 mRNA and neuropathological hallmarks were assessed including neuritic plaque density, Braak neurofibrillary staging, and brain weight correlations.

Results: Quantitative analysis revealed that Rbbp4 is significantly upregulated in the ent cortex of patients with AD relative to young and aged controls. Similarly, we found increased Rbbp4 mRNA expression in the mtg of the second cohort in AD patients. Further analysis of mtg tissue showed that Rbbp4 mRNA expression is positively correlated with neuritic plaque density in AD brains, and a non-significant positive correlation between Rbbp4 and Braak staging. Interestingly, we found that Rbbp4 and Rbbp7 are negatively correlated in AD post-mortem brain tissue, illustrating that as Rbbp4 goes up, the levels of Rbbp7 go down. There was no significant correlation between Rbbp4 and brain weight.

Conclusions: These results highlight a potential association of Rbbp4 in AD related pathologies. Future studies will investigate if the increase in Rbbp4 leads to a pathogenic decrease in Rbbp7 to compensate, further deciphering the role of the Rbbps' in the context of AD and related tauopathies.

EXTRACRANIAL CAROTID ATHEROSCLEROSIS CONTRIBUTIONS TO COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE RISK. Vitali F, Branigan GL, Arias JC, Nagae L, Edwards M, Bernstein A, Guzman G, Bruck D, Berman S, Leon L, Pacanowski J, Zhou W, Goshima K, Tan T-W, Taylor Z, Altbach M, Beach TG, Serrano GE, Trouard T, Reiman EM, Brinton RD, Weinkauf C. University of Arizona; University of Arizona College of Medicine; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Vascular contributions to cognitive impairment and dementia (VCID) have largely focused on intracranial small vessel disease and associated risk factors. In contrast, the potential impact of asymptomatic extracranial large vessel disease of the carotid arteries on Alzheimer's disease (AD) risk is poorly studied. The carotid arteries supply the majority of the blood to the brain and asymptomatic carotid disease has a prevalence as high as 10% in the population of those over 50 years of age. Using retrospective population-based studies, we found that ECAD is associated with a 20% and 39% increased risk for AD and non-AD dementia, respectively. Still more, we found that surgical treatment of ECAD significantly mitigates this risk.

Methods: To understand how ECAD may be affecting AD-related brain pathology we evaluated NFT, Aβ plaque and CAA burden in post-mortem brains from the Arizona Study of Aging and Neurodegenerative Disorders and Brain and Body Donation Program by histopathology.

Results: We found that ECAD is associated with significantly increased NFT burden, but not Aβ plaque and CAA. In our small, prospective trial to understand how ECAD affects the aging brain, we found that ECAD is associated with lower cognitive scores, decreased measures of brain white matter integrity, and decreased hippocampus and AD Signature brain volumes. In contrast, ECAD was not associated with measures of cerebral small vessel disease.

Conclusions: These data are relevant because they indicate that so called *asymptomatic* carotid stenosis may be an underappreciated but treatable risk factor for AD and cognitive impairment. Still more, they build on previous data that show ECAD is being undertreated clinically, as no evaluation or treatment is directed toward cognitive outcomes.

ULTRASOUND-ASSISTED LUMBAR PUNCTURE IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS RESEARCH: A PILOT STUDY. Goldfarb D, Viramontes D, Callan M, Liebsack C, Goddard M, Reade M, Malek-Ahmadi MH, Weidman D, Tsai PH, Wu T, Grimsman J, Atri A. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Banner University Medical Center; Harvard Medical School; Brigham and Women's Hospital; Arizona Alzheimer's Consortium.

Background: Lumbar puncture (LP) and collection of cerebrospinal fluid (CSF) are increasingly essential in Alzheimer's disease and related dementias (ADRD) research. Ultrasound-assisted lumbar puncture (Us-LP) has not been studied in ADRD research and could improve LP success rates through more accurate anatomical site selection, precise planning, and individualized intra-procedure adjustments. This pilot study assessed the feasibility, utility, and tolerability of Us-LP in ADRD research.

Methods: LP clinician-researchers from ADRD centers completed simulation-based Us-LP training using the Philips Lumify system, a portable hand-held transducer connecting to a tablet. Thereafter, clinician-researchers had the option to use Us-LP during research LPs. Participant demographics and attitudes about LP were obtained prior to LP. The clinician-researchers completed a post-LP questionnaire assessing procedural details, choices, and LP performance.

Results: Following training, four clinician-researchers implemented Us-LP into their practices. Between August 2019-March 2020, 58 research participants underwent LP. Clinician-researchers used Us-LP on 37/58 (64%) participants. Compared to conventional-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 also 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.

Conclusions: Training clinician-researchers in Us-LP and implementing portable hand-held Us-LP for ADRD research studies demonstrated feasibility, utility and tolerability. Pilot data indicated that 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 ADRD research will improve LP success rates, tolerability, and participant willingness to undergo LP. Improving these factors will accelerate CSF biomarker, aging and ADRD research. Furthermore, with potential availability of AD disease-modifying treatments in the coming years, LP and CSF collection are likely to play a crucial role in patient selection for treatment.

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. Van Keuren-Jensen K, Alsop E, Antone J, Readhead B, Wang Q, Beach TG, Serrano GE, Liang W, Dudley J, Reiman EM. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Single cell assessments of gene dysregulation in Alzheimer's disease (AD) compared with matched healthy elderly controls are proving to be useful datasets for understanding AD dementia at the cellular level. Our resource, which will be made publicly available, will include multiple brain regions (frontal, temporal, parietal, occipital, hippocampus CA1 and entorhinal cortex) and technologies (single nuclei transcriptomics and laser capture microdissection) to achieve integration and validation of the most relevant vulnerabilities and changes associated with pathogenesis.

Methods: Superior frontal gyrus was dounce homogenized 10-15 times. Homogenate was passed through a 70 µm 1.5 ml mini strainer and centrifuged at 500 rcf for 5 minutes at 4ºC and washed. Nuclei pellets were resuspended in 1 ml of 1x wash/ resuspension buffer and centrifuged at 500 rcf for 5 minutes at 4ºC, resuspended in 500 ul of 1x wash/ resuspension buffer. Homogenate was incubated in 1-2 drops of NucBlue Live ReadyProbes Reagent and immediately sorted using the DAPI channel on ta Sony SH800S. Nuclei are sorted for 15,000 events directly into 10x 3' v3.1 RT Reagent Master Mix and immediately processed with the 10x Genomics Chromium Next GEM Single Cell 3' v3.1 kit. cDNA is amplified, and library constructed following the manufacturer's protocol.

Results: We completed the single nuclei sequencing of the 100 superior frontal gyrus samples. We identified 18 distinct clusters. Each subject contributed an average of 7259 cells with an average of 4,105 genes detected per cell. A total of 32,777 genes are detected in >10 cells. We observe distinct differences in gene expression in each of the clusters when comparing AD and elderly control groups. We will discuss some of the differentially expressed genes and pathways dysregulated with disease.

Conclusions: We have high quality single nuclei data, have generated cell clusters and have performed preliminary data analyses. We will integrate these data with the other brain regions to identify unique and overlapping gene changes as well as vulnerabilities in cell types associated with dementia.

THE IMMEDIATE EARLY GENE EGR3 INFLUENCES EXPRESSION OF ALZHEIMER'S DISEASE GENE TREM2. Ozols AB, Marballi KK, Meyers KT, Beck KL, Shrourou FY, Hossain AB, Morrison HW, Gallitano AL. University of Arizona; Arizona State University; Syracuse University; Arizona Alzheimer's Consortium.

Background: Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is a cell-surface immune receptor on microglia that has recently been linked to Alzheimer's Disease (AD). Rare coding-region variations in the TREM2 gene increase the risk to develop AD up to 4.7 fold. However, almost nothing is known about the mechanisms that regulate Trem2 gene expression. Recent studies have identified the transcription factor Early growth response 3 (EGR3) as a key regulator of differentially expressed genes in AD. Single-cell transcriptomics of mouse and human brain show that the Egr3 gene is highly expressed in microglia. As an activity-dependent transcription factor, the immediate early gene EGR3 is a strong candidate for regulation of the Trem2 gene.

Methods: Electroconvulsive seizure (ECS) was used to activate immediate early gene expression in Egr3-deficient (Egr3-/-) and wildtype (WT) littermate mice. An expression microarray study was conducted to identify target genes regulated by EGR3 in the hippocampus. Quantitative real-time PCR (qRT-PCR) was performed to validate the microarray results for the gene Trem2. RNAscope in situ hybridization studies were performed to analyze the expression of Trem2 and Egr3 in the dentate gyrus (DG), CA1, and CA2/3 of the hippocampus in Egr3-/- and WT mice following ECS, compared with sham treatment. IBA1 antibody staining, a microglia specific marker, was used to identify the number of microglia in the hippocampi of WT and Egr3-/- mice. To investigate the possibility that EGR3 may directly regulate Trem2 expression, we searched the Trem2 promoter for transcription factor binding sites using the TFBind program.

Results: The results of our expression microarray study showed that Trem2 was differentially expressed in the hippocampus of Egr3-/- mice compared to their WT littermates. Our qRT-PCR studies support the initial finding that expression of Trem2 is deficient in Egr3-/- mice compared with WT controls following ECS. RNAscope in situ hybridization studies show that Trem2 and Egr3 co-localize in microglia cells, and levels of Trem2 and Egr3 expression are positively correlated in the hippocampus. Preliminary immunohistologic analyses suggest that Egr3-/- mice have reduced levels of hippocampal Trem2 expression compared to WT mice. However, the number of microglia is not reduced in Egr3-/- compared to WT mice, indicating that the reduction in Trem2 expression is not due to loss of the cells that express the gene. Analysis of transcription factor binding sites using the TFBind program revealed several high probability EGR3 binding sites in the mouse Trem2 promoter.

Conclusions: Together, these findings suggest the possibility that EGR3, a stimulation-responsive transcription factor, may directly regulate expression of the AD-associated gene Trem2.

THE MINDCROWD PROJECT: PROGRESS, COLLABORATION, AND ELECTRONIC COHORT RECRUITMENT IN THE TIME OF COVID-19. Huentelman MJ, Talboom JS, Schmidt AM, De Both MD, Naymik MA, Lewis CR, Hay M, Barnes CA, Glisky E, Ryan L. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: One of the challenges in human research is recruiting large and diverse cohorts that can adequately power robust results that accurately inform public health advice. To address this critical need, in 2013, we developed the MindCrowd project (at www.mindcrowd.org). MindCrowd is an internet-based research study that has recruited over 225,000 participants from across the world. Each participant provides basic demographic, lifestyle, health, and medical information in addition to completing standardized reaction time and verbal memory testing. Using MindCrowd's data, we have identified multiple factors associated with reaction time and memory test performance – some that were predicted and validate prior research and others that are novel and hypothesis-generating. MindCrowd partners with researchers across the country to facilitate recruitment and data sharing into their studies.

Methods: In this presentation, we will discuss multiple results from MindCrowd, including the current associations between demographic, lifestyle, health, and medical factors with reaction time and verbal memory, results from recent collaborations with researchers outside of MindCrowd that make use of MindCrowd for recruitment, and our efforts to improve on the diversity of MindCrowd during the COVID-19 pandemic.

Results: We confirmed several factors known to influence verbal memory and reaction time – such as age, educational attainment, and biological sex – and identified several novel associations – such as the interaction between biological sex and smoking status as a predictor of verbal memory performance. Through our collaborations, we have demonstrated a high correlation between in-lab and remote electronic testing for multiple task paradigms. In 2020, we showed an approximate doubling in the recruitment rate for Latino, Black / African American, and Mixed race participants.

Conclusions: Overall, our findings demonstrate the utility of electronic-based recruitment and study for the cost-effective generation of a large and diverse cohort for research. The validity of self-assessed and remote electronic-based testing results was high and well correlated with in-person results. During the restrictions of the pandemic, our internet-based approach demonstrated significant resiliency and effectiveness at recruiting underserved minority groups. Finally, we emphasize that electronic recruitment and study is an essential component of a human research program. The coupling of remote and in-person approaches affords several benefits more significant than either approach alone.

Arizona Alzheimer's Consortium
22nd Annual Scientific Conference

Poster Presentation
Abstracts

POSTER #1

THE TELOMERE PROTECTIVE PROTEIN RAP1 AND AN ISOFORM OF GLIAL FIBRILLARY ACID PROTEIN AFFECT GAMMA SECRETASE ACTIVITY IN A YEAST SYSTEM. Abel KN, Strash G, Carpenter R, Bae NS, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

Background: One pathological hallmark of Alzheimer's disease (AD) is the accumulation of amyloid beta (A**β**) peptides that form plaques in the brain. A**β** peptides are naturally produced by the sequential cleavage of the amyloid precursor protein (APP) by **β**-secretase then **γ**-secretase. The presenilins (PS1 or PS2) are the catalytic subunits of **γ**-secretase. Early onset, familial Alzheimer's disease (eFAD) is caused primarily by mutations in the genes encoding amyloid precursor protein (APP) or the presenilins, indicating a critical role for cerebral amyloidosis as the cause of at least some cases of AD. Mutations in these genes either increase the total A**β** levels or produce more insoluble A**β** peptide than the soluble form. How A**β** production in cells is controlled remains largely unknown. An isoform of the glial fibrillary acidic protein, GFAP**ε**, was shown to interact with PS1. Our lab discovered that the telomere protective protein RAP1 is able to form a ternary complex with GFAP**ε** and PS1. To test whether this interaction may have an effect on **γ**-secretase activity, we used a yeast **γ**-secretase system to avoid complications that may be caused by effects on **γ**-secretase or the expression of APP and **γ**-secretase subunits.

Methods: We developed two yeast strains with reporter genes for quantifying activity. These strains will have **γ**-secretase subunits expressed from plasmids. As a target for **γ**-secretase, we fused the APP fragment remaining after **β**-secretase cleavage (C99) to the yeast GAL4 transcriptional activator. In our strains, the GAL4 gene was deleted from the chromosome. The C99-GAL4 protein is imbedded in the plasma membrane, sequestering the GAL4 portion in the cytosol, and GAL4 responsive genes remain inactive. When **γ**-secretase cleaves C99, GAL4 will be freed from the membrane, translocate into the nucleus and activate reporter genes.

Results: Expression of both RAP1 and GFAP**ε** led to increased expression of GAL4-responsive genes, indicating an increase in **γ**-secretase activity. Neither protein alone altered the activity.

Conclusions: The RAP1 and GFAP**ε** interaction with PS1 increases **γ**-secretase in the yeast system, indicating a possible role for these proteins in regulating **γ**-secretase in human cells. Our system can also be used for screens to identify novel protein effectors of **γ**-secretase activity.

POSTER #2

NANOLIPOSOMAL TREATMENT REDUCES STROKE INJURY FOLLOWING MIDDLE CEREBRAL ARTERY OCCLUSION IN MICE. Ahmad S, Kindelin A, Truran S, Karamanova N, Lozoya M, Griffiths DR, Weissig V, Lifshitz J, Ducruet AF, Migrino RQ. Barrow Neurological Institute; Phoenix VA; Midwestern University; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Neuroprotective strategies for stroke are lacking leading to significant disability and death. Liposomes phospholipid particles are commonly used as molecular carriers of therapeutic agent cargos. We previously showed that cargo-less nanoliposomes (NL, <100 nm size particles) composed of phosphatidylcholine, cholesterol and monosialoganglioside (70:25:5 molar ratios) were previously shown to induce an antioxidant protective response in endothelial cells exposed to oxidative stress-mediated amyloid injury. We are testing the hypotheses that NL will preserve neuroblastoma cell viability in the setting of hypoxic injury and will reduce functional and histologic injury in mice following middle cerebral artery occlusion (MCAO).

Methods: SH-SY5Y neuroblastoma cells were exposed to 20-hour physoxic (5% oxygen) condition or hypoxic (1% oxygen) condition without or with NL (100 or 300 μg/mL). Viability was measured using calcein-AM fluorescence and SH-SY5Y gene expression of antioxidant proteins heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1) and superoxide dismutase 1 (SOD1) were measured by quantitative polymerase chain reaction. C57BL/6J mice were treated with saline (N=8) or NL (10000 ug/mL, N=7) while undergoing 60-minute MCAO followed by reperfusion. Day 2 post-injury neurologic impairment scoring was compared as well as post-mortem brain infarction size.

Results: Neuroblastoma cells showed reduced viability following hypoxia that was reversed by treatment with NL. NL increased gene expression of HO-1, NQO1 and SOD1 compared to untreated controls. NL-treated mice showed reduced neurologic function impairment and reduced brain infarct size compared to controls (18.8±2% versus 27.3±2.3%, p=0.017).

Conclusions: Cargo-less NL reduced functional and structural stroke injury in mice subjected to MCAO likely mediated in part through induction of an antioxidant stress response. NL is a candidate novel agent to mitigate stroke injury.

POSTER #3

AAC TOOLS WEBSITE. Amador RR, Bauer R, Parizek D, Saner D. Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: The AAC Data Explorer is a website created with the intention to inform users and visitors of the data collected by the Arizona Alzheimer's Consortium (AAC). This is a user-friendly platform that present information in several reports.

Methods: Most of these reports can be subdivided by different criteria. One example of such report is the enrollment report; which includes a list of patients with their year of enrollment, their last visit date, attrition year and the reasons for the discontinuation or dropped from the study, all these factors can be subdivided by different categories to include race, gender and enrollment type.

Results: The site also includes many summary reports, which provide total number of enrollees, division of participants from the clinical core or affiliated programs, number of active or inactive participants, autopsy consent counts and categories for the major diagnoses.

Conclusions: There are also other reports available along with documentation resources and several administrate application that include data elementary directories of the data collected by the consortium.

POSTER #4

DATA MANAGEMENT AND STATISTICAL CORE. Amador RR, Bauer R, Parizek D, Saner D. Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: The Data Management and Statistical Core (DMSC) serves as the liaison between all the collaborating sites that form the Arizona Alzheimer's Consortium (AAC). The AAC participates in the data collection of the Uniform Data Set (UDS) for the National Alzheimer's Coordinating Center (NACC). The DMSC responsibilities include data quality management, database creation, data distribution and the implementation of advance data processes.

Methods: The advance data processes include the validity and accuracy checks of the data collected by the AAC. The DMSC extract and upload the data directly into the NACC's working database. The validation checks are documented in the Issue Tracker, a website created to track and document any request made by NACC to correct data and resolve discrepancies.

Results: These discrepancies are identified during the review of the automated validation output checks done by NACC. The discrepancies are divided into two sections marked as Errors or Alerts. The Errors will constitute missing forms and inconsistencies that require changes to the data prior to the data packets to be move to the current database and be considered as clean data .The Alerts are contradictory values within and across forms and visits that might be correct as entered but need to be verified with an explanatory note forwarded to the DMSC. The DMSC team is responsible for verifying the alerts with NACC. This will ensure future data validation efforts on the same data will not create a discrepancy for the same data point.

Conclusions: Once all pre-processing errors have been corrected, the DMSC proceeds with the second and final upload of the data. The clean and error free data will now be move from NACC's working database to the current database, which is now ready to be share with the research community upon request.

POSTER #5

ARIZONA'S DEMENTIA CAPABLE SYSTEM – TARGETING THREE UNDERSERVED GROUPS. Angulo A, Cortés M, Carbajal B, Carbajal L, Cordova L, Weatherall Z, Gómez-Morales A, Glinka A, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: Among the 5.8 million people living with Alzheimer's disease (AD), there are three vulnerable groups where community partners can join efforts to serve the community more comprehensively. These include (a) people living alone with Alzheimer's disease and other related dementias (ADRD) who may or may not have a family caregiver, (b) people with Down Syndrome or another intellectual or developmental disability aging with ADRD and their family caregivers, and (c) people with ADRD and their family caregivers in the Latino community. The Administration on Community Living (ACL) estimates that approximately 14.3 million older adults are living alone. Latinos/Hispanics are 1.5 times more likely to develop Alzheimer's disease or other related dementias when compared to non-Hispanic white older adults. Furthermore, individuals with DS/IDD have a genetic propensity to develop early onset ADRD, affecting between 50% and 70% of the individuals by the age 60. Dementia capable systems are designed to address the needs and concerns of all individuals, families, and communities impacted by ADRD. The overall aim of this project is to develop and expand ADRD programs and services across Maricopa/Pima counties through educational workshops, case management services, and evidence-based programs addressing the needs of these three target groups. The current presentation highlights the perspectives and characteristics of the participants; data was gathered through assessments offered at the end of each educational workshops to date.

Methods: Community partners delivered, in-person or virtually, three different educational presentations on ADRD and the target groups in English and Spanish, depending on audience: Living Alone with ADRD, ADRD in the Latino Community, and Dementia and DS/IDD. Presentations were offered to a variety of professionals and community members ranging from Promotoras/CHW's (Community Health Workers), case managers, to family caregivers and people with dementia. Assessment tools captured workshop attendee demographics, and information about their care recipients (if applicable) as well as their perception of benefit from the presentations provided. The assessment includes questions about meeting expectations, satisfaction, acquisition of new and useful information, and likeliness to recommend the program.

Results: The community partners delivered a total of 67 presentations and reached 2,272 participants throughout Maricopa and Pima counties. Of the 1,353 participants (n) completing the assessments, 63.0% self-identified as Hispanic or Latino/a, and 84.5% were females. The largest percentage of participants were case managers, care coordinators, or discharge planners (19.0%). The proportion of presentations broken down by topic were: 42.4% Latino community, 33.6% living alone, and 24.0% DS/IDD. The perception of benefit ratings were overwhelmingly positive and reflected the willingness of participants to attend other community education programs. 84.9% Participants stated that they were "very likely" to recommend the project to others and 72.6% agreed that they felt confident that they could help these populations.

Conclusions: Data revealed that presentations were highly accepted by participants and contributed to increased awareness in ADRD among all the community members. Community partners and the community at large are interested in case management and evidence-based workshops provided by partners though the project. Lessons learned from project will be shared in the presentation/poster.

POSTER #6

THE EFFECT OF AGING AND NEUROLOGICAL DISORDERS ON MUSCLE FIBER SIZE IN THE PSOAS MUSCLE: A PILOT STUDY. Arce R, Serrano GE, Russell A, Vargas D, Intorcia A, Walker J, Glass M, Oliver J, Papa J, Nelson C, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Loss of muscle mass, termed sarcopenia, is common in aging and in neurological disorders of aging such as Alzheimer's and Parkinson's diseases, and may affect mobility and performance of daily tasks. It is unknown how these neurological disorders affect the skeletal muscle fiber composition in comparison with normal aging, and how muscles adapt to movement impairment caused by neurological diseases. The purpose of this study was to analyze type 1 and type 2 fibers in the psoas muscle of aging individuals with and without neurodegenerative disorders to gain insight into age and disease-related sarcopenia.

Methods: Psoas muscle was collected at autopsy from human subjects that were part of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Subject selection was based on clinicopathological diagnoses of Parkinson's disease, Alzheimer's disease, progressive supranuclear palsy, and Controls. A longitudinal and cross-sectional portion of the psoas muscle was dissected at autopsy at the level of the L5 of the spinal column and fixed in neutral buffered formalin for two days, then changed to 50% ethanol. Samples were then paraffin-embedded, cut at 6 microns, and mounted on histological slides. Anti-fast and anti-slow myosin heavy chain unconjugated antibodies diluted at 1:3000 with a 97°C sodium citrate antigen retrieval step were used to identify Type I and Type II muscle fiber types. Each section was photographed in three representative areas following staining and a Zeiss AxioVision software was used to determine mean fiber cross-sectional areas.

Results: The group age means were not significantly different, with all groups having a mean of 82 years. Muscle fiber size means for untyped fibers had considerable variation; AD muscle fiber means were smaller than those of controls while PD and PSP means were larger. Type I fibers were similar in the diagnostic groups while Type II fibers were significantly smaller in AD. For PD and PSP, Type II fiber size means were larger than those of controls.

Conclusions: This pilot study showed that Type II muscle fibers may be atrophied in AD but hypertrophied in PD and PSP. Tissue atrophy may explain the findings for AD. For PD and PSP, we hypothesize that tremor and other involuntary muscle movements may induce hypertrophy. Expanding this study to larger subject numbers may provide insight as to how neurological disorders affect skeletal muscles.

POSTER #7

EXTRACRANIAL CAROTID ATHEROSCLEROSIS IS ASSOCIATED WITH INCREASED NEUROFIBRILLARY TANGLE ACCUMULATION. Arias JC, Edwards M, Vitali F, Nagae L, Beach TG, Serrano GE, Weinkauf CC. University of Arizona; University of Arizona College of Medicine; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: NFT (neurofibrillary tangle), beta-amyloid (Aβ) plaques, and cerebral amyloid angiopathy (CAA) are key histopathological hallmarks of AD, and are found in other types of dementias and forms of cognitive dysfunction. Vascular risk factors linked to this neurodegenerative pathology include cerebral ischemia, which can be associated with vascular diseases including diabetes, hypertension, and intracranial vascular disease. However, it is unknown if other forms of vascular pathology such as extracranial carotid atherosclerotic disease (ECAD) is associated with increased (NFT), (Aβ) plaques or (CAA) accumulation.

Methods: Our prospective longitudinal clinicopathological study, the Arizona Study of Aging and Neurodegenerative Disorders/Brain and Body Donation Program, records the presence or absence of clinically-diagnosed ECAD and does semi-quantitative density estimates of NFT, beta amyloid plaques and CAA at death. After adjusting for potential confounding factors determined by logistic regression analysis, histopathology density scores were evaluated in individuals with ECAD (n=66) and individuals without ECAD (n=125).

Results: We found that the presence of ECAD is associated with a 21% greater NFT burden at death compared to no ECAD (P=.02). Anatomically, increased NFT burden was seen throughout the brain regions evaluated, but was only significant in the temporal lobe (P <.05) and the entorhinal cortex (P=.02). Complimentary to this finding, we found that subjects with carotid endarterectomy (CEA), the surgical treatment of ECAD (n=32), had decreased NFT densities compared to those who had ECAD without CEA (n=66) (P=.04). In contrast to NFT, we found that ECAD was not associated with beta-amyloid plaque or CAA density.

Conclusions: These findings indicate that ECAD is associated with NFT burden in the temporal lobe and entorhinal cortex, which has clinical significance for AD and non-AD dementias and cognitive dysfunction. Further understanding of whether ECAD increases risk for neurodegenerative brain changes is highly relevant because ECAD is a treatable disease that is otherwise not evaluated for or specifically treated as a dementia risk factor.

POSTER #8

STUDIES ON THE TELOMERE PROTECTION PROTEIN RAP1 AS A NEURONAL TRANSCRIPTION FACTOR. Bae NS, Virdi S, Abel KN, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

Background: In mammalian cells, the RAP1 protein is part of the shelterin complex that protects telomeres from degradation and repair mechanisms. Despite having a myb domain, mammalian RAP1 has not been shown to bind telomeric sequences directly. Instead, it is recruited to telomeres by the shelterin subunit TRF2, which binds telomeric repeats via its myb domain. RAP1 was also shown to associate with non-telomeric DNA, presumably through TRF2 and other DNA binding proteins. Although deleting RAP1 from mouse or human cells affects gene expression, it is not clear if the effect is direct since RAP1 also plays a role in NF-κB signaling in the cytoplasm. We have found that RAP1 responds to oxidative stress in human cells. To investigate additional roles of RAP1, we used a yeast 2-hybrid screen (Y2H) and found that RAP1 interacts with TET3, an enzyme that demethylates DNA to express nearby genes that is predominantly found in neuronal cell.

Methods: In order to determine specificity and domain interactions between RAP1 and TET3, we used the Y2H system and expression of tagged proteins in E. coli for affinity purification. Determination of DNA binding was done using a bacterial 1-hybrid (B1H) system. To measure gene expression in human cells, we used the U251 glioblastoma and SH-SY5Y neuroblastoma cell lines. Cells were untreated or oxidatively stressed with hydrogen peroxide. Isolated total RNA was converted to cDNA then amplified and measured by qPCR.

Results: Data from the Y2H system indicate that the interaction between RAP1 and TET3 is specific as the closely related TET1 protein did not exhibit an interaction. Using tagged proteins and protein domains expressed in E. coli, we found that the RAP1 myb domain interacted with the C-terminus of TET3. By expressing the full-length RAP1 protein or various domains of RAP1, we found that RAP1 can bind DNA in the B1H system. The RAP1 BRCT-myb domains bound to telomere-like sequences though the full-length protein did not. Since RAP1 responds to oxidative stress, we measured the expression of several genes that RAP1 or TET3 regulate and found that these genes change expression when neuronal cell lines are exposed to hydrogen peroxide, whereas genes not under control of RAP1 or TET3 do not change expression.

Conclusions: Our data suggest that RAP1 may be a transcription factor that binds to DNA to regulate gene expression. The interaction with TET3 suggests that RAP1 may regulate some target genes through demethylation of CpG islands. Since the full-length RAP1 protein does not bind DNA but the BRCT-myb domains do, we hypothesize that RAP1 contains inhibitory domains preventing DNA binding until RAP1 interacts with other factors.

POSTER #9

EXPLORING THE UTILITY OF TMS MOTOR RESPONSE FOR PREDICTING RESPONSIVENESS TO TMS BASED INTERVENTIONS IN MILD COGNITIVE IMPAIRMENT.

Baham JM, Sundman MH, Chen AYC, Chou YH. University of Arizona; Arizona Alzheimer's Consortium.

Background: Transcranial Magnetic Stimulation (TMS) is a noninvasive electromagnetic tool capable of stimulating brain regions and inducing temporary changes. Though TMS is established as an FDA approved therapy to alleviate symptoms of medication-resistant depression, it has demonstrated therapeutic potential for many other applications. Individual responsiveness to TMS varies largely, with some studies reporting that 50%-73% of participants lack response to the intervention. Categorizing responders and non-responders is important to better predict and select who is most likely to respond to lengthy multi-week clinical trials or established therapies.

Methods: We used theta burst stimulation (TBS), a highly efficient repetitive TMS paradigm, to examine the relationship of TBS responses when applied at different brain regions. Our analysis included 8 older adults with apparent cognitive decline according to the NACC UDSNB-3. Due to the clear physiological outputs of M1 stimulation, motor evoked potentials (MEPs) were acquired before and after the application of intermittent TBS (iTBS) at the left M1. The same participants then returned for 3 sessions of TBS (iTBS, continuous TBS (cTBS), and sham TBS) applied to a uniquely identified superficial parietal region for each individual that was demonstrated to be structurally connected to the hippocampus. Associative memory, quantified by the relative change in the percent correct on the Face-Name Associative Memory Test (FNAME), was assessed immediately before and after each parietal TBS condition.

Results: We examined the correlation of iTBS-induced change in MEPs with ranked memory performance across each of the 3 parietal TBS conditions. Our findings revealed that a significant relationship was only observed between iTBS-induced MEP change and memory change in the parietal iTBS condition ($r = .70$, $p = .05$). Though not statistically significant, a logistic regression for a positive memory response in this parietal iTBS suggested that an individual may be ~50% more likely to respond to parietal stimulation for every 5% increase in their MEP response. In this analysis, responders were defined as those with >20% relative increase in performance on the FNAME task.

Conclusions: Response heterogeneity is a challenge for all TMS based interventions, but it may be particularly problematic for older adults. One study reported that the response rate to TMS-based therapy was 56% in their young participants but dropped to 23% among elderly participants. This information is important to consider in the context of future TMS studies on cognitive aging diseases and FDA approved therapies. These findings suggest there may be merit in integrating a precursory iTBS protocol for the motor cortex to predict responsiveness to iTBS before treatment or participation in a research study. A larger study is needed to validate our preliminary findings.

This work was supported by the NIH P30 AG019610 Arizona Alzheimer's Consortium Pilot Study Program (Pilot Project PI: Chou YH).

POSTER #10

ALZHEIMER'S DISEASE NEUROPATHOLOGICAL COMORBIDITIES ARE COMMON IN THE YOUNGER-OLD. Beach TG, Malek-Ahmadi M. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

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

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

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

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

POSTER #11

NEUROPATHOLOGICAL DIAGNOSES OF SUBJECTS AUTOPSIED IN THE PHASE 3 CLINICOPATHOLOGICAL STUDY OF FLORTAUCIPIR F18 PET IMAGING. Beach TG, Montine TJ, Serrano GE, Sue LI, Intorcia AJ, Walker J, Glass M, Fleisher AS, Pontecorvo MJ, Devous Sr. MD, Lu M, Mintun MA, on behalf of the A16 study investigators. Banner Sun Health Research Institute; Stanford University School of Medicine; Avid Radiopharmaceuticals; Arizona Alzheimer's Consortium.

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

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

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

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

POSTER #12

LONGITUDINAL ASSESSMENT OF INTRAVOXEL INCOHERENT MOTION DIFFUSION-WEIGHTED MRI (IVIM-DWI) METRICS IN ALZHEIMER'S DISEASE. Bergamino M, Steffes L, Burke A, Baxter L, Caselli RJ, Sabbagh MN, Walsh RR, Stokes AM. Barrow Neurological Institute; Mayo Clinic Arizona; Lou Ruvo Center for Brain Health, Cleveland Clinic; Arizona Alzheimer's Consortium.

Background: Cognitive impairment (CI) is a common complaint in elderly people and can include forgetfulness, reduced memory, concentration difficulties, and loss of higher reasoning. Common forms of CI include two Alzheimer's disease-related conditions: mild cognitive impairment (MCI) and dementia (AD), where MCI is often considered a prodromal form of AD. Various magnetic resonance imaging (MRI) techniques have been used to study CI; however, these methods are often limited in their sensitivity to underlying neuropathological changes. Recently, we showed that intravoxel incoherent motion diffusion-weighted images (IVIM-DWI) may yield unique insight into complementary white matter (WM) and gray matter (GM) changes associated with CI. The objective of this study was to assess standard DWI metrics, such as the apparent diffusion coefficient (ADC), and IVIM-DWI metrics in aging populations. We analyzed WM and GM differences in CI and cognitively normal individuals over a period of 12 months.

Methods: Twelve patients with CI, which included both MCI and mild AD (3 males; 75±8 years at baseline), and 13 healthy controls (HC; 4 males; 73±87 years at baseline) were included in this study. MRI data were acquired at 3T (Ingenia, Philips) at baseline and after 12 months. IVIM-DWI was performed using 7 b-values (25, 50, 75, 100, 200, 500, and 1000 s/mm2) with three orthogonal directions for each b-value; TR/TE, 6000/67.98 ms; acquisition matrix, 96×96; voxel size 2.5×2.5 mm; slice thickness, 2.5 mm. DYPI libraries for IVIM were used for the quantification of three parameters: D, D*, and f, which represent the pure diffusion coefficient, the pseudo-diffusion coefficient, and the perfusion fraction, respectively. ADC maps were generated from b=0 and 1000 s/mm2 images using a mono-exponential model fit. Two-way repeated measures ANCOVA was used to evaluate the main effect of group and time; p-values were corrected for multiple comparisons by FDR. A two-sample t-test was used for the post-hoc comparison between groups, and a paired two-sample t-test was used for post-hoc comparison between time. All post-hoc p-values were corrected using Bonferroni.

Results: The two groups did not differ significantly in age (t=0.958; p=0.35). The main effect of the group showed higher values of ADC, D, and f in the CI group than HCs in several brain areas, consistent with our prior cross-sectional results. The main effect of time showed higher diffusion values after 12 months principally in the amygdala, thalamus, and hippocampus. Post-hoc comparisons showed higher diffusion metrics after 12 months than baseline in the CI group. Significant clusters were located mainly in the hippocampus and amygdala. No significant differences over time were found for HCs. Additionally, compared with the HC group, higher diffusion metrics were detected in CI for both time-points.

Conclusions: This study demonstrates the potential of the IVIM-DWI method for assessing cognitive impairment in aging populations. This technique can provide complementary information regarding both diffusion and perfusion, and these metrics may be sensitive to the temporal evolution of AD pathology. In conclusion, this preliminary study demonstrates that IVIM-DWI biomarkers may provide unique insight into temporal diffusion and perfusion changes associated with cognitive deficits.

POSTER #13

PATIENT-BASED POSTMORTEM FIBROBLAST BANKING FOR AGE-RELATED NEURODEGENERATIVE DISEASE RESEARCH. Beh ST, Frisch C, Brafman DA, Churko J, Serrano G, Beach TG, Lue L-F. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: The Brain and Body Donation Program (BBDP) at the Banner Sun Health Research Institute (BSHRI) annually banks postmortem tissues from 60-90 autopsy cases who were non-demented elderly or had neurological disorders. The Human Cells Core for Translational Research (HCCTR), established in 2018, takes advantage of the BBDP tissue resource to build a human fibroblast banking program using postmortem scalp tissues. Fibroblasts are widely used for inducible pluripotent stem cells reprogramming and differentiation. The purpose of banking postmortem fibroblasts from clinically and neuropathologically characterized patients is to provide human cells to academic and pharmaceutical communities to facilitate translational research and drug development for age-related diseases that are currently without a cure.

Methods: Postmortem human scalp tissues from BBDP donors have been routinely used to obtain fibroblasts by direct culturing of scalp explants. Dermal tissues were rinsed, chopped into 1-mm3 pieces, and placed in 6-well plates for explant cultures in a 37°C incubator with 5% CO2. Cells were harvested when they reached 80-90% confluence and expanded in T75 culture flasks at 1:2 ratios. Confluent passage-3 cells were harvested, counted, resuspended in cryoprotectant. Cryoprotected cell aliquots were stored in the vapor phase inside a liquid nitrogen tank. The viability of the cells from cryopreservation was evaluated by hemocytometer counting of trypan blue dye-excluded cells. All banked passage-3 cells were routinely characterized by a set of proteins and genes [vimentin, fibronectin, fibroblast-specific protein 1 (FSP), fibroblast activation protein (FAP), alpha-smooth muscle actin (α-SMA), and Thy-1 cell surface antigen] that have a cellular property and functional significance to the fibroblasts by immunofluorescence staining and qPCR. Commercially available primary fibroblasts and keratinocytes served as positive and negative cell-type controls, respectively. The apolipoprotein E (APOE) genotype was determined by qPCR techniques. A non-integrating Sendai viral approach was used to generate human-induced pluripotent stem cells (hiPSCs) from one of the established patient fibroblast lines. Several clones were isolated and subjected to detailed phenotypic characterization.

Results: Currently, we have banked cryoprotected fibroblasts from 43 cases of different ages, APOE genotypes, and disease diagnoses. The postmortem fibroblasts maintained high cell viability (90-95%) during cryo-storage. Positive immunofluorescent reactivities of FSP, FAP, fibronectin, α-SMA, and vimentin are observed in the banked passage-3 fibroblasts. The results of mRNA analysis also showed positive expression of FAP, vimentin, fibronectin, and Thy-1 cell surface antigen. Fibroblasts from our culture were negative for cytokeratin in both immunofluorescence and qPCR assay. We also demonstrated that the banked fibroblasts from a postmortem elderly donor were successfully reprogramed to hiPSCs.

Conclusions: Our results have demonstrated the feasibility of routine banking of patient scalp-derived fibroblasts. The cells exhibited protein and gene expression profiles similar to commercially available primary fibroblasts and maintained high viability in cryoprotectant. Long-term efforts in this cell banking program will result in a valuable human cell resource to use for a better understanding of normal aging and age-related neurodegenerative diseases. The cryogenically preserved cells are available for request at the program website of the BSHRI.

POSTER #14

IMPROVED COGNITION AND PRESERVED HIPPOCAMPAL FRACTIONAL ANISOTROPY IN SUBJECTS UNDERGOING CAROTID ENDARTERECTOMY. Bernstein A, Guzman G, Arias J, Bruck D, Berman S, Leon L, Nagae L, Pacanowski J, Zhou W, Goshima K, Tan T-W, Taylor Z, Altbach M, Trouard T, Weinkauf C. University of Arizona; Arizona Alzheimer's Consortium.

Background: A growing body data indicates that extracranial carotid artery disease can contribute to cognitive impairment. However, there have been mixed reports regarding the benefit of carotid endarterectomy (CEA) as it relates to preserving cognitive function. In this work, diffusion magnetic resonance imaging (dMRI) is used to provide insight into structural brain changes that occur because of significant carotid artery stenosis, as well as changes that occur in response to CEA.

Methods: The study design was a prospective, non-randomized, controlled study that enrolled patients with asymptomatic carotid stenosis. Fourteen subjects had severe ECAD ≥70% stenosis in at least one carotid artery and were scheduled to undergo surgery). Thirteen had ECAD with <70% stenosis or occluded, therefore not requiring surgery. All subjects underwent neurocognitive testing using the Montreal Cognitive Assessment test and high angular resolution, multi-shell diffusion magnetic resonance imaging (dMRI) of the brain at baseline and at foursix months follow-up. Changes in MoCA scores as well as in Fractional anisotropy along the hippocampus were compared at baseline and follow-up.

Results: At baseline, fractional anisotropy (FA) was significantly lower along the ipsilateral hippocampus in subjects with severe ECAD compared to subjects without severe ECAD. MoCA scores were lower in these individuals but this did not reach statistical significance. At follow-up, MoCA scores increased significantly in subjects who underwent CEA (24.23 ± 2.55 at baseline to 25.92 ± 2.25 at 4-6 month follow-up, P = 0.02) and remained statistically equal in control subjects that did not have CEA (25.85 ± 2.41 at baseline to 26.54 ± 1.33 at follow up, P=0.11). FA remained unchanged in the CEA group, and decreased in the control group.

Conclusions: This study suggests that CEA improves cognition and preserves hippocampal white matter structure compared to control subjects not undergoing CEA. Overall, this study builds on a growing body of evidence that ECAD contributes to cognitive dysfunction and identifies quantifiable brain parameters that corroborate those findings and may be relevant, objective outcomes that merit further study in this patient population.

POSTER #15

ACCELERATING DIFFUSION TENSOR IMAGING OF THE RAT BRAIN USING DEEP LEARNING. Bilgin A, Do L, Martin P, Lockhart E, Bernstein AS, Ugonna C, Dieckhaus L, Comrie C, Hutchinson E, Chen N, Alexander GE, Barnes CA, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Background: Diffusion MRI (dMRI) is an important tool for characterization of the microstructural architecture of tissues. dMRI techniques such as diffusion tensor imaging (DTI) have been employed in rodents to study a wide range of structural and pathological processes such as neuronal connectivity, ischemia, tumor growth and response to therapy. One of the major challenges when incorporating dMRI in rodent imaging protocols is the long data acquisition times required to obtain a large number of DWIs to ensure accurate estimation of the diffusion tensor. Recently, deep learning (DL) techniques have been proposed to accelerate dMRI. In this work, we present a novel DL technique for accelerating DTI of the rat brain.

Methods: Ninety-seven male Fischer 344 rats were used in this experiment. Brain MRI was collected using a 7T Bruker Biospec (Bruker, Billerica, MA). Single-shot spin-echo diffusion-weighted echo planar imaging was carried out with an in-plane resolution of 300μm, slice thickness of 900μm, 64 directions with b=1000 s/mm2, and 4 b=0 s/mm2 acquisitions. TORTOISE software8 was used for eddy current and motion correction, and for denoising. These DWIs were then used to estimate the diffusion tensor. Tensor-derived metrics of Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD) and Radial Diffusivity (RD), were calculated. The metrics derived from N=64 DWIs were used as reference values in subsequent analysis. Datasets to simulate accelerated data acquisition with K=6,8,10 and 12 DWIs were generated by subsampling the full set using the first K DWIs of the reference dataset. The proposed DL-DTI pipeline is designed to predict DWIs corresponding to unacquired diffusion directions using the small number of acquired DWIs. The acquired and predicted DWIs are then combined to estimate the diffusion tensor. The DL network was implemented in Python using Keras with Tensorflow backend and executed on an NVIDIA Tesla P100 GPU. Overlapping patches from 50 randomly selected datasets were used for training, 3 other datasets were used for validation, and the remaining 44 datasets were used for testing. DTI metrics from accelerated acquisitions were calculated and compared to the DTI metrics obtained from the reference datasets. Pearson Correlation Coefficient (PCC) between accelerated and reference DTI metrics were calculated over the entire test cohort.

Results: While the conventional DTI pipeline resulted in noticeable reduction of PCC with increasing acceleration, the DL-DTI pipeline provided consistently high PCCs, even at very high acceleration ratios. At roughly 10X acceleration (K=6), DL-DTI PCC values were 0.86, 0.98, 0.96, 0.97 for FA, MD, AD, and RD respectively, while these values were 0.26, 0.94, 0.49, and 0.77 for conventional DTI.

Conclusions: We have introduced a novel DL approach to accelerate dMRI of the rat brain. The proposed approach allows prediction of unacquired DWIs and yields DTI metrics that are highly correlated with those obtained using acquisitions that are an order of magnitude longer. The results suggest that use of DL techniques may enable shorter MRI exams reducing cost and patient discomfort.

POSTER #16

THE NUCLEAR PORE COMPLEX AND NUCLEOCYTOPLASMIC TRANSPORT: NEURONS AND GLIA IMPLICATED IN ALZHEIMER'S DISEASE. Brokaw DL, Goras M, Tran M, Delvaux E, Coleman PD. Arizona State University; Arizona Alzheimer's Consortium.

Background: Survival and growth of eukaryotes is inherently dependent on the movement of proteins and RNA between the nucleus, where the genome is housed, and the cytoplasm, where protein synthesis and cellular respiration, among other essential functions, occur. The nuclear pore complex (NPC) is one of the largest structures in the eukaryotic cell; it is composed of more than thirty types of subunits, or nucleoporins (NUPs), which mediate the selective transportation of cargo to and from the nucleus. Molecules larger than 40 kDa are unable to diffuse independently through the NPC and rely on an assortment of specialized protein chaperones, termed transport factors, to efficiently transport the cargo between the nucleoplasm and cytoplasm. Previous work in our laboratory has demonstrated that nuclear proteins are mislocalized into the cytoplasm in early stages of Alzheimer's disease (AD) progression, suggesting that structural changes to the NPC or functional aberrations to nucleocytoplasmic transport are occurring in AD. Changes to the NPC have been described in neurodegenerative diseases, including amyotrophic lateral sclerosis, Huntington's disease, and AD. Specifically, in AD, tau has been implicated in mislocalization of NUPs from the NPC to the cytoplasm and in functional deficits in nucleocytoplasmic transport.

Methods: We performed bioinformatic analysis of NUP and nucleocytoplasmic transport factor expression in homogenate brain tissue, laser-capture micro-dissected (LCM) neurons, and 10X single cell expression data from public data repositories and identified significant results. Additionally, we performed immunohistochemistry and Western blotting on postmortem human tissue samples to further explore protein level changes in AD cells.

Results: Our findings indicate expression changes to NUPs in AD neurons but not AD glia, as well as mislocalization of some NUPs to the cytoplasm in postmortem human tissue in AD. The results also indicate significant differential expression of nucleocytoplasmic chaperones and regulators in neurons and glia in AD, hinting at a potential parallel mechanism among cell types in AD.

Conclusions: Together, these results suggest a converging impact of NPC structural disruption and aberrant nucleocytoplasmic transport in AD, and future work will focus on the mechanistic relationship between AD neuropathology and NPC abnormalities, as well as implications of disrupted NPC-nucleocytoplasmic transport on downstream nuclear function in AD.

POSTER #17

IMPROVED COMPARABILITY BETWEEN MEASUREMENTS OF MEAN CORTICAL AMYLOID PLAQUE BURDEN DERIVED FROM DIFFERENT PET TRACERS USING MULTIPLE REGIONS-OF-INTEREST AND MACHINE LEARNING. Chen K, Ghisays V, Luo J, Chen Y, Lee W, Benzinger TLS, Wu T, Reiman EM, Su Y. Banner Alzheimer's Institute; Washington University, St. Louis; Arizona State University; Arizona Alzheimer's Consortium.

Background: The conversion of standard uptake value ratios (SUVRs) to Centiloid units using previously described methods has partially but not completely improved the ability to compare measurements of mean cortical amyloid plaque burden, classify positive versus negative amyloid PET scans, assess changes over time, and evaluate amyloid-modifying treatment effects using different radiotracers. Here, we demonstrate improved harmonization between PiB and florbetapir (FBP) PET measurements of mean cortical SUVRs (mcSUVRs) using multiple regions-of-interest (ROIs) and machine learning algorithms.

Methods: PiB and FBP PET image pairs from 91 subjects in the Open Access Series of Imaging Studies (https://www.oasis-brains.org/) were used as the training set to optimize the algorithms to generate each subject's pseudo-PiB mcSUVR measurements from his or her FBP multi-ROI SUVRs . PiB and FBP image pairs from 46 subjects in the Avid-related Centiloid Project (www.gaain.org/centiloid-project) were then used as the test set to compare Pearson's correlation coefficients (r) between the pseudo and actual PiB mcSUVR measurements using our approach to that used in the Centiloid method. SUVRs with cerebellar reference were extracted from multi-ROIs using FreeSurfer with partial volume correction. Pseudo mcSUVRs were generated using ensemble regression, partial least square regression (PLSR) and artificial neural network (ANN) separately, and their correlations with the actual PiB mcSUVR were compared to the PiB-FBP correlation on Centiloid in both training and test sets.

Results: In the training set, the Centiloid based PiB-FBP correlation was r=0.904. An ANN with 7/6 neurons in the 1st/2nd hidden layers improved it to 0.987 ($p \leq 8.3e-12$) and PLSR to 0.973 ($p \leq 3.8e-5$). In the independent test set, ANN improved r to 0.981 from 0.927 ($p \leq 6.6e-4$) and PLSR to 0.964 ($p=0.011$). Ensemble regression did not improve r.

Conclusions: The ANN and PLSR algorithms mapping multi-ROI FBP SUVRs to PiB mcSUVR appear to increase the comparability between measurements of mean cortical amyloid plaque burden using different PET tracers. Additional studies are needed to demonstrate the generalizability to other amyloid PET tracers, clarify its comparability in distinguishing between positive and negative amyloid PET scans, demonstrate its value in longitudinal studies and clinical trials, and extend our approaches to different tau PET ligands.

POSTER #18

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

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

Background: As a complement to other analyses, we previously used Statistical Parametric Mapping and a voxel-based Monte-Carlo Simulation (MCS) algorithm developed in our lab to study the spatial extent of flortaucipir (tau) PET elevations in Arizona-Boston (DETECT) Study of 26 former National Football League (NFL) players than in 31 normal controls—a procedure that enabled us to detect tau PET abnormalities in the player group free from the inflated Type 1 error associated with multiple comparisons (Stern et al, NEJM 2019). We now confirm this finding in a larger group of former NFL players, former college football players and asymptomatic controls without exposure to repetitive head impacts or TBI, from the DIAGNOSE CTE Research Project.

Methods: Flortaucipir PET images were acquired in 106 former NFL players, 51 former college players, and 53 unexposed controls, 57.71+8.37 years of age. An automated algorithm (SPM version 12) and co-registered MRIs were used to spatially normalize each person's PET image into Montreal Neurological Institute (MNI) template coordinate space, control for the participants' age and race, and compute statistical brain maps of group differences in regional cerebral-to-cerebellar crus1 flortaucipir standard uptake value ratio (SUVR) differences, control for the participants' age and race in the three participant groups with $P \leq 0.005$, uncorrected for multiple comparisons. Our MCS was then applied with 1,000 iterations to test the hypothesis that there would be a greater number of cerebral voxels with SUVR elevations in the combined player group versus control group, as well as between the NFL versus college player groups.

Results: As predicted, the NFL, college player and aggregate player groups had significantly more cerebral voxels with flortaucipir SUVR elevations than in the control group (i.e., 53,879, 79,552 and 100,837 voxels in the postulated direction vs 79, 89 and 86 in the opposite direction, respectively, $P<0.001$). While former NFL players had more voxels with SUVR elevations than in former college players (482 versus 306), this difference was not significant ($P=0.305$).

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

POSTER #19

SUCCESSFUL RECRUITMENT OF EARLY-STAGE ADRD PARTICIPANTS THROUGH COMMUNITY PARTNERSHIPS AND HIPAA-COMPLIANT FAX REFERRAL PROCESS.

Cortes M, Angulo A, Carll P, Glinka A, Stotler K, Gonzalez-Pyles MS, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: The EPIC (Early-Stage Partners in Care) II study is a randomized clinical trial of a psychoeducational skill-building intervention that targets the relative lack of stage-appropriate community services for dyads. These dyads involve the care recipient in the early stages (EP) of ADRD and their current or future care partner (CP). Recruitment and delivery of EPIC is a coordinated effort of an academic research institution with local Alzheimer's Association Chapters, Area Agencies on Aging, a promotores network, other community-based organizations, and the Arizona Alzheimer's Disease Research Center. Recruitment strategies were modeled on the pilot study's successes, utilizing the extensive network of research, healthcare, and community organizations with which the project team has strong ties. The cornerstone of successful recruitment has been a HIPAA-compliant, IRB-approved fax referral process used among partners, community organizations, and potential participants. This process reduces referral lag time by allowing community partners to obtain and document up-front permission from interested individuals who wish to be contacted by the study team for screening. Close partnerships with community providers and early contact with potential participants is crucial to help ensure study recruitment and retention success.

Methods: This presentation reviews all 256 EPIC II study referrals received from October 2017 through February 2020 (pre-COVID). The data were analyzed to characterize referral sources and compare the outcome of referrals by source.

Results: Of the total number of referrals (N=256), fax referrals from community partners made up the largest proportion (73.0%). In the first two years, 85.9% of referrals were received through HIPAA-compliant faxes from community partners. In the third year, the proportion of fax referrals dropped to 29.3% and referrals through the registry dashboard made up 60.3% of the total referrals.

Conclusions: Findings are consistent with the pilot study's successful recruitment using the HIPAA-compliant fax referral process with community partners. The registry has shown promise as a new strategy that could serve to fill a critical gap going forward, even though the proportion of referrals that ended up both qualifying and enrolling is comparatively low. It is important to note that the Alzheimer's registry was a new successful recruitment strategy implemented in the third year of the study.

POSTER #20

DECREASED DYNAMIC RANGE OF HIPPOCAMPAL CA1 GAMMA IN AGED RATS. Crown LM, Gray DT, Schimanski LA, Barnes CA, Cowen SL. University of Arizona; Arizona Alzheimer's Consortium.

Background: Decreased episodic memory is a common age-associated cognitive change that significantly impairs quality of life in the elderly. Changes within the hippocampus and surrounding regions including the medial entorhinal cortex (MEC) likely contribute to these impairments in humans and animal models of brain aging. One mechanism through which these regions are thought to communicate is through synchronized gamma oscillations. Gamma oscillations (30 Hz-120 Hz) are implicated in numerous cognitive processes including sensory binding, memory, and attentional selection. Within the rodent hippocampus, gamma has been shown to be modulated by running speed (Ahmed & Mehta, 2012), suggesting that gamma frequency reflects the speed of sensory or cognitive processing.

Methods: In this study we examine gamma oscillations in the CA1 region of the hippocampus in 6 middle aged (9-12 months) rats and 5 old (25-28 months) rats as they ran back and forth on a horseshoe shaped maze while performing a spatial eye-blink conditioning task. We hypothesized that cognitive slowing in aged animals would result in impaired CA1 gamma frequency modulation by running speed. To assess how gamma frequency changed as a function of running speed, normalized power spectral densities were acquired and binned by running speed and averaged for each animal. After obtaining the frequency of maximum gamma power for each speed bin, a robust regression was performed to obtain the slope and intercept of the relationship.

Results: We found that aged animals had significantly shallower slopes than younger animals ($t(5.6)=3.92$, $p=0.009$) as well as a higher intercept ($t(8.9)=-3.45$, $p=0.007$).

Conclusions: This suggests that aged animals have a narrower dynamic range for gamma frequencies which may be indicative of early age-related cognitive slowing.

POSTER #21

ADULTHOOD DIETARY CHOLINE DEFICIENCY; A RISK FACTOR FOR OBESITY, IMPAIRED GLUCOSE TOLERANCE, CARDIAC PATHOLOGY AND SUBSEQUENT ALZHEIMER'S DISEASE. Decker A, Winslow W, Blackwood E, Bilal A, Mcdonough I, Winstone J, Tallino S, Dave N, Glembotski C, Velazquez R. Arizona State University; University of Arizona College of Medicine – Phoenix; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is rapidly increasing with the aging population. Dietary nutrients play a key role in mediating mechanisms associated with brain function. Recent reports suggest that increased AD cases may be associated with choline deficiency. Choline, a nutrient found in common foods, is required to produce acetylcholine, a neurotransmitter responsible for memory and muscle control. It also builds cell membranes, plays a vital role in regulating gene expression, and reduces homocysteine (Hcy), a toxic amino acid; elevated Hcy levels increase the risk of developing AD. In 1998, the U.S. established an adequate intake (AI) of daily dietary choline for adult women (425mg/day) and men (550mg/day). Notably, epidemiology studies show that 90% of Americans fail to reach the daily AI. Thus, it is imperative to determine whether choline deficiency increases AD risk.

Methods: Here, we took the 3xTg-AD mouse model of AD and NonTg controls and provided them with either a choline normal (ChN) or deficient (Ch-) diet from early adulthood throughout life. Mice were assessed for motor and metabolic function, and tissue was assessed for heart and brain pathology. A subset of hippocampal tissue underwent unbiased proteomics to determine protein abundance changes with a Ch- diet.

Results: A Ch- diet induced motor deficits, increased weight, and impaired glucose metabolism in both NonTg and 3xTg-AD mice, with AD mice showing greater deficits. Additionally, we found evidence of cardiac pathology with a Ch- diet. In 3xTg-AD mouse brains, a Ch- diet elevated the levels of toxic oligomeric and insoluble Amyloid-ß (Aß). Unbiased proteomic analysis revealed several altered pathways as a result of a Ch- diet, most notably structural constituent of myelin sheath and microtubule motor activity.

Conclusions: Collectively, these results suggest that simply modifying diet to include adequate choline could offset some risk of developing AD.

POSTER #22

AN MRI MICROSCOPY TOOLKIT FOR TRACKING MICROSTRUCTURAL CHANGES LINKED TO AGING. Dieckhaus L, Barnes CA, McDermott K,Gray DT, Hutchinson E. University of Arizona; Arizona Alzheimer's Consortium.

Background: We have developed a robust MRI microscopy battery that utilizes diffusion MRI (dMRI), relaxometry based MRI (rMRI), and magnetic susceptibility techniques to quantify changes in brain structures related to normal aging. Twelve, female non-human primates (bonnet macaques) with ages ranging from 10 to 25 years old (30 to 75 human equivalent years) underwent behavioral and electrophysiological assessments of cognitive and sensory function prior to transcardial perfusion and brain extraction. The ex-vivo MRI battery that we developed to examine these brains extracts high resolution quantitative data prior to histologic sectioning. Since imaging biomarkers that are indicative of age-related brain dysfunction are critical to understanding age-related memory impairment, our goal was to evaluate new microstructural MRI methods. With improved sensitivity to normative aging progression using MR markers, we can improve detection of age-related microstructural and macromolecular alterations in tissue, and better understand changes that occur in pathological conditions such as Alzheimer's disease. Our pipeline for obtaining such data has been preliminarily tested on the entire cohort.

Methods: Brains from "Young" (n=7 mean age =10.45 years)) and "Aged" (n=7, mean age = 22.11 years) were imaged to obtain a broad field of view of the anatomical structures and connections. The MRI battery included: higher resolution anatomical (HRA) T1, QSM (Quantitative Susceptibility Mapping), dMRI, and rMRI. HRA images (200 micron isotropic voxels) offer visualization of small anatomical structures such as the locus coeruleus while the other methods utilized report microscale features of the tissue using quantitative MRI mapping of diffusion or relaxometry at lower resolution: SWI (Susceptibility Weighted Image; 400x400x600 micron), MSE (Multi-Spin Echo; 600 micron isotropic), SIR (Selective Inversion Recovery; 600 micron isotropic), and DTI (Diffusion Tensor Image; 600 micron isotropic). dMRI was acquired by 3D Echo Planar Imaging (EPI) and incorporated the collection of high b shell values (1500-4500). DTI data was processed through TORTOISE pipeline to correct motion and EPI distortion. rMRI included selective inversion recovery (SIR) for T1 and bound pool fraction (BPF) mapping and multi-spin echo (MSE) for T2 and myelin water fraction (MWF) mapping. MSE and SIR maps offer insight into macromolecular contributions such as white matter hyperintensities and volumetric changes in myelin, respectively. MSE and SIR were processed using the REMMI toolkit in Matlab. Template generation and voxelwise analysis were tested using Advanced Normalization Tools and Functional Brain Image Analysis Tools.

Results: Acquired scans from each brain have been processed resulting in high quality and high-resolution maps for each quantitative method including DTI metrics, BPF and MWF. Structural template and voxelwise analysis were demonstrated for DTI maps as an initial step toward bias-free assessment of the correlation between age and different microstructural metrics.

Conclusions: Resolution of the MSE data had to be modified as the signal to noise ratio (SNR) was not optimal. To improve quality, a denoising post-processing technique is being explored to the MSE data. HRA acquisition had signal artifacts that made locating microstructural regions challenging therefore default spoiler values were modified and improved image quality. Preparation of Non-DTI maps (such as BPF and MWF) are currently underway. The analysis of these MRI outcome measures from distinct sensory and higher-order associative brain regions can identify how brain function changes during healthy aging.

POSTER #23

QUANTITATIVE AND VOLUMETRIC AND DIFFUSION WEIGHTED MRI ANALYSIS OF RODENT BRAINS AS A FUNCTION OF AGE AND COGNITION. Do L, Zempare MA, Bernstein AS, Bharadwaj P, Ugonna C, Chen N, Alexander GE, Barnes CA, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Background: Animal models play an important role in preclinical and translational studies of the human brain. MRI, being both non-invasive and inherently translational, can play an important role in comparing brain anatomy in animal models and humans. Furthermore, diffusion weighted MRI is an established tool for the examination of white matter connectivity and microstructural changes as a function of age. Volumetric and diffusion weighted MR imaging have the potential to detect differences in rat brains as a function of age and cognition. The volumes and structural integrity of important brain regions as a function of age and cognition are continuing to be explored and these results will give important information as to the connectivity of different brain regions during both healthy cognitive aging as well as characterizing structural differences in rat brains with various levels of cognitive aptitude.

Methods: Young (6mo), middle-aged (15mo) and old (23mo) male F344 rats were used in this study. A T2-weighted template image was registered to each animal's anatomical image using rigid body, affine and non-linear techniques and the deformation fields produced were applied to an 85 region labeled atlas to calculate the volume of individual regions of interest (ROIs) in the brain. This allowed for volumetric measurements across age and cognitive groups regionally. Image processing for the diffusion weighted images involved eddy current corrected and motion corrected, denoising, brain extraction and diffusion tensor generation. Scalar parameters such as fractional anisotropy (FA) can then be used to microstructurally characterize the white matter tracts.

Results: Volumetric MR imaging detected differences in rodent total intracranial volume and the data suggests that the rat brains are continuing to grow past 6 months of age. Body weight measurements confirm the imaging findings to middle aged however there is a deviation at old age where total intracranial volume (TIV) plateaus and body weight decreases significantly.

Conclusions: These results will inform future analysis comparing regional brain volumes with age and cognitive performance. Diffusion MRI analysis is in progress and will show the microstructural integrity of white matter tracts both globally and regionally and those results will be compared across age and cognitive groups by comparing scalar indices such as fractional anisotropy, mean diffusivity and radial diffusivity.

POSTER #24

CSF AMYLOID-BETA, TAU, NEURODEGENERATIVE, AND INFLAMMATORY BIOMARKERS IN COGNITIVELY UNIMPAIRED LATE MIDDLE-AGED & OLDER ADULT APOE ε4 HOMOZYGOTES, HETEROZYGOTES, & NON-CARRIERS FROM THE ARIZONA APOE COHORT. Ghisays V, Jansen WJ, Chen Y, Protas H, Malek-Ahmadi M, Luo J, Lee W, Chen K, Su Y, Caselli RJ, Zetterberg H, Blennow K, Reiman EM. Banner Alzheimer's Institute; Mayo Clinic Arizona; Sahlgrenska University Hospital, Mölndal, Sweden; University of Gothenburg, Sweden; Arizona Alzheimer's Consortium.

Background: APOE4 gene dose, the number of apolipoprotein E -ε4 (APOE4) ε4 alleles in a person's genotype, is associated with higher Alzheimer's disease (AD) risk and younger median age at dementia onset. We previously found relationships between PET, plasma, and CSF measurements of amyloid-β (Aβ) pathophysiology in APOE4 gene dose. Here, we characterize the core AD CSF biomarkers (Aβ42/40, pTau181, tTau), the neurodegeneration marker neurofilament light chain (NfL) and the glial biomarkers soluble TREM2 (sTREM2), and glial fibrillary acidic protein (GFAP) measurements in age-matched 48-70 year-old cognitively unimpaired (CU) APOE4 homozygotes (HMs), heterozygotes (HTs) and non-carriers (NCs) from the Arizona cohort.

Methods: CSF biomarker measurements were performed at the University of Gothenburg using Lumipulse and ELISA immunoassays. CSF biomarker measurements were characterized and compared using linear-tend ANOVAs in 12 HMs, 17 HTs, and 20 NCs who were CU, 48-70 years old and did not differ significantly in their age, sex, or educational level.

Results: As expected, CSF Aβ42/40 ratios were inversely associated with APOE4 gene dose (linear trend, HM<HT<NC, $p<0.05$), and tTau/Aβ42 and pTau181/Aβ42 ratios were directly associated with APOE4 gene dose (HM>HT>NC $p<0.05$). Non-significant trends suggested that CSF sTREM2 and sTREM2/pTau181 measurements were inversely associated with APOE4 gene dose (HM<HT≤NC, ($0.05<p\leq0.06$). We failed to detect significant differences or linear trends in CSF pTau181, tTau, GFAP, or NfL measurements among these small subject groups.

Conclusions: APOE4 gene dose is associated with measures of CSF Aβ42/40 and Aβ-related tau pathophysiology, reflecting higher Aβ plaque burden in CU subjects close to their estimated ages at clinical onset. Additional studies are needed to clarify relationships between different Aβ, tau, neurodegenerative, inflammatory, and other CSF, or blood-based biomarkers, and APOE4 gene dose in larger subject groups and at other ages.

POSTER #25

PLASMA AB42/40 RATIOS IN COGNITIVELY UNIMPAIRED LATE MIDDLE-AGED & OLDER ADULT APOE E4 HOMOZYGOTES, HETEROZYGOTES, & NON-CARRIERS. Ghisays V, Jansen WJ, DeMarco K, Boker C, Chen K, Chen Y, Luo J, Protas H, West T, Meyer M, Kirmess K, Verghese P, Hu H, Yarasheski K, Caselli RJ, Su Y, Reiman EM. Banner Alzheimer's Institute; C2N Diagnostics; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: APOE4 gene dose, the number of apolipoprotein-ε4 (APOE4) alleles in a person's genotype, is associated with higher Alzheimer's disease (AD) risk & younger median age at dementia onset. We previously characterized relationships between age, tau PET, amyloid-β (Aβ) PET & MRI measurements in 160 cognitively unimpaired (CU) 47-86-year-old APOE4 homozygotes (HMs), heterozygotes (HTs) & non-carriers (NCs) from the Arizona APOE Cohort & Mayo Clinic study on Aging—including HMs & HTs who remained CU at older ages. Here, we used plasma data from 80 47-70 & 41 71-85-year-old CU HMs, HTs & NCs in the Arizona APOE cohort to characterize relationships between plasma Aβ42/40 ratios, which are inversely related to Aβ plaque burden & APOE4 gene dose, as well as percentage of HMs, HTs & NCs with a positive (Aβ+) blood test in each age group.

Methods: Plasma Aβ42 & Aβ40 assays were performed by C2N Diagnostics using peptide-specific ultra performance liquid chromatography-tandem mass spectrometry. Aβ42/40 ratios were compared in the 47-70 & 71-85-year-old CU HMs, HTs & NCs with 2-way ANOVA. Optimal plasma Aβ42/40 ratio cutoff value that maximized sensitivity and specificity (Youden index) was used to characterize Aβ+ & chi-square to compare proportions of Aβ+ & Aβ- in each age group.

Results: In the 47-70-year-old group, plasma Aβ42/40 ratios were inversely associated with APOE4 gene dose(HM<HT<NC, $p < 0.0001$). In the 71-85-year-old age group, HTs had significantly lower ratios than NCs ($p=0.035$) & a non-significant trend for lower ratios than HMs ($p= 0.062$). Three of the four 71-85-year-old HMs had a negative Aβ blood test.

Conclusions: As predicted, APOE4 gene dose is associated with lower plasma Aβ42/40 ratios, reflecting higher Aβ-plaque burden in CU subjects ≤70 years of age—and 3 out of 4 CU HMs over age 70 had normal Aβ42/40 ratios, suggesting they may have factors leading to their resistance to Aβ-plaque deposition & the clinical onset of AD.

POSTER #26

ULTRASOUND-ASSISTED LUMBAR PUNCTURE IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS RESEARCH: A PILOT STUDY. Goldfarb D, Viramontes D, Callan M, Liebsack C, Goddard M, Reade M, Malek-Ahmadi MH, Weidman D, Tsai PH, Wu T, Grimsman J, Atri A. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Banner University Medical Center; Harvard Medical School; Brigham and Women's Hospital; Arizona Alzheimer's Consortium.

Background: Lumbar puncture (LP) and collection of cerebrospinal fluid (CSF) are increasingly essential in Alzheimer's disease and related dementias (ADRD) research. Ultrasound-assisted lumbar puncture (Us-LP) has not been studied in ADRD research and could improve LP success rates through more accurate anatomical site selection, precise planning, and individualized intra-procedure adjustments. This pilot study assessed the feasibility, utility, and tolerability of Us-LP in ADRD research.

Methods: LP clinician-researchers from ADRD centers completed simulation-based Us-LP training using the Philips Lumify system, a portable hand-held transducer connecting to a tablet. Thereafter, clinician-researchers had the option to use Us-LP during research LPs. Participant demographics and attitudes about LP were obtained prior to LP. The clinician-researchers completed a post-LP questionnaire assessing procedural details, choices, and LP performance.

Results: Following training, four clinician-researchers implemented Us-LP into their practices. Between August 2019-March 2020, 58 research participants underwent LP. Clinician-researchers used Us-LP on 37/58 (64%) participants. Compared to conventional-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 also 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.

Conclusions: Training clinician-researchers in Us-LP and implementing portable hand-held Us-LP for ADRD research studies demonstrated feasibility, utility and tolerability. Pilot data indicated that 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 ADRD research will improve LP success rates, tolerability, and participant willingness to undergo LP. Improving these factors will accelerate CSF biomarker, aging and ADRD research. Furthermore, with potential availability of AD disease-modifying treatments in the coming years, LP and CSF collection are likely to play a crucial role in patient selection for treatment.

POSTER #27

AUDITORY AND VISUAL SYSTEM FUNCTION AND WHITE MATTER CONDITION IS DIFFERENTIALLY IMPACTED BY NORMATIVE AGING IN MACAQUES. Gray DT, De La Peña NM, Umapathy L, Burke SN, Engle JR, Trouard TP, Barnes CA. University of Arizona; University of Florida, Gainesville; Arizona Alzheimer's Consortium.

Background: Normative brain aging results in decreased function across multiple sensory systems that compromises an older individual's ability to detect and process behaviorally relevant information and can substantially reduce quality of life. Deficits in auditory and visual processing, in particular, are commonly encountered by older individuals due to age-associated pathologies at the level of the cochlea and eye, and from multiple changes that occur along the ascending auditory and visual pathways that further reduce sensory function in each domain. One fundamental question that remains to be directly addressed is whether the structure and function of the central auditory and visual systems follow similar trajectories across the lifespan, or sustain the impacts of brain aging independently. Advances in the quality and precision of sensory prosthetics have made it clear that distinct sensory deficits require unique approaches, and precisely understanding how particular age-associated neurobiological changes impact different facets of sensory processing is critical for optimizing intervention strategies that maintain sensory function in older individuals.

Methods: The present study used diffusion magnetic resonance imaging and electrophysiological assessments of auditory and visual system function in adult and aged macaques to better understand how age-related changes in white matter connectivity at multiple levels of each sensory system might impact auditory and visual function.

Results: Sensory processing and sensory system fractional anisotropy (FA) were both reduced in older animals compared to younger adults. Corticocortical FA was significantly reduced only in white matter of the auditory system of aged monkeys, while thalamocortical FA was lower only in visual system white matter of the same animals. Importantly, these structural alterations were significantly associated with sensory function within each domain.

Conclusions: Together these results indicate that age-associated deficits in auditory and visual processing emerge in part from microstructural alterations to specific sensory white matter tracts, and not from general differences in white matter condition across the aging brain. Accounting for this sort of specificity will aid in designing individualized intervention strategies that optimally correct and maintain brain function across the lifespan.

POSTER #28

ASSOCIATION BETWEEN CEREBROVASCULAR FUNCTION AND CHRONIC COGNITIVE DYSFUNCTION FOLLOWING MILD-MODERATE TRAUMATIC BRAIN INJURY IN RATS AND LACK OF A MODULATING INFLUENCE BY DIABETES. Griffiths DR, Fuentes A, Law LM, Bell L, Karamanova N, Truran S, Emerson H, Turner G, Quarles CC, Reaven P, Migrino RQ, Lifshitz J. University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute; Phoenix VA; Arizona Alzheimer's Consortium.

Background: Observational studies implicate mild or moderate traumatic brain injury (mTBI) as a factor in later development of cognitive dysfunction and dementia, but experimental evidence is lacking. Whereas cerebral blood flow (CBF) perturbations are well-established in the pathology of acute, severe TBI, its role in chronic mTBI remains unclear. Diabetes is a known risk factor for dementia and cerebrovascular dysfunction and the interaction between diabetes and mTBI remains unknown. Our aims are: 1) compare chronic (6 month) cognitive and cerebrovascular function between mTBI and sham treated rats while establishing the relationship between cognitive and vascular function, 2) assess whether post-mTBI development of diabetes would worsen outcomes in mTBI, 3) assess whether pretreatment with lipopolysaccharide (LPS), previously shown to protect cerebrovascular function in stroke models, would mitigate mTBI.

Methods: Rats underwent either midline fluid percussion mTBI (N=46) or sham surgery (N=43) and 3- and 6-month cognitive function (novel object recognition NOR, novel object location NOL and temporal order object recognition TOR) was compared as well as 6-month regional cerebral blood volume (BV) and CBF by magnetic iron oxide nanoparticle contrast MR imaging. A subgroup was injected with streptozotocin (STZ, 50 mg/kg IP, N=13) or saline control 3 months post-mTBI/sham to induce diabetes and another subgroup received lipopolysaccharide (LPS 0.3 mg/kg IP, N=21) or saline control 3 days before mTBI/sham surgery.

Results: On repeated measures ANOVA (time x treatment), there was significant impairment in NOR (p=0.003), NOL (p=0.016) and TOR (p=0.016) in TBI versus sham rats. BV was significantly higher in medial hippocampus of TBI rats versus sham (36.2±13.7 versus 30.3±9.0 ml/100 ml tissue, p=0.03, N=39-40) with a similar trend in lateral hippocampus (p=0.05). Global and regional CBF flow did not significantly differ (N=26-27). Inverse correlations existed between NOL and BV in medial hippocampus (R=-0.23, p=0.04), deep brain (R=-0.22, p=0.048), and between TOR and BV in the deep brain (R=-0.28, p=0.01) and S1BF (R=-0.22, p=0.047). There were significant correlations between NOR and CBF in the lateral hippocampus (R=0.35, p=0.01), medial hippocampus (R=0.28, p=0.04) and S1BF (R=0.32, p=0.02), but not global CBF. Post-mTBI induction of diabetes with STZ (blood glucose 379±19 mg/dL) did not influence any significant change in cognitive function, BV and CBF compared to TBI alone. Contrary to our hypothesis, pretreatment with LPS prior to TBI caused worse TOR versus vehicle control, with no significant difference in NOR and NOL.

Conclusions: Mild to moderate TBI in rats resulted in chronic (3 and 6 month) cognitive dysfunction and increased regional hippocampal BV (6 months). Whether the observed relationship between regional cerebral blood volume/flow and cognitive dysfunction is causal is not established and needs to be investigated. Development of type 1 diabetes post-mTBI did not modulate TBI injury, but whether this applies to other diabetes models remains to be seen.

POSTER #29

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

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

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

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

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

POSTER #30

REMOTE, UNSUPERVISED FUNCTIONAL MOTOR TASK EVALUATION IN OLDER ADULTS ACROSS THE UNITED STATES USING THE MINDCROWD ELECTRONIC COHORT.
Hooyman A, Talboom J, DeBoth MD, Ryan L, Huentelman M, Schaefer SY. Arizona State University; The Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The COVID-19 pandemic has impacted the ability to evaluate motor function in older adults, as motor assessments typically require face-to-face interaction. This study tested whether motor function can be assessed at home.

Methods: One hundred seventy-seven older adults nationwide (recruited through the MindCrowd electronic cohort) completed a brief functional upper-extremity assessment at home and unsupervised. Performance data were compared to data from an independent sample of community-dwelling older adults (N=250) who were assessed by an experimenter in-lab.

Results: The effect of age on performance was similar between the in-lab and at-home groups for both the dominant and non-dominant hand. Practice effects were also similar between the groups.

Conclusions: Assessing upper-extremity motor function remotely is feasible and reliable in community-dwelling older adults. This offers a practical solution not only in response to the COVID-19 pandemic, but also for telehealth practice and other research involving remote or geographically isolated individuals.

POSTER #31

THE MINDCROWD PROJECT: PROGRESS, COLLABORATION, AND ELECTRONIC COHORT RECRUITMENT IN THE TIME OF COVID-19. Huentelman MJ, Talboom JS, Schmidt AM, De Both MD, Naymik MA, Lewis CR, Hay M, Barnes CA, Glisky E, Ryan L. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: One of the challenges in human research is recruiting large and diverse cohorts that can adequately power robust results that accurately inform public health advice. To address this critical need, in 2013, we developed the MindCrowd project (at www.mindcrowd.org). MindCrowd is an internet-based research study that has recruited over 225,000 participants from across the world. Each participant provides basic demographic, lifestyle, health, and medical information in addition to completing standardized reaction time and verbal memory testing. Using MindCrowd's data, we have identified multiple factors associated with reaction time and memory test performance – some that were predicted and validate prior research and others that are novel and hypothesis-generating. MindCrowd partners with researchers across the country to facilitate recruitment and data sharing into their studies.

Methods: In this presentation, we will discuss multiple results from MindCrowd, including the current associations between demographic, lifestyle, health, and medical factors with reaction time and verbal memory, results from recent collaborations with researchers outside of MindCrowd that make use of MindCrowd for recruitment, and our efforts to improve on the diversity of MindCrowd during the COVID-19 pandemic.

Results: We confirmed several factors known to influence verbal memory and reaction time – such as age, educational attainment, and biological sex – and identified several novel associations – such as the interaction between biological sex and smoking status as a predictor of verbal memory performance. Through our collaborations, we have demonstrated a high correlation between in-lab and remote electronic testing for multiple task paradigms. In 2020, we showed an approximate doubling in the recruitment rate for Latino, Black / African American, and Mixed race participants.

Conclusions: Overall, our findings demonstrate the utility of electronic-based recruitment and study for the cost-effective generation of a large and diverse cohort for research. The validity of self-assessed and remote electronic-based testing results was high and well correlated with in-person results. During the restrictions of the pandemic, our internet-based approach demonstrated significant resiliency and effectiveness at recruiting underserved minority groups. Finally, we emphasize that electronic recruitment and study is an essential component of a human research program. The coupling of remote and in-person approaches affords several benefits more significant than either approach alone.

POSTER #32

INVESTIGATION OF THE STRUCTURE AND ACTIVITY OF TAU PROTEIN AGGREGATE FORMATION. Huseby CJ, Ranaweera E, Mossman KC, Lowry D, Serrano GE, Hansen DT, Coleman PD, Fromme P. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is a complex neurodegenerative disease of aging with clinical symptoms of mental decline and postmortem markers such as intraneuronal hyperphosphorylated tau neurofibrillary tangles (NFT) in the brain. In AD and other neurodegenerative diseases, collectively known as tauopathies, abnormal tau conformations and inclusions are surrogate markers for neurodegeneration, a tool for differential disease diagnosis and staging, a source of toxicity to molecular complexes, and a potential vector for disease propagation. It was recently shown that the tau molecule fold at the core of tau fibril inclusions can differentiate between tauopathies. Candidates for aberrant intracellular tau folding and aggregation have been identified such as liquid-liquid phase separation (LLPS) and micro crystal growth at ribosomes. It has been observed that intrinsically disordered proteins with low sequence complexity result in a condensed folding often found in many proteins associated with neurodegenerative disease such as FUS, TDP43, and hyperphosphorylated tau. It has been observed that proteins can form micro-size crystal aggregates in insect cells below the level of resolution for classic imaging techniques. It is hypothesized that disease specific changes in the cellular environment of tau such as patterns of hyperphosphorylation or ribosomal induction of aggregates or micro crystal formation could lead to a differential core structures of tau protein in specific disease.

Methods: We are using advanced state-of-the-art structural methods for the discovery of mechanisms of formation of tau aggregates and structural differences of affected protein complexes in AD. We use a combination of cryo-EM and cryo electron tomography with focused Ion Beam technology. These instruments allow us to directly image the tau aggregates in cell culture models of tau aggregation and in autopsy samples derived from the AD brain. With the advanced structural determination methods available at CASD, we will capture liquid-liquid phase separation and/or micro crystals in cellular models and human tissue for further investigation of the role in intracellular tau aggregate pathway

Results: Early preliminary results include the design of Gateway plasmids with inserts for the six human tau protein isoforms. Using the Gateway system, tau can be transferred to any organismal vector and we have completed vector assembly. Transfection of insect cells and mammalian cells has been successful evident by the appearance of fluorescence within cells. Additionally, we have begun optimization of sample prep for use in the focused ion beam electron microscope for slice and view of fixed whole cellular structure.

Conclusions: Our work toward exploring aggregation in cellular models over-expressing the human tau protein is underway. The investigation of the intracellular aggregation of tau will include an interrogation of the environmental influences to the aberrant folding of tau protein including hyperphosphorylation and the subsequent toxic effects on macromolecules within human neuroblastoma cells. In parallel, the information gained from our cellular models will be verified in human tissue extracted from AD diseased and control brains.

POSTER #33

SYSTEMATIC ANALYSIS OF BLOOD TRANSCRIPT BIOMARKERS IDENTIFIES SIMILARITIES AND DIFFERENCES ACROSS NEURODEGENERATIVE DISEASES INCLUDING ALZHEIMER'S DISEASE. Huseby CJ, Delvaux E, Brokaw D, Coleman PD. Arizona State University; Arizona Alzheimer's Consortium.

Background: Clinical diagnosis of neurodegenerative diseases is notoriously inaccurate and current methods are often expensive, time-consuming, or invasive. Simple inexpensive and noninvasive methods of diagnosis could provide valuable support for clinicians when combined with cognitive assessment scores. Biological processes leading to neuropathology progress silently for years and are reflected in both the central nervous system and vascular peripheral system. A blood-based screen to distinguish and classify neurodegenerative diseases is especially interesting having low cost, minimal invasiveness, and accessibility to almost any world clinic. Neurodegenerative diseases come with diverse clinical syndromes, genetic heterogeneity, and distinct brain pathological changes, but studies across multiple diseases often report overlap of these markers. The study of blood-based changes in mRNA gene expression provides a way to explore this overlap and heterogeneity as it is determined by the combined effects of expression changes due to environmental insults and genetic variation. In this study, we set out to discover a small set of blood transcripts that can be used to distinguish healthy individuals from those with Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, or frontotemporal dementia.

Methods: Using existing public datasets, we developed a machine learning algorithm for application on transcripts present in blood and discovered small sets of transcripts which distinguish a number of neurodegenerative diseases with high sensitivity and specificity.

Results: Our results highlight shared blood similarities and differences across these six familial and sporadic neurodegenerative diseases. Although only four transcripts were selected in more than one disease, the remaining classifiers fell into seven main cellular processes including transcription regulation, degranulation, immune response, protein synthesis, apoptosis, cytoskeleton components, and metabolomic complexes.

Conclusions: We validated the usefulness of blood RNA transcriptomics for classification of neurodegenerative diseases. Information about features selected for the classification can direct the development of possible treatment strategies. Our chosen transcripts reveal that neurodegenerative diseases have common themes which after removal, bare the unique transcripts of each disease.

POSTER #34

ROBUST NEUROPSYCHOLOGICAL NORM DEVELOPMENT BASED ON COGNITIVELY NORMAL OLDER ADULTS: EXAMINING TRUE NEUROCOGNITIVE NORMALITY. James EJ, Malek-Ahmadi MH, Moorley N, Evans B, Auman B, Beach TG, and the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND). Banner Sun Health Research Institute; Banner Alzheimer's Institute; Midwestern University; Arizona Alzheimer's Consortium.

Background: Age-based neurocognitive performance is often underestimated due to the tendency to include individuals with prodromal neurodegenerative disorders in normative samples of neuropsychological assessments for older adults (Clouston et al., 2015; Deary et al., 2009), such as those aged 55 and above. This inclusion likely results in overestimation of cognitive impairment in older adults (Harrington et al., 2017) and may result in failure to detect subtle impairments, which could delay diagnosis. Thus, this study aims to develop robust norms for performance of cognitively intact older adults on several commonly-used neuropsychological tests, to gain a true sense of neurocognitive normality across individuals aged 60 and older.

Methods: Neuropsychological test data was collected from 210 adults, aged 60 and above, who are currently enrolled in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). The included subjects had at least five years of data and maintained a consensus expert diagnosis of "cognitively normal" for the two most recent years of data. These cognitive designations were established within a consensus conference of a neurologist, neuropsychologist, and clinical research coordinator. Subjects with neurological and psychiatric comorbidities were excluded from analysis. The neuropsychological test data examined was derived from the following measures, some of which are included in the Uniform Data Set of the National Alzheimer's Coordinating Center: Rey Auditory Verbal Learning Test (AVLT), Animal Fluency, Controlled Oral Word Association Test (COWAT), Judgment of Line Orientation (JLO), and the Trail Making Test (TMT).

Results: Baseline performance on the above assessments were examined across the 210 subjects. The sample consists of 72% female (152) and 28% male (58) participants, with a relatively even distribution across age groups, ranging from a maximum of 58 subjects in the 70 to 74 age range to a minimum of 14 subjects in the 85 and above age range. The mean age of the sample is 74 years (SD = 7), the mean years of education throughout the sample is 15 (SD = 2.6), and subject ethnicity is 99% Caucasian (208) and 1% Asian (2). The mean follow-up length (years of data after baseline) is 10.7 years (SD = 4.2), which provides valuable data on within-subject variability across evaluations. Norms obtained in this study were similar to currently-used norms, except for JLO and TMT, particularly amongst the younger age cohort.

Conclusions: The current study established a cohort of participants that can be confidently classified as cognitively normal. The exclusion of prodromal cognitive decline within this data set increases its sensitivity for use in clinical and research settings. Normative data for several measures were similar to commonly-used datasets, but varied on measures assessing attention and visuospatial skills. Based on this normative data set, better performance can be expected than previously thought in these areas. This data may be more sensitive to detect early change in parietal function and subcortical networks. Additionally, this study uniquely features a long follow-up period and provides data regarding within-subject variability, which offers unique insight into expected annual performance variation in neurotypical adults. This repeat assessment data can inform clinical judgement regarding meaningful change over time.

POSTER #35

INTESTINAL MICROBIOTA DYSBIOSIS IN TRANSGENIC ALZHEIMER'S DISEASE MOUSE MODELS. Jentarra G, Jones D, Dodiya H, Chu P, Gonzalez F, Vallejo J, Huang V, Potter P, Jones TB. Midwestern University; University of Chicago; Arizona Alzheimer's Consortium.

Background: Studies of the microbiota-gut-brain axis are yielding increasingly valuable data relevant to a wide variety of disorders and to our basic understanding of how our microbiomes influence our health and mental status. Intestinal dysbiosis has been associated with many neurologically based conditions, including depression, anxiety, autism, and Parkinson's disease. Interactions between the microbiota, the enteric nervous system, and the central nervous system are understood to be bidirectional and can affect metabolic, neurological, immunological, and endocrine functions. Dysbiosis of the gut microbiota has been implicated in the development of Alzheimer's disease (AD) and a variety of studies have found multiple bacterial taxa that are significantly altered in AD patients in comparison to cognitively normal controls. Some changes were also associated with an increase in cerebrospinal fluid biomarkers of AD, suggesting a link between the dysbiosis and abnormalities consistent with AD. While investigating the possible presence of bacteria within the brains of AD mouse models using germ-free mice as controls, we also collected fecal pellets from those animals to compare gut microbiome composition between the mouse models and test for correlations with bacterial sequences in brain tissue from those mice.
Methods: Germ-free mice were bred and raised in the University of Chicago animal facility. All other mice were bred and raised in the MWU animal facility. All dissections and tissue collection were performed under sterile conditions in a biosafety cabinet. Following perfusion with cold, sterile saline to remove blood, mouse brain tissues were collected from 4 month-old germ-free mice (controls), along with brain tissue from 6-12 month-old APOE3, APOE4, and 3xTg mice. Brain tissue was subsequently dissected to separate cortex, cerebellum, and olfactory bulbs. Fecal pellets from the terminal colon of each of the mice were also collected at the time of sacrifice. DNA was extracted from tissues and pellets using the Qiagen DNeasy PowerSoil kit. Methylated mouse genomic DNA was then removed from the DNA samples using the NEBNext Microbiome DNA Enrichment Kit. DNA was sent to Translational Genomics Research Institute (TGen) for 16S rRNA gene sequencing.

Results: We ultimately found only very low levels of microbial DNA in the brain tissue samples. These low levels were not useful in discriminating between mice from different genotypes. However, we did note a striking difference in the gut microbiomes of APOE3 and APOE4 transgenic mice versus 3xTg mice. In APOE transgenic mice, Lactobacillus and Muribaculaceae accounted for ~75% of the reads in each sample. In 3xTg mice, the microbiota was dominated primarily by Lachnospiraceae_NK4A136 and Lachnospiraceae, with smaller amounts of Turicibacter and Roseburia. Lactobacillus and Muribaculaceae were nearly absent from the 3xTg mice, which is particularly notable since they normally make up a large part of the intestinal microbiota of mice.

Conclusions: Substantial unexplained differences were found between the gut microbiomes of APOE and 3xTG mouse models of AD. The level of the differences observed indicate that there may be strong mechanisms affecting the ability of different types of bacteria to effectively colonize the intestinal tracts of these two mouse models, and it is possible that these mechanisms are directly related to the transgenes present in these mice. We are planning additional experiments to confirm these initial results, co-house mice to see if they can adopt the gut microbiomes of cage mates, and further explore the mechanisms which may affect bacterial colonization of the gut in these mice.

POSTER #36*

ADENOSINE TRIPHOSPHATE BINDING CASSETTE SUBFAMILY C MEMBER 1 (ABCC1): A POTENTIAL THERAPEUTIC TARGET FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

Jepsen WM, De Both M, Siniard AL, Ramsey K, Piras IS, Naymik M, Henderson A, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: ABCC1 has been demonstrated to export amyloid beta (Abeta) from the endothelial cells of the blood–brain barrier to the periphery, and that activation of ABCC1 can reduce amyloid plaque deposition. Here, we show that ABCC1 overexpression significantly reduces Abeta production and increases the ratio of alpha- versus beta-secretase mediated cleavage of the amyloid precursor protein (APP).

Methods: BE(2)-m17 neuroblastoma cells were transfected for APP overexpression, and either ABCC1 or empty-vector control using the Sleeping Beauty Transposon system. For APP metabolite experiments, supernatants were harvested and Abeta1-40, Abeta1-42, sAPPalpha, and sAPPbeta were measured via ELISA or MSD. For Abeta export assay, cells were treated with fluorescently labelled Abeta1-42, and the percentage of fluorescent cells was measured via flow cytometry. Transcriptomes were sequenced to identify differentially expressed genes that may account for altered APP processing. TaqMan was used to confirm differential expression of genes of interest in a neuron/astrocyte co-culture.

Results: Across four APP metabolite experiments, ABCC1-overexpressing cells had significantly lower extracellular levels of Abeta1-40 and Abeta1-42 compared to the control line. The mean extracellular ratio of sAPPalpha to sAPPbeta was increased in the ABCC1-overexpressing cells, indicative of increased alpha-secretase or decreased beta-secretase cleavage of APP. For Abeta export assay, ABCC1-overexpressing cells had a lower population percentage of fluorescent cells than the empty-vector control cells. When also treated with thiethylperazine, a small molecule shown to increased ABCC1-meditated export of Abeta, ABCC1-overexpressing cells showed a larger decrease in population fluorescence compared to the control. Transcriptomic analysis revealed significant decreases in expression of TIMP3 and CD38 in the ABCC1-overexpressing cells compared to the control, and this was confirmed in the neuron/astrocyte co-culture.

Conclusions: We have confirmed that ABCC1 is capable of exporting Abeta from the cytoplasm to the extracellular space. We add to the literature that increasing ABCC1 expression results in a significant decrease in the extracellular levels of Abeta and skews APP processing away from the beta- and towards the alpha-secretase pathway. This likely occurs due to modulation of the expression levels of TIMP3, CD38, or both. Many drug development pipelines have already been used to identify molecules that decrease ABCC1 expression, or that inhibit ABCC1 export. Drugs identified that can do the opposite of this should be studied in the context of Alzheimer's disease.

*Abstract accepted for publication in lieu of poster presentation

POSTER #37

DO YOU KNOW WHO I AM? A PERSON CENTERED CARE INTERVENTION IN AN ACUTE CARE SETTING. Johnson K. Honor Health Thompson Peak Medical Center.

Background: Hospitalized older adults present with diverse needs and cognitive and functional limitations. Person-centered care (PCC) is an approach to help personalize interventions among older adults with cognitive and functional limitations to provide safe empathic care. The concept of PCC extends and develops the concept of patient centeredness which focuses mainly on patients and their significant others and how the culture of care and a care environment can enable them to provide PCC.

Methods: Evaluate whether introduction and implementation of a PCC intervention using an "All About Me Board" (AAMB) could change workplace climate perception among registered nurses (RN)s during patient interactions and increase patient satisfaction. A pre/post design among 25 RNs on a 28 bed Adult Medical Surgical unit. The AAMB PCC tool was used to display information about what patients liked to be called, what made them feel calm, favorite music, past occupation, hobbies, and names of family members and pets. The AAMB tool has been used in long term care facilities. With an increase in hospitalized older adults, communication boards need to be used to enhance person centered care.
Outcome Measures: The Patient Centered Climate Questionnaire Staff (PCQ-S) measured the climate of the unit environment perceived as being person centered by RNs. Patient satisfaction was measured using a Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) patient perspectives on care question; "During this hospital stay how often did nurse's listen carefully to you". RN's were educated about the concepts of PCC and the purpose of and use of the AAMB tool. The AAMB was placed in patient rooms. The RN explained the purpose of the AAMB to patients and families and invited them to complete items on the AAMB. Staff were asked to present one item from the AAMB during shift report.

Results: Increase from pre/post-test means for all subscales; Safety, pre-test ($m = 1.573$, sd .8248) post-test ($m = 1.640$, sd .7286); Community, pre-test ($m = 1.773$, sd .7982) post-test ($m = 3.293$, sd 8.6895); Everydayness pre-test ($m = 1.893$, sd .7273) post-test ($m = 3.347$, sd 8.6595); and Comprehensibility ($m = 1.467$, sd .6438) post-test ($m = 1.867$, sd .1160). There was a statistically significant difference for the subscale Comprehensibility ($t(74) = 2.742$, $p < .008$). For HCAHPS, there was an increase in "always" three months pre (84% to 86%) and post, (80% to 95%). There was an increase in the perception that nurses listened to their patients. Staff reported when they entered a patients room they would see the poster displayed and would mention one thing on that board to start a conversation or to engage patients. Nurses mentioned the majority of patients and their families took the AAMB with them at discharge to keep at home. One patient reported that he felt that he was heard and was not just a number while he was a patient. When the AAMB was first introduced to nursing, some nurses felt this was one more task to add to their day. It was suggested at a unit huddle that other healthcare providers caring for the patient could add information to the AAMB.

Conclusions: Acute care settings that embrace PCC can provide optimal care for the anticipated 55 million older adults that will make up the $500 billion in annual Medicare spending, a population who represent a majority of an inpatient population. With a robust older adult population in acute care hospitals a PCC approach can improve the quality of patient care and improve outcomes by including patients and families in all aspects of care and decision making. It is crucial for nurses to pursue opportunities to ensure that PCC interactions are part of daily practice.

POSTER #38

DYSREGULATION OF HOMOLOGS RETINOBLASTOMA BINDING PROTEIN (RBBP) 4 AND 7 IN THE CONTEXT OF ALZHEIMER'S DISEASE. Judd JM, Piras IS, Dave N, Mastroeni D, Huentelman MJ, Velazquez R. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Recently, we identified the retinoblastoma binding protein 7 (Rbbp7) as a mediator against tau pathology observed in Alzheimer's disease (AD) and related tauopathies. Indeed, in human post-mortem brain tissue, AD patients have significantly lower Rbbp7 mRNA expression in the middle temporal gyrus (mtg) compared to age-matched controls and Rbbp7 mRNA expression is negatively correlated with Braak staging (a measure of pathological tau inclusions). We also found evidence that rescuing Rbbp7 levels in mouse models of tauopathies reduces tau acetylation and phosphorylation, key steps leading to tau tangle pathology. Notably, Rbbp7 and Rbbp4 share 92% homology and are expressed in many shared complexes, including complexes implicated in diseased aging and neurodegeneration. Interestingly, decreases in Rbbp4 in the entorhinal cortex has been implicated in normal cognitive aging in both humans and rodent models. Given this homology, in the present study, we examined Rbbp4 mRNA expression levels in various regions of AD post-mortem brain tissue and its changes relative to Rbbp7.

Methods: We used two cohorts of post-mortem brain tissue obtained from the Arizona Study of Aging and Neurodegenerative Disorders/Brain and Body Donation Program. The first cohort included a total of 56 brain samples of young (n = 21, M = 35.4yrs), aged (n = 18, M = 80.7yrs) and AD (n = 17, M = 86.7yrs) patients. The brain area examined for the first cohort included the entorhinal (ent) cortex. The second cohort included a total of 187 brain samples (n = 89 AD, M = 84.66yrs; n = 98 age-matched controls, CTL, M = 84.98yrs) and the brain area examined included the mtg (Broadmann area 21). Subject age, gender, and postmortem autopsy intervals were not significantly different per groups. Rbbp4 mRNA expression was measured by microarray for both the ent cortex and mtg. In the mtg, Rbbp4 mRNA and neuropathological hallmarks were assessed including neuritic plaque density, Braak neurofibrillary staging, and brain weight correlations.

Results: Quantitative analysis revealed that Rbbp4 is significantly upregulated in the ent cortex of patients with AD relative to young and aged controls. Similarly, we found increased Rbbp4 mRNA expression in the mtg of the second cohort in AD patients. Further analysis of mtg tissue showed that Rbbp4 mRNA expression is positively correlated with neuritic plaque density in AD brains, and a non-significant positive correlation between Rbbp4 and Braak staging. Interestingly, we found that Rbbp4 and Rbbp7 are negatively correlated in AD post-mortem brain tissue, illustrating that as Rbbp4 goes up, the levels of Rbbp7 go down. There was no significant correlation between Rbbp4 and brain weight.

Conclusions: These results highlight a potential association of Rbbp4 in AD related pathologies. Future studies will investigate if the increase in Rbbp4 leads to a pathogenic decrease in Rbbp7 to compensate, further deciphering the role of the Rbbps' in the context of AD and related tauopathies.

POSTER #39

AMYLOIDOGENIC MEDIN INDUCES ENDOTHELIAL CELL PROTHROMBOTIC ACTIVATION. Karamanova N, Truran S, Davies H, Madine J, Migrino RQ. Phoenix VA Health Care System; University of Liverpool; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Vascular aging is characterized by acquisition of a pro-inflammatory and prothrombotic phenotype independent of cardiovascular metabolic risk factors through still unknown mechanisms. Medin is an amyloidogenic peptide formed as a cleavage product of milk fat globule EGF factor 8 protein. It accumulates in the vasculature with aging and is one of the most common yet poorly understood human amyloid proteins. Cerebrovascular medin was shown to be strongly associated with vascular dementia and Alzheimer's disease. It was shown to induce endothelial pro-inflammatory activation and endothelial dysfunction. We aim to test the hypothesis that medin induces prothrombotic activation in endothelial cells.

Methods: Recombinant medin was expressed in Lemo 21 (DE3 cells) and purified. Human umbilical vein endothelial cells (HUVECs) were exposed to either vehicle or medin (5 μM, a dose found to be physiologically relevant in human tissue) for 20 hours. Cell lysates were measured for protein content of tissue factor (TF, receptor and cofactor for factor VII and initiates coagulation), plasminogen activator inhibitor-1 (PAI-1, inhibits plasminogen activators that promote fibrinolysis) and thrombomodulin (cell surface glycoprotein that inhibits procoagulant function of thrombin) using standard Western blot and compared.

Results: Physiologic dose of medin induced increased endothelial cell protein expression of TF (3.15±0.8x, $p=0.02$), PAI-1 (1.76±0.14x, $p<0.001$) and reduced protein expression of thrombomodulin (0.55±0.1, $p=0.006$).

Conclusions: Medin induces prothrombotic activation in human endothelial cells and may be a key novel mediator in the development of vascular aging phenotype. This may have pathophysiologic translational implication in cerebrovascular disease, vascular dementia and Alzheimer's disease.

POSTER #40

COMPLEMENT C3A RECEPTOR (C3AR) DEFICIENCY IS NEUROPROTECTIVE IN MOUSE VCID MODEL. Kindelin A, Nadeem M, Bhatia K, Preul MC, Waters MF, Ducruet AF, Ahmad S.
Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Vascular contributions to cognitive impairment and dementia (VCID) makes up 50% of the cases of dementia however, till date the mechanisms involved in development and progression of VCID are unknown. The complement pathway is a well-established regulator of innate immunity in the brain. We and others have reported that genetic deficiency of complement C3a receptor (C3aR) or its pharmacological inhibition in rodents protect against cerebral ischemia and AD. In the current study we evaluated the role of complement C3a-C3aR signaling in VCID.

Methods: Male C3aR knockout (C3aR-/-) and wild-type (C3aR+/+) mice (Age: 12 weeks; N=8-10/gp) were subjected to either VCID with bilateral common carotid artery stenosis (BCAS) or sham surgery. At 4-mo post-BCAS, changes in cerebral blood flow (CBF) were determined with laser speckle contrast analysis. Histopathology with Luxol-Fast Blue (LFB) staining, and protein biochemistry with immunostaining/Western blotting were also performed for inflammatory and oxidative stress markers.

Results: BCAS resulted in reduced CBF in both groups (WT and KO) compared to their sham controls however, BCAS-KO demonstrated improved CBF than BCAS-WT. BCAS-WT showed significantly higher expression of C3a in plasma and C3aR in brain lysates compared to their sham-controls. Greater neuroinflammation-glial, endothelial and oxidative stress markers (Iba1, ICAM1, STAT3, DHE) were increased in BCAS-WT animals vs Sham but these inflammatory/oxidative stress signaling were reduced in BCAS-KO mice.

Conclusions: Increased C3a/C3aR signaling in brain leads to increased neuroinflammatory/oxidative stress molecules and reduced CBF. However, C3aR deletion attenuates this effects thereby offering protection in VCID. Future studies warrant investigation into C3aR inhibitors to represent a therapeutic option for treatment of VCID.

POSTER #41

LARGE-SCALE BIOMANUFACTURING: PURIFICATION AND CRYOPRESERVATION OF NEURAL CELL TYPES. Knittel J, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Many current models are used to elucidate the pathogenesis and contributing risk factors of Alzheimer's disease (AD). Our lab has focused efforts on using isogenic human induced pluripotent stem cells (hiPSCs) to uncover the mechanism behind amyloid beta plaque formation noted in AD. Isogenic models reduce the genetic variation between samples, however we have demonstrated that our cortical neuron differentiation protocol yields a small number of astrocytes, which increases variability. Purifying the populations produced from our differentiations may be useful when investigating AD mechanisms. To that end, large-scale biomunfacturing provides the platform to produce reliable cell populations. Moreover, the ability to cryopreserve the purified populations allows for invariable, reproducible studies.

Methods: The large-scale differentiations of hiPSC-derived neural progenitor cells (NPCs) started on polystyrene microcarriers coated with a defined substrate, vitronectin derived peptide (VDP). Cell aggregates formed and were cultured with neural differentiation media including brain derived neurotrophic factor (BDNF) and glial derived neurotrophic factor (GDNF) for 30 days. After 30 days, the neural aggregates were dissociated with a papain solution and magnetically sorted for CD44. The CD44- fraction was separated from the CD44+ fraction and seeded onto Matrigel coated plates and cultured using neural differentiation media or astrocyte media, respectively. The CD44- cells were cryopreserved with CyroStor® and the CD44+ with fetal bovine serum (fetal bovine serum) and 10% dimethyl sulfoxide (DMSO). Pre-sort and post-sort cells were characterized with flow cytometry for PI and calcein AM as a viability measure. Pre-sort and post-sort cell phenotypes and purity were assessed with immunofluorescence and CD44 flow. Cell functionality was assessed by calcium imaging. Pre- and post-thaw populations were characterized with RNA sequencing, calcium imaging, and immunofluorescence to demonstrate the maintenance of purity and cell phenotype. The CD44- cells were additionally characterized pre- and post-thaw with an Apolipoprotein E (APOE) ELISA to assess cell functionality.

Results: Our large-scale culture method generated on average 4.2 million neural cells per mL of culture media. All cell populations (mixed, CD44-, and CD44+) were <98% viable. These three populations were further characterized with immunofluorescence which suggested the CD44- fraction contained neurons positive for NEUN, MAP2 and TUJ1 while the CD44+ fraction contained astrocytes positive for S100. The CD44- and CD44+ calcium imaging demonstrated prototypical traces for neurons and astrocytes, respectively. The neurons and astrocytes maintained their cell phenotypes and functionality after cryopreservation as demonstrated by RNA sequencing, calcium imaging, immunofluorescence and ELISAs.

Conclusions: This study outlines a method used to magnetically separate a pure astrocyte and neuron culture from our large-scale differentiations on microcarriers coated with VDP. Additionally, we describe a method to freeze and thaw the two cell types, while maintaining their viability. With this protocol, our lab will continue investigating the cell specific roles of neurons and astrocytes in the pathogenesis of AD.

POSTER #42

A NOVEL TAU-BASED RHESUS MONKEY MODEL OF ALZHEIMER'S PATHOGENESIS.
Kordower JH, Beckman D, Chakrabarty P, Donis-Cox K, Morrison JH. Arizona State University; University of California Davis; University of Florida, Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a devastating condition with no effective treatments, with promising findings in rodents failing to translate into successful therapies for patients.

Methods: Targeting the vulnerable entorhinal cortex (ERC), rhesus monkeys received two injections of an adeno-associated virus expressing a double tau mutation (AAV-P301L/S320F) in the left hemisphere, and control AAV-green fluorescent protein in the right ERC. Noninjected aged-matched monkeys served as additional controls.

Results: Within 3 months we observed evidence of misfolded tau propagation, similar to what is hypothesized to occur in humans. Viral delivery of human 4R-tau also coaptates monkey 3R-tau via permissive templating. Tau spreading is accompanied by robust neuroinflammatory response driven by TREM2+ microglia, with biomarkers of inflammation and neuronal loss in the cerebrospinal fluid and plasma. At six months, the model evolved to include neuronal loss in the subiculum and hippocampal subfields, the progression of AT8 pretangle pathology to thioflavin S neurofibrillary tangle formation, and permissive templating across the entorhinal cortex connectome to include retrospenial cortex, contralateral entorhinal cortex and multiple neocortical regions. The tauopathy was easily discerned in vivo using tau PET ligands.

Conclusions: These results highlight the initial stages of tau seeding and propagation in a primate model, a more powerful translational approach for the development of new therapies for AD.

POSTER #43

COMPENSATORY AND LIFESTYLE-BASED BRAIN HEALTH PROGRAM FOR SUBJECTIVE COGNITIVE DECLINE: SELF-IMPLEMENTATION VERSUS COACHING. Locke D, Liou H, Shah A, Buckner S, Stonnington C. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Subjective Cognitive Decline (SCD) is currently estimated to affect 11% of adults in the U.S. and is a risk factor for further cognitive decline. Numerous studies have shown the benefit of brain health behaviors (e.g., cognitive exercise, physical exercise) as well as multi-component brain health maintenance programs (e.g., FINGER study). However, there is currently no consensus regarding the standard of care for SCD beyond monitoring for abnormality, nor are there any proposals for translating the brain health intervention research literature into practical clinical programs. Our goal with this pilot project was to bridge this gap through initial evaluation of a potentially scalable, patient-centered, cognitive health program. This intervention is an extension of the Brain Booster's program originally developed by collaborators at University of California-Davis (Denny et al., 2019).

Methods: Patients seen by geriatricians in primary care or the neurology service at Mayo Clinic were offered enrollment in this pilot project. Inclusion criteria included age 50 or older, subjective cognitive concerns, normal cognitive performance on the MoCA for age and education, self-reported independent function (IADL=8), English speaking, and approval from a physician for the exercise component. All participants completed a one-hour consultation with a neuropsychologist for discussion of behavioral recommendations for cognitive compensation and brain health and were provided a packet of materials with which they were encouraged to implement those recommendations. Participants were then randomized to either self-implement the recommendations (n=11) or to participate in 10, 2-hour group coaching classes to implement these recommendations.

Results: Of the 29 patients who agreed to be contacted for the study who were reached, 21 enrolled in the study. 2 patients were ineligible after the enrollment screening. 6 opted not to enroll. For those who completed the coaching classes, they completed 86% of the classes and a median of 80% of the assigned homework.

There were no statistically significant differences between groups on the primary and secondary self and informant-report measures. However, on the primary measures, all participants showed in increase in physical exercise minutes by treatment end with no difference between those who self-implemented and those who attended the classes [effect size (ES)=.54]. There was also significant increase in compensatory strategy use, rated by the participant themselves and an informant, again in both treatment groups and sustained at the 6-month follow-up (ES=.51 & .76). On secondary measures, both treatment groups showed reduction in self-report anxiety symptoms at 6 months (ES=.62) and their informants reported sustained improvement in daily functioning at 6 months (ES=.81).

Conclusions: Older adults want increased attention to brain health by their medical providers. Despite robust research literature showing the impact of single component or multi-component brain health interventions, there is a dearth of translational research aimed at the development of sustainable clinical interventions to meet patient needs. This pilot project suggests that self-implementation after a single consultation with specific materials provided and a short trial of group-coaching classes may be viable translational clinical services. Further research that involves patient-choice, with larger samples, and further investigation of reducing barriers to coaching classes is recommended.

POSTER #44

PLASMA NFL IS ASSOCIATED WITH APOE E4 ALLELIC DOSE, HIPPOCAMPAL ATROPHY AND ALZHEIMER'S-RELATED CEREBRAL HYPOMETABOLISM IN COGNITIVELY UNIMPAIRED LATE-MIDDLE-AGED AND OLDER ADULTS. Malek-Ahmadi M, Su Y, Devadas V, Luo J, Ghisays V, Protas H, Chen K, Blennow K, Zetterberg H, Caselli RJ, Reiman EM. Banner Alzheimer's Institute; University of Gothenburg; Mayo Clinic Arizona; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: Plasma neurofilament light (NfL) measurements appear to provide an indicator of neuronal neurodegeneration and/or injury in persons with Alzheimer's disease (AD) and a wide range of other neurological disorders. Here, we used an ultra-sensitive assay to characterize plasma NfL measurements in cognitively unimpaired (CU) late-middle-aged and older adults with two, one or no copies of the APOE4 allele, the major genetic risk factor for AD, test our hypotheses that this plasma NfL concentrations are associated with APOE4 allelic dose, MRI measurements of hippocampal atrophy, and FDG PET "hypometabolic convergence index (HCI)" measurements that reflect cerebral glucose hypometabolism in brain regions preferentially affected by AD. We also explored associations with PET measurements of cerebral amyloid plaque and tau tangle burden and MRI measurements of white matter hyperintensity (WMH) volume.

Methods: Plasma NfL concentration was measured using a Single molecule array (Simoa) assay on an HD-X Analyzer in 194 CU 69±9 year-old participants from the Arizona APOE Cohort Study, including 43 APOE4 homozygotes (HM), 51 heterozygotes (HT), and 100 non-carriers (NC). Generalized linear models were used to characterize associations with APOE4 allelic dose before and after adjustment for age, sex, and education to characterize associations with hippocampal volume, HCI, mean cortical PiB PET measurements of amyloid plaque burden, meta-region-of-interest (meta-ROI) flortaucipir PET measurements of tau tangle burden, and VMH volume before and after adjustment for age and APOE4 allelic dose. The association between NfL and the Delayed Recall portion of the Rey auditory verbal learning test (AVLT) was also explored.

Results: Plasma NfL levels were associated with APOE4 allelic dose after adjustment for age, sex and education ($p=0.006$, HM>HT>NC), and they were also associated with our brain imaging measurements of neurodegeneration after adjustment for age, sex, education, and APOE4 allelic dose ($p<0.001$ for hippocampal volume and $p = 0.003$ for HCI). A non-significant trend suggested a possible association between plasma NfL levels and tau tangle burden ($p=0.07$), which according to a post hoc analysis may be moderated through the associated effect on brain imaging measurements of neurodegeneration ($p = 0.008$). There were no significant associations with amyloid plaque burden or WMH volume. A weak, but statistically significant, correlation was noted for NfL and AVLT Total Learning ($r = -0.27$, $p<0.001$).

Conclusions: Plasma NfL measurement, a promising blood-based biomarker of neuronal degeneration, is associated with APOE4 allelic dose and brain imaging measurements of neuronal degeneration in CU adults, adding further support for its value as an indicator of neuronal degeneration in the preclinical study of AD.

POSTER #45

AMYLOID BETA PROTECTS ELDERLY MICE FROM SUCCUMBING TO INFECTION WITH THE NEUROTROPIC PARASITE TOXOPLASMA GONDII. McGovern KE, Koshy AA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Data suggest that amyloid beta (Aβ), produced by processing of the amyloid precursor protein, is a major initiator of Alzheimer's disease (AD) and a highly conserved anti-microbial peptide. Although Aβ accumulation is thought to be detrimental to the brain as a trigger of pathology, like neuroinflammation, efforts to cure AD by clearing Aβ have failed in part because this strategy can lead to reactivation of latent disease. Thus, more work is needed to understand how Aβ may be needed in the brain, where the actions of the adaptive immune system are more restricted compared to other organs in the body. Using the intracellular, neurotropic parasite Toxoplasma gondii, we are exploring how infection impacts Aβ levels in the brain, how Aβ may combat the parasite, and whether Aβ's importance may change as organisms age.

Methods: To address whether Aβ is an effective antimicrobial peptide in response to T. gondii infection, in vitro experiments were performed to determine if and how Aβ may protect against infection. Further, in vivo infection studies were performed to assess whether the presence of excess Aβ is helpful during infection and whether young adult and elderly mice benefit from the accumulation of excess Aβ in the brain.

Results: We found that Aβ is effective at protecting cells from invasion by the parasite as the concentration of the peptide in culture media increases. We also found that parasites that have been exposed to Aβ replicate more slowly within cells once they do invade. In vivo, while excess Aβ does not protect the brain from colonization by the parasite, mice with excess Aβ have a significantly lower parasite burden in the brain, indicating that Aβ may help clear the brain of pathogens that have breached the blood-brain barrier. Further, we have found that these protective effects are only beneficial to elderly mice as aged (18mo+) mice with excess Aβ are able to survive T. gondii infection, while their WT littermates are not.

Conclusions: These data are supportive of the idea that the presence of Aβ could be beneficial as we age. Current work is focused on whether Aβ is directly toxic to T. gondii or if, as seen in viruses, the aggregation of Aβ traps the pathogen, making it more vulnerable to clearance by the immune system. Future work will include examining how excess Aβ impacts the functions of the immune system and how pathogens like T. gondii may have evolved ways to subvert the antimicrobial actions of Aβ.

POSTER #46

THE IMMEDIATE EARLY GENE EGR3 INFLUENCES EXPRESSION OF ALZHEIMER'S DISEASE GENE TREM2. Ozols AB, Marballi KK, Meyers KT, Beck KL, Shrourou FY, Hossain AB, Morrison HW, Gallitano AL. University of Arizona; Arizona State University; Syracuse University; Arizona Alzheimer's Consortium.

Background: Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is a cell-surface immune receptor on microglia that has recently been linked to Alzheimer's Disease (AD). Rare coding-region variations in the TREM2 gene increase the risk to develop AD up to 4.7 fold. However, almost nothing is known about the mechanisms that regulate Trem2 gene expression. Recent studies have identified the transcription factor Early growth response 3 (EGR3) as a key regulator of differentially expressed genes in AD. Single-cell transcriptomics of mouse and human brain show that the Egr3 gene is highly expressed in microglia. As an activity-dependent transcription factor, the immediate early gene EGR3 is a strong candidate for regulation of the Trem2 gene.

Methods: Electroconvulsive seizure (ECS) was used to activate immediate early gene expression in Egr3-deficient (Egr3-/-) and wildtype (WT) littermate mice. An expression microarray study was conducted to identify target genes regulated by EGR3 in the hippocampus. Quantitative real-time PCR (qRT-PCR) was performed to validate the microarray results for the gene Trem2. RNAscope in situ hybridization studies were performed to analyze the expression of Trem2 and Egr3 in the dentate gyrus (DG), CA1, and CA2/3 of the hippocampus in Egr3-/- and WT mice following ECS, compared with sham treatment. IBA1 antibody staining, a microglia specific marker, was used to identify the number of microglia in the hippocampi of WT and Egr3-/- mice. To investigate the possibility that EGR3 may directly regulate Trem2 expression, we searched the Trem2 promoter for transcription factor binding sites using the TFBind program.

Results: The results of our expression microarray study showed that Trem2 was differentially expressed in the hippocampus of Egr3-/- mice compared to their WT littermates. Our qRT-PCR studies support the initial finding that expression of Trem2 is deficient in Egr3-/- mice compared with WT controls following ECS. RNAscope in situ hybridization studies show that Trem2 and Egr3 co-localize in microglia cells, and levels of Trem2 and Egr3 expression are positively correlated in the hippocampus. Preliminary immunohistologic analyses suggest that Egr3-/- mice have reduced levels of hippocampal Trem2 expression compared to WT mice. However, the number of microglia is not reduced in Egr3-/- compared to WT mice, indicating that the reduction in Trem2 expression is not due to loss of the cells that express the gene. Analysis of transcription factor binding sites using the TFBind program revealed several high probability EGR3 binding sites in the mouse Trem2 promoter.

Conclusions: Together, these findings suggest the possibility that EGR3, a stimulation-responsive transcription factor, may directly regulate expression of the AD-associated gene Trem2.

POSTER #47

MEMORY AND THE HIPPOCAMPAL SYSTEM IN AGING ADULTS WITH AUTISM SPECTRUM DISORDER: LONGITUDINAL VERSUS CROSS-SECTIONAL FINDINGS. Pagni BA, Walsh MJM, Sullivan G, Ofori E, Alvar J, Chen K, Braden BB. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Research aimed at understanding aging in adults with autism spectrum disorder (ASD) is growing, but critical longitudinal work in middle-age and older adults has yet to emerge. Adults with ASD struggle with tasks involving verbal memory compared with matched neurotypicals (NTs). This may be related to differences in size or integrity of the hippocampus and its primary structural pathway, the fornix. The aim of this study was to explore cross-sectional and longitudinal aging differences in immediate and delayed verbal memory abilities in individuals with ASD compared with NTs. We also measured hippocampal size and fornix fractional anisotropy (FA).

Methods: We recruited 192 adults between the ages of 18-70 years with (n=103, 72 male, 40.01±16.17 years) and without (n=89, 52 male, 40.74±16.81 years) ASD who were intellectually-able (IQ≥70). NT adults and adults with ASD who were over the age of 40 (ASD n=24; NT n=22) were evaluated at two time points two to three years apart. Hippocampal volume was measured by analyzing T1-weighted MRI images with FreeSurfer. Fornix FA was measured from diffusion tensor imaging (DTI) scans with custom scripts in Matlab. Verbal memory ability was measured with the Rey Auditory Verbal Learning Test. For cross-sectional relationships with age, multiple regression analyses were conducted with diagnosis, age, diagnosis by age interaction, and sex as a covariate. For longitudinal analyses in middle-age adults, repeated measures ANCOVA were conducted with sex as a covariate.

Results: Cross-sectionally, there were main effects of diagnosis on immediate and delayed verbal memory where NT adults performed better than adults with ASD. There was also a diagnosis by age interaction on immediate verbal memory such that increasing age correlated with worse recall in NT adults, but there was no age relationship in adults with ASD. No diagnosis main effects or interactions for hippocampal volume or fornix FA were found. Longitudinally, diagnosis group by time interactions were detected for immediate verbal memory and hippocampal volume, such that adults with ASD declined over time, while performance and volume were stable in NT adults. There were no longitudinal group differences for fornix FA.

Conclusions: Findings suggest age-related vulnerabilities for memory and hippocampal system in adults with ASD. Longitudinal findings highlight vulnerabilities in immediate verbal memory and hippocampal volume. Cross-sectional divergent age findings could be due to cohort effects, highlighting the need to account for between-subject difference and larger sample sizes. Future longitudinal research should also examine cognitive and brain sex differences and seek to identify brain correlates of cognitive decline.

POSTER #48

ASSOCIATIONS BETWEEN DIFFERENT FDG PET INDICES AND CLINICAL RATINGS IN COGNITIVELY UNIMPAIRED OLDER ADULTS. Protas HD, Chen K, Chen Y, Luo J, Raichle M, Morris JC, Benzinger T, Goyal M, Vlassenko A, Reiman EM, Su Y. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona State University; Washington University School of Medicine; Arizona Alzheimer's Consortium.

Background: FDG PET measurements of cerebral glucose hypometabolism in brain regions that are preferentially affected by Alzheimer's disease (AD) are known to be associated with clinical decline. However, commonly used FDG PET indices such as the standard uptake value ratio (SUVR) lack the sensitivity to detect early metabolic changes associated with cognitive decline. In this study we examine whether the full quantitative FDG net uptake rate (Ki) can track metabolic change in cognitive unimpaired elderly (CU) and compare that with indices that do not require full dynamic acquisition including the AD-related hypometabolic convergence index (HCI), the AD-related statistical region of interest (sROI), and regional SUVRs from known AD affected brain regions, e.g. precuneus (SUVRpre), posterior cingulate (SUVRpc) and hippocampus(SUVRhipp).

Methods: Dynamic FDG PET images were acquired between 0 and 60 min after intravenous radiotracer administration in 75 subjects (all with CDR=0, age 67±7 years) from Washington University cohort. Full quantification of FDG PET was achieved using an image-derived arterial input function to estimate hippocampal Ki. A Patlak model with reference region was used to estimate the hippocampal relative uptake rate Ri. HCI, sROI, SUVRpre, SUVRpc, SUVRhipp were also estimated using the last 30 minutes of data from each dynamic scan. Using Pearson correlation (r), we examined MMSE association with Ki, Ri, SUVRpre, SUVRpc, SUVRhipp, HCI and sROI each separately. Using statistical Steiger test, we compared the difference of these correlation strengths.

Results: Lower hippocampal Ki and AD-related sROI FDG measurements were significantly correlated with lower MMSE in CU older adults ($r=0.31$, $p=0.007$, $r=0.27$, $p=0.019$), but not Ri, HCI, SUVRpre ,SUVRpc, and SUVRhipp ($r=0.09,-0.06,0.13,0.12,0.03$, $p>0.28$). MMSE correlations with hippocampal Ki and AD-related sROI measurements were not significantly different ($p=0.74$, Steiger test). Among the FDG indices that did not require full dynamic scan, sROI also had the strongest correlation with Ki ($r=0.39$, $p<0.001$).

Conclusions: Among the tested FDG PET indicators of AD, lower Hippocampal Ki and AD-related sROI measurements were associated with lower clinical ratings in CU older adults. Additional studies are needed to clarify the extent to which they predict subsequent cognitive decline.

POSTER #49

PHYSICAL ACTIVITY IS ASSOCIATED WITH INCREASED RESTING-STATE FCMRI IN NETWORKS PREDICTIVE OF COGNITIVE DECLINE IN CLINICALLY UNIMPAIRED OLDER ADULTS. Pruzin JJ, Klein H, Rabin JS, Schultz AP, Kirn DR, Yang H-S, Buckley RF, Chou H-C, Scott MR, Properzi M, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP. Massachusetts General Hospital, Harvard Medical School; Banner Alzheimer's Institute; Sunnybrook Health Sciences Centre, Toronto; University of Toronto; Brigham and Women's Hospital; University of Melbourne; Arizona Alzheimer's Consortium.

Background: While physical activity (PA) may promote resilience to cognitive decline and AD dementia, the mechanisms underlying this effect are poorly understood. Our group previously demonstrated lower levels of functional connectivity (rs-fcMRI) in the default, salience, and control networks were associated with greater prospective cognitive decline, both alone and synergistically with β-amyloid (Buckley and Schultz et al., 2017). In this context, we assessed whether higher PA may be associated with greater connectivity, and whether PA effects on connectivity may mediate the relationship of PA to prospective cognitive decline.

Methods: A waist mounted pedometer was used to record PA (steps/day during one week) in 167 cognitively unimpaired adults aged 63-90 (mean 74.0; SD 6.1) participating in the Harvard Aging Brain Study. Participants underwent baseline rs-fcMRI and β-amyloid imaging with Pittsburgh Compound B PET. We analyzed rs-fcMRI in the 3 networks previously associated with cognitive decline (default, salience, and control) as well as in 4 motor or sensory networks in which connectivity strength is not associated with cognitive change . Cognition was measured annually with the Preclinical Alzheimer Cognitive Composite (PACC). We used linear regression to examine associations between PA and connectivity in these networks, controlling for age, sex, and APOE e4 status. We conducted exploratory analyses using linear mixed effects models to examine if associations between PA and connectivity strength may partially explain PA associations with cognitive decline in the context of elevated β-amyloid.

Results: Higher baseline PA was significantly associated with increased connectivity in the default, salience, and control networks (all $p<0.017$) after adjusting for covariates and controlling for multiple comparisons. PA was not associated with connectivity in any of the other networks examined. Greater connectivity in these networks was a weak partial mediator of PA's association with longitudinal PACC decline in participants with elevated β-amyloid.

Conclusions: Greater PA is associated with increased connectivity in three networks (default, salience, and control) in which greater connectivity is associated with less cognitive decline. One potential mechanism by which PA may promote resilience to cognitive decline is through increased functional connectivity in a core set of AD-relevant cognitive networks.

POSTER #50

APOE4 DISRUPTS NEURON-TO-ASTROCYTE LIPID CLEARANCE. Qi G, Mi Y, Shi X, Gu H, Brinton RD, Yin F. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: The ε4 variant of apolipoprotein E (ApoE4) is the greatest genetic risk factor for late-onset Alzheimer's disease (AD). ApoE4 is known to not only impair amyloid-β (Aβ) clearance and promote its aggregation, but also perturb lipid homeostasis and energy metabolism in the brain. Metabolic coordination between neurons and astrocytes is critical for the health of the brain. However, the mechanistic role of ApoE4 in modulating the clearance and metabolism of lipid species across neurons and astrocytes is unknown.

Methods: To determine whether and how ApoE isoform affects neuron-astrocyte coupling of lipid metabolism, we co-cultured primary neurons with primary astrocytes of either ApoE3 or ApoE4 genotype using a trans-well co-culture system, in which neurons and astrocytes can exchange secreted contents without any physical contact. Neuron-astrocyte coupling of lipid metabolism was assessed in terms of the clearance of lipids from neurons and the transport to astrocytes for degradation.

Results: Either ApoE3 or ApoE4 astrocytes dramatically reduced the number and volume of neutral lipid content (lipid droplet, LD) in ApoE3 or ApoE4 neurons, with ApoE4 astrocytes showing a reduced ability to eliminate neuronal LDs. Consistent with reduced LD load, ApoE3 astrocytes, but not ApoE4 astrocytes, reduced total neuronal triglycerides and fatty acid (FA) levels. Targeted metabolomic analysis further confirmed that neuronal levels of saturated, medium- to long-chain FAs (C8-C19) were reduced in neurons but elevated in astrocytes after co-culture. Importantly, pulse-chase assay suggested that neutral lipids stored in neuronal LDs were transported into astrocytes, and the transport efficiency was reduced by ApoE4 expressed in either neurons or astrocytes. Functionally, we demonstrated that the lesser metabolic and synaptic support to neurons by ApoE4 astrocytes could be attributed to their impaired capability to clear neurotoxic lipids.

Conclusions: Collectively, our findings reveal a detrimental role of ApoE4 in regulating brain lipid metabolism that is coupled across neurons and astrocytes. Such a previously unappreciated mechanism could underlie the accelerated lipid dysregulation and energy deficits and increased AD risk for ApoE4 carriers.

POSTER #51

AMYLOID-B PLAQUES IN THE OLFACTORY BULB IN RELATION TO THE PATHOLOGIC PROGRESSION OF THAL AMYLOID STAGE IN ALZHEIMER'S DISEASE. Serrano GE, Russell A, Vargas D, Intorcia A, Walker J, Glass M, Arce R, Oliver J, Papa J, Nelson C, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Thal amyloid stage is correlated with cognitive function and is a measure of the progression of Alzheimer's disease (AD) within the brain. Higher Thal stages (> 3) are strongly predictive of the presence of diagnostic levels of Alzheimer's disease neuropathological change (ADNC). Previous work has shown that alpha-synuclein, tau and amyloid-β (aβ) can be detected in the olfactory bulb and tract (OBT) of elderly individuals. However, to our knowledge no study has evaluated OBT aβ pathology with respect to its possible value for predicting Thal amyloid stage and dementia due to ADNC.

Methods: Autopsied subjects with available Thal amyloid staging were selected by a database search of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). We analyzed neuropathologically-confirmed cases of ADD (N = 35), and no ADD (N= 30). ADD was defined as the presence of dementia with Intermediate or High ADNC (moderate or frequent CERAD cortical neuritic plaque density and Braak neurofibrillary stage III-VI). The OBT were stained for Aβ using immunoperoxidase methods (6E10 antibody); results were graded using CERAD templates. Demographic data were compared with t-tests and Fisher exact tests. Diagnostic accuracy was estimated by calculating sensitivity and specificity.

Results: There were no differences in age at death or gender ratios between ADD and non-ADD. The presence of OBT Aβ deposits was 82.6% sensitive and 75.5% specific for predicting Thal Aβ stage > 3, with a positive predictive value of 63.3% and a negative predictive value of 87.9%.

Conclusions: These results suggest that olfactory bulb biopsies may be useful for detecting diagnostic levels of multiple different brain pathologies, including Thal amyloid stage.

POSTER #52

MAPPING OF SARS-COV-2 BRAIN INVASION AND HISTOPATHOLOGY IN COVID-19 DISEASE. Serrano GE, Walker JE, Arce R, Glass MJ, Vargas D, Sue LI, Intorcia AJ, Nelson CM, Oliver J, Papa J, Russell A, Suszczewicz KE, Borja CI, Belden C, Goldfarb D, Shprecher D, Atri A, Adler CH, Shill HA, Driver-Dunckley E, Mehta SH, Readhead B, Huentelman MJ, Peters JL, Alevritis E, Bimi C, Mizgerd JP, Reiman EM, Montine TJ, Desforges M, Zehnder JL, Sahoo MK, Zhang H, Solis D, Pinsky BA, Deture M, Dickson DW, Beach TG. Banner Sun Health Research Institute; Brigham and Women's Hospital and Harvard Medical School; Mayo Clinic Arizona; Barrow Neurological Institute; Arizona State University; Translational Genomics Research Institute; Banner Boswell Medical Center; Banner University Medical Center; Boston University; Banner Alzheimer's Institute; Stanford University; Centre Hospitalier Universitaire Sainte-Justine; Mayo Clinic Florida; Arizona Alzheimer's Consortium.

Background: The coronavirus SARS-CoV-2 (SCV2) causes acute respiratory distress, termed COVID-19 disease, with substantial morbidity and mortality. As SCV2 is related to previously-studied coronaviruses that have been shown to have the capability for brain invasion, it seems likely that SCV2 may be able to do so as well. To date, although there have been many clinical and autopsy-based reports that describe a broad range of SCV2-associated neurological conditions, it is unclear what fraction of these have been due to direct CNS invasion versus indirect effects caused by systemic reactions to critical illness. Still critically lacking is a comprehensive tissue-based survey of the CNS presence and specific neuropathology of SCV2 in humans.

Methods: We conducted an extensive neuroanatomical survey of RT-PCR-detected SCV2 in 16 brain regions from 20 subjects who died of COVID-19 disease. Targeted areas were those with cranial nerve nuclei, including the olfactory bulb, medullary dorsal motor nucleus of the vagus nerve and the pontine trigeminal nerve nuclei, as well as areas possibly exposed to hematogenous entry, including the choroid plexus, leptomeninges, median eminence of the hypothalamus and area postrema of the medulla. Subjects ranged in age from 38 to 97 (mean 77) with 9 females and 11 males.

Results: Most subjects had typical age-related neuropathological findings. Two subjects had severe neuropathology, one with a large acute cerebral infarction and one with hemorrhagic encephalitis, that was unequivocally related to their COVID-19 disease while most of the 18 other subjects had non-specific histopathology including focal β-amyloid precursor protein white matter immunoreactivity and sparse perivascular mononuclear cell cuffing. Four subjects (20%) had SCV2 RNA in one or more brain regions including the olfactory bulb, amygdala, entorhinal area, temporal and frontal neocortex, dorsal medulla and leptomeninges. The subject with encephalitis was SCV2-positive in a histopathologically-affected area, the entorhinal cortex, while the subject with the large acute cerebral infarct was SCV2-negative in all brain regions.

Conclusions: Like other human coronaviruses, SCV2 can inflict acute neuropathology in susceptible patients. Much remains to be understood, including what viral and host factors influence SCV2 brain invasion and whether it is cleared from the brain subsequent to the acute illness.

POSTER #53

WHOLE SOMA DISSOCIATED SUSPENSION ANALYSIS IN HUMAN BRAIN NEURODEGENERATIVE DISEASE: A PILOT STUDY. Serrano G, Walker J, Intorcia A, Glass M, Arce R, Piras I, Talboom J, Oliver J, Nelson C, Papa J, Cutler B, Sue L, Lue L-F, Huentelman M, Beach TG. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Biochemical analysis of human neurodegenerative brain tissue is typically done by homogenizing whole pieces of brain and separately characterizing 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. 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 this project we developed a new method for the generation of whole-soma-dissociated-suspensions (WSDS) in fresh human brain that could be shared with scientists as a resource to study human single cells or cell types populations.

Methods: Characterization of WSDS was done in paraffin-embedded sections stained with H&E, by immunophenotyping with antibodies specific and by fluorescence-activated cell sorting (FACS) utilizing the same antibodies. Additionally, we compared extracted RNA from WSDS with RNA from adjacent intact cortical tissue (CT) from the same 12 randomly selected cases, using RT-qPCR for cell-type-specific RNA for the same markers as well as whole transcriptome sequencing.

Results: Each examined dissociated cell suspension always had a diverse population, typically including approximately 40% neurons, 25% astrocytes, 21% microglia, 5% oligodendrocytes and 4% endothelial cells. RNA integrity number (RIN) for unfixed WSDS incubated for 4hrs in enzyme ranged from 2 to 8, with a mean RIN of 6.2 and 2.1 standard deviation. The yield of RNA ranged from 4-350ng/million cells, with a mean yield of 55 ng/million cells. RNA extraction from WSDS and WTH were done on twelve random selected cases. RIN mean for those 12 WSDS was 6.3 +/-2.0, while WTH had a RIN mean of 6.5 +/-2.0. q-PCR results suggest that neuronal NEU-N and astrocyte GFAP RNA expression was not different between WSDS and WTH, while RNA expression of the well know microglia protein IBA1 was upregulated in WSDS. More than 11,626 gene transcripts were successfully sequenced and classified either as being mainly expressed in neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, or mixed (in two or more cell types).

Conclusions: Our results demonstrate that we are currently capable of producing WSDS with full representation of different brain cell types together with RNA quality suitable for use in biochemical analysis.

POSTER #54

A 3D INTERACTIVE REPRESENTATION OF LOCUS COERULEUS NUCLEUS MORPHOLOGY IN AGED MACAQUE MONKEYS. Sinakevitch I, Deer C, McDermott K, Khattab S, Gray DT, 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. Dysregulation of LC systems contribute to cognitive dysfunctions in both healthy aged brains and brains that succumb to Alzheimer's disease. Importantly, the LC is heterogeneous along both the rostral-caudal and dorsal-ventral axes with respect to neuron morphology, projection targets, and vulnerability to the impacts of normative brain aging and neurodegenerative disease. In particular, the rostral LC projects to cortical and hippocampal brain regions critical to cognition.

Methods: The aim of the present study is to examine the LC in a nonhuman primate model of aging, using a system that standardizes the 3D morphology of the LC nucleus to enable precise comparisons of neuronal morphology and densities in immunolabelled brain sections from individual monkeys. To this end, coronal brainstem sections were examined every 240 microns along the rostral-caudal axis of the LC from a colony of 30 cognitively assessed rhesus macaque monkeys ranging in age from 7 to 32 years (human equivalent ~21 – 96 years) were used. Three young and three aged monkeys from this sample were used in the present study. To create the 3-dimensional volume, digitized Nissl-stained images of 30 micron thick frozen brain sections at the level of the pons were first collected. High-resolution 5x microscopy images of each LC that had been immunolabeled with a fluorescent morphological marker of catecholaminergic neurons (tyrosine hydroxylase) were then acquired, followed by a 40x high-resolution confocal stack of the LC on the same section. AMIRA software was employed to reconstruct the LC. The volume of the nucleus was delineated using cell bodies positive for TH and large cell bodies in Nissl stains characteristic of this nucleus as boundaries.

Results: Preliminary data from these animals indicate that the macaque LC extends approximately 2000 um along the rostro-caudal axis. We observed a core LC nucleus with high TH+ cell densities that became more scattered in more rostral brain sections. Overall volumes varied between 1 and 2.2 mm3, and the older monkeys tended to have smaller LC volumes compared to the younger individuals, but this will need to be replicated in the full sample of 30 animals.

Conclusions: This analysis pipeline will allow specific sites of vulnerability along the rostral-caudal axis of the LC to be identified for further molecular analyses aimed at understanding the mechanisms responsible for LC vulnerability and its impacts of cognition in normative aging and disease.

POSTER #55

THE CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM – A PLATFORM FOR PRE-COMPETITIVE DATA SHARING, STANDARDIZATION, AND ANALYSIS TO SUPPORT QUANTITATIVE TOOLS FOR AD DRUG DEVELOPMENT. Sivakumaran S, Cui Z, Burton J, Priest E, Lau C, White H, Romero K, Karten Y. Critical Path Institute; Arizona Alzheimer's Consortium.

Background: The primary objective of the pre-competitive Critical Path for Alzheimer's Disease (CPAD) consortium is to promote, support, and manage pre-competitive data and knowledge sharing from Alzheimer disease (AD) drug development stakeholders. Since the launch of the Industry Data Sharing Initiative, CPAD has acquired fluid and imaging biomarker-rich data sources for development of novel tools to quantify disease progression across the AD continuum. CPAD leverages these data to address drug development challenges in AD by developing regulatory-grade modeling and simulation tools that can convert these data into knowledge to improve strategies in ongoing or future drug development programs.

Methods: Patient-level data from contemporary Phase2/Phase3 AD clinical trials and observational studies are being acquired through formal data contribution agreements within CPAD, curated, mapped to CDISC standards, and integrated for analysis. The integrated data is being transformed to analysis ready subsets for development of a comprehensive set of disease progression models across the continuum of the disease. Models will characterize the time course of clinically relevant measures (ADAS-Cog, CDR-SB, other clinical assessment scales and biomarkers). Covariates including demographics, time from and to diagnosis, genetic status (APOE4), co-morbidities and medication use will be assessed using non-linear mixed effects methods. Monte Carlo simulations will be performed to compare the statistical power by sample size in trials with and without enrichment using relevant covariates.

Results: The CPAD clinical trial repository currently contains 42 studies with 21,078 individual anonymized patient records. CPAD has acquired contemporary AD clinical trial datasets focused on early stages of the disease, providing a rich source of key amyloid, tau and neurodegeneration biomarkers, assessed through magnetic resonance and positron emission tomography neuroimaging and through analysis of biofluids (plasma and cerebrospinal fluid). Model selection based on the log-likelihood ratio and goodness-of-fit plots will be used to select the model structure that most adequately describes the integrated database. Covariate analyses will be performed to identify variables that constitute relevant predictors of baseline severity and disease progression rates. Trial simulations for a therapeutic effect using standard drug effect models for symptomatic and disease-modifying effects will be conducted to estimate an optimal sample size when trials are enriched with a clinically relevant covariate.

Conclusions: The precompetitive end-to-end data acquisition and analysis efforts in CPAD are providing sponsors with regulatory grade tools to optimize AD trial design. This will provide confidence for the industry drug development teams to adapt these tools into their respective research and drug development efforts to accelerate and advance therapeutic innovation in AD.

POSTER #56

POSTMORTEM INTERHEMISPHERIC DIFFERENCES IN THE DISTRIBUTION PATTERN OF AD-TYPE TAUOPATHY. Tremblay C, Serrano GE, Sue L, Intorcia A, Walker J, Arce R, Nelson C, Vargas D, Suszczewicz K, Cline M, Borja C, Hemmingsen S, Qiji S, Fleisher AS, Pontecorvo MJ, Montine TJ, Beach TG. Banner Sun Health Research Institute; Avid Radiopharmaceuticals; Stanford University; Arizona Alzheimer's Consortium.

Background: The spreading of tau neurofibrillary pathology is an important hallmark of Alzheimer's disease (AD), shown to correlate with cognitive decline, and is currently the target of diverse therapeutic interventions. Even though the distribution of tau pathology mostly shows a stereotypical pattern of topographical progression in the cerebral cortex, different subtypes showing atypical patterns have been described. Moreover, recent tau PET imaging studies have suggested the presence of specific clinical profiles associated with hemispheric tau pathology asymmetry. Postmortem investigations have typically been limited by the practice of using only one hemisphere for histological studies while freezing the other hemisphere for biochemical evaluation. There have been relatively few reports that deliberately assessed hemispheric asymmetry of AD-related histopathology, and these have generally been limited by small numbers of subjects and cortical regions. Therefore, this study aimed to specifically assess tau pathology for interhemispheric differences and the presence of topographically atypical neocortical spreading patterns.
Methods: Cases were selected from a larger prospective end-of-life study of flortaucipir F18 PET imaging (AV-1451-A16) conducted by Avid Radiopharmaceuticals from October 2015 through June 2018. The original study included a total of 67 autopsy cases, from which we excluded 10 because of the presence of atypical, non-AD tau pathology or hippocampal sclerosis, leaving 30 women and 27 men (age of death of 81.23 ± 9.8), with premortem cognitive status ranging from clinically normal to dementia. Tissue sampling included bilateral neocortical and limbic regions required for AD neuropathological diagnosis and NIA-AA classification, along with additional cortical areas for a total of 25 regions of interest (ROI) per hemisphere. AT8 immunohistochemical staining was performed for specific detection of tau protein neurofibrillary pathology that was then semi-quantitatively scored (0 for absent, 1 for rare, 2 for sparse, 3 for moderate, and 4 for frequent) in each ROI of the left and right hemisphere.
Results: The main results demonstrate that mild discrepancy of one point difference in the density of tau pathology between corresponding left and right hemispheric ROIs was frequent in all participants and ROIs while moderate to severe discrepancy of 2 to 3 points was rare. No significant mean interhemispheric differences were found for any ROI and only one case ($U = 40.0$; $p = 0.017$) showed a significantly different aggregate interhemispheric mean difference, with lower scores in the right hemisphere. When compared to other ROIs, occipital regions showed significantly higher proportions of cases with interhemispheric discrepancies. These asymmetric variations led to Braak stage differences between hemispheres in 9 cases (16 %), with a higher stage in the left side in 6 cases, but leading to a difference in the NIA-AA ADNPC level (between high and intermediate) in only one case. One atypical topographical pattern, where occipital tau pathology density scores exceeded the scores in the frontal lobe, was identified in 5 cases, but without any left/right side predominance.
Conclusions: In conclusion, discrepancies between the hemispheres were noted but these had minimal effects on ADNPC level assignment. We speculate, however, that hemispheric tau pathology asymmetry and atypical topographical progression patterns might have clinically evident effects. Future studies should test this hypothesis with comprehensive clinicopathological correlations.

POSTER #57

CHRONIC PIAL CEREBRAL ARTERIAL FUNCTION AND COGNITIVE FUNCTION FOLLOWING MILD-MODERATE TRAUMATIC BRAIN INJURY IN RATS. Truran S, Karamanova N, Young C, Griffiths D, Law LM, Emerson H, Gonzales R, Reaven PD, Quarles CC, Lifshitz J, Migrino R. Phoenix VA Health Care System; Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Severe traumatic brain injury (TBI) is associated with cognitive dysfunction in part due to vascular perturbations. In contrast, the long-term vasculo-cognitive pathophysiology of mild-moderate diffuse TBI (mTBI) remains unknown. We aimed to evaluate the effects of mTBI on chronic cognitive and pial cerebral arterial function and their interrelationships.

Methods: Male Sprague-Dawley rats received either midline fluid percussion injury (N=20) or sham (N=21). At 3- and 6-months, cognitive function was assessed (novel object recognition (NOR), novel object location (NOL) and temporal order object recognition (TOR)) and at 6 months post-sacrifice, isolated pial arterial myogenic tone (post- 30 and 60 mm Hg intraluminal pressure) was assessed; additionally, endothelial function (10-9-10-4M acetylcholine) and smooth muscle function (10-4M DETA NONOate) were measured at baseline and following 1-hour exposure to vascular agonists angiotensin II (20 μM), Aβ1-42 (1 μM) and high glucose (33 mM).

Results: Repeated measures ANOVA (treatment, time) showed impaired NOR discrimination ratio in mTBI versus sham rats ($p=0.02$), with similar trends in NOL ($p=0.07$; TOR $p=0.17$). There was no significant difference in baseline myogenic tone, endothelial and smooth muscle-dependent function. There was an inverse relationship between smooth muscle dilator response and NOR ($R=-0.34$, $p=0.03$). Change in smooth muscle dilator response following exposure to angiotensin II when compared to baseline response showed significant reduction in sham (-16.1±6.2%) versus mTBI arteries (-2.1±5.7%, $p=0.03$). Arterial dilator responses to Aβ1-42 and high glucose did not differ significantly between sham and mTBI.

Conclusions: mTBI leads to chronic cognitive impairment and altered pial arterial smooth muscle dilator response following angiotensin II exposure. These chronic vasculo-cognitive changes could be relevant in understanding the long-term sequela and underlying mechanisms of human mild-moderate TBI.

POSTER #58

THE EFFICACY OF MUSIC THERAPY INTERVENTIONS ON QUALITY OF LIFE FOR INDIVIDUALS WITH DEMENTIA: A SYSTEMATIC REVIEW. Turner T, Bayer K, Neale H. Midwestern University.

Background: This systematic review was conducted to synthesize current findings related to quality of life (QOL) and music therapy for persons living with dementia (PWD). This fills a great need for occupational therapy practitioners to access more evidence-based interventions for this population. The research question explored the efficacy of music therapy interventions provided in inpatient settings on increasing QOL for PWD. A meta-analysis was conducted to extract data and further analyze QOL.

Methods: Two databases were searched from the years 2010-2020, PubMed and COCHRANE, although all articles selected came from PubMed. All articles were randomized control trials providing active and passive music therapy sessions for PWD using QOL as an outcome measure. Data abstraction forms were collected to compare the validity and quality between the studies. Inclusion criteria; diagnosis of dementia or Alzheimer's disease, music therapy intervention, RCT, articles in English, inpatient settings. Exclusion criteria; hearing impairments.

Results: A total of three quantitative randomized controlled trials with a total of 169 participants with differing diagnosis of dementia were included in the meta-analysis. The active and passive music therapy interventions showed little or no effect on QOL with an overall effect size for active music therapy of 0.116 and an overall effect size for passive music therapy of .021.

Conclusions: The evidence showed an increase, however no statistically significant findings were noted. Further research needs to be designed to assess the efficacy of inpatient music therapy interventions on QOL for PWD. Occupational therapy practitioners need to be involved in the development of future research exploring music therapy interventions that address QOL. Current research promises that QOL improvements are in the right direction but because of the limited nature of the level of evidence practitioners cannot fully recommend music therapy interventions to increase QOL for PWD at this time.

POSTER #59

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. Van Keuren-Jensen K, Alsop E, Antone J, Readhead B, Wang Q, Beach TG, Serrano GE, Liang W, Dudley J, Reiman EM. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Single cell assessments of gene dysregulation in Alzheimer's disease (AD) compared with matched healthy elderly controls are proving to be useful datasets for understanding AD dementia at the cellular level. Our resource, which will be made publicly available, will include multiple brain regions (frontal, temporal, parietal, occipital, hippocampus CA1 and entorhinal cortex) and technologies (single nuclei transcriptomics and laser capture microdissection) to achieve integration and validation of the most relevant vulnerabilities and changes associated with pathogenesis.

Methods: Superior frontal gyrus was dounce homogenized 10-15 times. Homogenate was passed through a 70 µm 1.5 ml mini strainer and centrifuged at 500 rcf for 5 minutes at 4ºC and washed. Nuclei pellets were resuspended in 1 ml of 1x wash/ resuspension buffer and centrifuged at 500 rcf for 5 minutes at 4ºC, resuspended in 500 ul of 1x wash/ resuspension buffer. Homogenate was incubated in 1-2 drops of NucBlue Live ReadyProbes Reagent and immediately sorted using the DAPI channel on ta Sony SH800S. Nuclei are sorted for 15,000 events directly into 10x 3' v3.1 RT Reagent Master Mix and immediately processed with the 10x Genomics Chromium Next GEM Single Cell 3' v3.1 kit. cDNA is amplified, and library constructed following the manufacturer's protocol.

Results: We completed the single nuclei sequencing of the 100 superior frontal gyrus samples. We identified 18 distinct clusters. Each subject contributed an average of 7259 cells with an average of 4,105 genes detected per cell. A total of 32,777 genes are detected in >10 cells. We observe distinct differences in gene expression in each of the clusters when comparing AD and elderly control groups. We will discuss some of the differentially expressed genes and pathways dysregulated with disease.

Conclusions: We have high quality single nuclei data, have generated cell clusters and have performed preliminary data analyses. We will integrate these data with the other brain regions to identify unique and overlapping gene changes as well as vulnerabilities in cell types associated with dementia.

POSTER #60

ALZHEIMER'S DISEASE PREVENTION WITHIN REACH BY 2025: TARGETED-RISK-AD-PREVENTION (TRAP) STRATEGY. Vitali F, Branigan GL, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease that results in cognitive decline, psychiatric symptoms and loss of independent living. Biological mechanisms driving AD progression can occur up to 20 years which provides an extended window for therapeutic intervention to alter the course of AD risk. In 2015, the National Plan to Address Alzheimer Disease as part of the National Alzheimer's Project Act was signed into law which proposed to effectively prevent AD by 2025. Timeline to achieve this goal is rapidly approaching.

Methods: We developed a targeted-risk-AD-prevention (TRAP) strategy based on a novel combination of text-mining and natural language processing strategies to identify (i) AD risk factors mining PubMed literature, (ii) FDA-approved therapeutics targeting risk factor pathways using drug-target databases, and (iii) studies supporting therapeutics in the currently published PubMed database. To classify the literature relevant to AD preventive strategies, we developed a relevance score based on STRING score for protein-protein interactions and a confidence score on Bayesian inference. This led to generation of a ranked list of significantly relevant and confident candidate therapeutics to reduce AD risk. We finally conducted network analysis of selected drug-target interactions.

Results: Based on the TRAP strategy, 364 AD risk factors were identified based on mining 9,625 publications. Using drug databases, 629 FDA-approved drugs for identified AD risk factors were selected based on drug indications relevant to a given risk factor. These results were used to generate a pipeline to identify publications reporting a risk factor therapeutic with risk of AD, which resulted in 11,139 publications for 445 drugs. The computation of relevance and confidence scores enabled exclusion of publications that did not meet inclusion criteria and ranked 46 drugs associated with reduced risk. Within this list,16 drugs were reported in at least one clinical study of AD risk reduction, while the remaining 30 were in the in preclinical pipeline and not supported by clinical studies. Top therapeutics supported by clinical studies with reduced AD risk included five anti-inflammatories (e.g., ibuprofen, indomethacin), four lipid-lowering (e.g., pravastatin, simvastatin), two metabolic-related (pioglitazone and metformin), two hormone (estradiol and testosterone), one psychiatric (valproic acid), one cardiac (lisinopril) therapeutic, and vitamin A. Network analysis aimed at analyzing targets of these drugs resulted in 96 nodes (16 drugs and 80 target proteins) and 102 edges, where on average a drug was associated with six proteins.

Conclusions: Outcomes of the TRAP strategy support therapeutic targeting of biological mechanisms and pathways underlying AD risk factors. Analysis of the drug-target interaction network revealed different biological networks of drug actions. On average, identified preventive therapeutics target six proteins, which indicates the efficacy multi-target profile required for AD prevention likely due to the multi-system biology contributing to AD. Because risk factor biology is linked to the pathophysiology of AD, combination therapy that targets the full preclinical risk factor profile could provide a combinatorial strategy to prevent AD. From this analysis, the most impactful risk factors that target biological mechanisms and pathways underlying AD risk include the immune, metabolic, cardiovascular, and endocrine systems. Based on our analyses, we propose that early interventions that target pathways associated with increased risk of AD has the potential to achieve the goal of effectively preventing AD by 2025.

POSTER #61

ASYMPTOMATIC CAROTID ATHEROSCLEROSIS IS ASSOCIATED WITH INCREASED ALZHEIMER'S AND NON-ALZHEIMER'S DEMENTIA RISK. Vitali F, Branigan GL, Arias JC, Nagae L, Reiman EM, Brinton RD, Weinkauf C. University of Arizona; University of Arizona College of Medicine; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Extracranial carotid artery disease (ECAD) can infrequently lead to stroke, which has been associated with dementia. However, asymptomatic ECAD (aECAD), those with no recent stroke or transient ischemic attack, has a high prevalence in aging populations and is not considered a risk factor for Alzheimer's disease (AD) and non-AD dementia.

Methods: This retrospective cohort study queried the Mariner insurance claims data set. 784,062 patients met enrollment criteria of being 45 years or older, no previous diagnosis of dementia, and at least 3 years of continuous follow-up after enrollment. After propensity score matching for all factors associated with aECAD defined by regression analysis, 247,119 subjects with aECAD and 247,119 subjects without ECAD were followed through data records. Analyses were performed to evaluate the relative risk of developing AD and non-AD dementia in unmatched and matched cohorts with and without aECAD.

Results: Over a mean claims data follow-up period of 4.8 years, the aECAD cohort had increased relative risk of 1.2 (1.15 to 1.25, $p<.001$) for AD dementia and 1.39 (1.35 to 1.43, $p<.001$) for non-AD dementia compared to the propensity score matched cohort.

Conclusions: Asymptomatic ECAD is associated with increased risk of developing AD and non-AD dementias. This is a novel finding and should prompt further prospective evaluation of interactions between aECAD and dementia, which could have important implications for clinical evaluation and therapy in both of these large patient populations.

POSTER #62

MEASURING UP: A COMPARISON OF TAPESTATION 4200 AND BIOANALYZER 2100 AS MEASUREMENT TOOLS FOR RNA QUALITY. Walker JE, Serrano G, Arce R, Oliver J, Intorcia A, Glass M, Nelson C, Vargas D, Suszczewicz K, Cline M, Borja C, Hemmingsen S, Qiji S, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The RIN (RNA Integrity Number) based on Agilent's Bioanalyzer 2100 is widely accepted in the scientific community as the gold standard for objectively assessing a sample's RNA quality for downstream applications. For many years, scientist have been using RIN values to identify acceptable samples for specific downstream applications (e.g. RIN >6.5 is acceptable for most gene expression assays). However, in recent years, new instruments for measuring RNA integrity have been developed. Two of these measures, RINe (RIN equivalent) and DV200 (percent of RNA fragments greater than 200 nucleotides), both based on the Agilent Tape station, have gained more popularity. The Tapestation offers increased throughput by analyzing 96 samples in a single run as compared to 12 with Bioanalyzer and Agilent claims that the RINe is highly correlated with RIN with a median error < ± 0.4 RIN units. In this study, we compared RINe and DV200 to the gold standard RIN to see how well the measurements align.

Methods: Total RNA was extracted from frozen cerebellum from each of 183 human subjects that were part of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and donated their brain to the Brain and Body Donation Program (BBDP). Qiagen RNeasy Plus mini kits were used to extract RNA from 25 mg of frozen cerebellum according to the manufacturer's instructions. The concentration and purity of each RNA sample was assessed using a Nanodrop spectrometer. Each sample was then run in parallel on the Agilent Tapestation 4200 and Bioanalyzer 2100 using the RNA screen tape and RNA 6000 Nano kit respectively. RIN was recorded from the Bioanalyzer and RINe and DV200 were recorded from the Tapestation 4200. RIN and RINe are assigned to the sample automatically. DV200 is the percent of sample that is above 200 nucleotides and was determined post assay by entering 200 as the lower limit in the regional settings of the Tapestation 4200 software. Both the RIN and RINe are expressed as a number between 1 -10, while the DV200 is expressed as a percentage. A cut-off value of RIN 6.5 was used to determine how many samples would be suitable for most downstream applications.

Results: For 183 samples, The RIN range was 3-10 with an average of 8.8 ± 1.06 and median of 9.1 whereas the RINe range was 2.6-7.5 with an average of 5.6 ± 1.07 and median of 5.8. A 2-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. A linear regression was performed and although the RIN and RINe did significantly correlate ($p<0.0001$), the correlation was weaker at R2 of 0.393 than R2 of 0.936 which has been previously reported by Agilent. Applying the cut-off value of 6.5, for RIN 175/183 (95.6%) samples would be fit for downstream applications, whereas, only 43/183 (23.5%) would be for RINe. DV200 ranged from 80.72% - 95.06% with an average of 91.08% ± 2.60% and a median of 91.76%. Applying cut-off value of 70% DV200, established by Illumina for sequencing, 183/183 (100%) samples would meet this standard.

Conclusions: RIN and RINe are not equivalent measurements. If most of the scientific community are working under the premise that <6.5 RIN is not adequate for downstream applications and apply the same standard to RINe, many RINe samples will fail Quality Control (QC) that would pass with RIN. If RINe continues to gain popularity as a quality assessment, more research may need to be done into what appropriate cut-off values are. In the meantime, DV200 has been shown to be a better predictor of sequencing success than RINe and may be a better RNA integrity measurement on the Tapestation.

POSTER #63

DEVELOPING UNIVARIATE NEURODEGENERATION BIOMARKERS WITH LOW-RANK AND SPARSE SUBSPACE DECOMPOSITION. Wang G, Wu J, Su Y, Caselli RJ, Reiman EM, Wang Y. Ludong University; Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: A univariate neurodegeneration biomarker (UNB) based on an individual patient's MRI with high diagnostic accuracy would be highly desirable for clinical use. However, existing UNB work either fails to model large group variances or does not capture AD dementia induced changes. To address the challenges, we proposed a low-rank and sparse subspace decomposition framework together with surface-based measures to compute robust and efficient UNBs that may be capable of reflecting the morphological changes induced by AD related diseases.

Methods: A nonlinear surface registration method is applied to register individual hippocampal surfaces to a standard template surface by constrained harmonic maps. Then the surface deformation statistics are computed to obtain the radial distance (RD). Due to the morphological similarity within the same group, we extracted each low-rank common group structure from each group RD matrix (Aβ+ AD and Aβ- cognitively unimpaired (CU)) based on our subspace decomposition algorithm. With group difference study, we identified significantly different areas between the low rank components of two groups, Aβ+ AD group and Aβ- CU group, as the regions-of-interest (ROI) and use them as the significant morphological change regions induced by AD disease. Based on the registration result of an individual hippocampal surface, the univariate morphometry index (UMI), defined as a UNB, of the individual subject was computed through the voxel-wise AD atrophy degrees and the individual atrophy degrees defined on the ROIs.

Results: For the longitudinal Aβ+ AD, Aβ+ MCI and Aβ+ CU , the p-values and effect sizes for UMIs mean differences are 7.74e-15 and 1.39, 3.54e-10 and 0.92, 1.28e-09 and 0.85, respectively. For raw RD measures (UMI-RDs), the p-values and effect sizes of the longitudinal Aβ+ AD, Aβ+ MCI and Aβ+ CU are 1.52e-03 and 0.79, 3.70e-03 and 0.65, 1.29e-02 and 0.56, respectively. For hippocampal volume measures, the p-values and effect sizes of the longitudinal Aβ+ AD, Aβ+ MCI and Aβ+ CU are 1.48e-13 and 1.31, 9.72e-09 and 0.90, 1.19e-08 and 0.74, respectively. And the minimum sample sizes of the UMIs of the longitudinal Aβ+ AD, Aβ+ MCI and Aβ+ CU groups are 116, 279 and 387, respectively. For UMI-RDs, the minimum sample sizes of the longitudinal Aβ+ AD, Aβ+ MCI and Aβ+ CU groups are 402, 590 and 787, respectively. For volume measures, the minimum sample sizes of the longitudinal Aβ+ AD, Aβ+ MCI and Aβ+ CU groups are 136, 352 and 451, respectively.

Conclusions: The results indicate that the subspace decomposition-based UMIs may have detected the essential morphological changes induced by AD disease better than the volume measures and UMI-RD measures.

POSTER #64

DEEP LEARNING IDENTIFIES BRAIN TRANSCRIPTOMIC SIGNATURES ASSOCIATED WITH THE NEUROPATHOLOGICAL AND CLINICAL SEVERITY OF ALZHEIMER'S DISEASE.

Wang Q, Readhead B, Chen K, Su Y, Reiman EM, Dudley, JT. Arizona State University; Banner Alzheimer's Institute; Icahn School of Medicine at Mount Sinai; Arizona Alzheimer's Consortium.

Background: Brain tissue gene expression from donors with and without Alzheimer's disease (AD) have been used to help inform the molecular changes associated with the development and potential treatment of this disorder.

Methods: Here, we use a deep learning method to analyze RNA-seq data from 1,114 brain donors from the AMP-AD consortium to characterize post-mortem brain transcriptome signatures associated with amyloid-β plaque, tau neurofibrillary tangles, and clinical severity in multiple AD dementia populations. Starting from the cross-sectional data in the ROSMAP cohort (n = 634), a deep learning framework was built to obtain a trajectory that mirrors AD progression. A severity index (SI) was defined to quantitatively measure the progression based on the trajectory. Network analysis was then carried out to identify key gene (index gene) modules present in the model underlying the progression.We also applied the model to additional transcriptomic datasets from different brain regions (MAYO, n = 266; MSBB, n = 214) for validation.

Results: Within the ROSMAP dataset, SIs were found to be very closely correlated with all the AD neuropathology biomarkers ($R \sim 0.5$, $p < 1e\text{-}11$) and global cognitive function ($R = -0.68$, $p < 2.2e\text{-}16$). In the external validation datasets (MAYO/MSSB), the model remained significantly predictive ($p < 1e\text{-}3$) of neuropathology and clinical severity. The index genes that significantly contributed to the model were integrated with AD co-expression regulatory networks, resolving two discrete gene modules that are implicated in vascular and metabolic dysfunction in different cell types respectively.

Conclusions: Our work demonstrates the generalizability of this signature to frontal and temporal cortex measurements and additional brain donors with AD, other age-related neurological disorders and controls; and revealed the transcriptomic network modules contribute to neuropathological and clinical disease severity. This study illustrates the promise of using deep learning methods to analyze heterogeneous omics data and discover potentially targetable molecular networks that can inform the development, treatment and prevention of neurodegenerative diseases like AD.

POSTER #65

EFFECTS OF AEROBIC EXERCISE ON COGNITION AND IMAGING BIOMARKERS IN OLDER ADULTS WITH ALZHEIMER'S DISEASE DEMENTIA. Yu F, Zhang L, Nelson N, Mathiason M, Salisbury D, Gunter J, Jones D, Botha H, Jack C. Arizona State University; University of Minnesota; University of Saint Thomas; Mayo Clinic Rochester.

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

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

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

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

POSTER #66

IMPROVED C11 PIB RADIOCHEMICAL PURITY. Yu M, Xu C, Hua Y. The Houston Methodist Research Institute.

Background: C11 PIB is a well-established Positron emission tomography (PET) imaging tracer to detect beta-amyloid in Alzheimer's disease. However, maintaining high radiochemical purity (RCP) is always a challenge in clinical manufacturing. Radiolysis is proposed as the reason for the decomposition, and sodium ascorbate was tested as a radiolysis stabilizer during C11 PIB manufacturing.

Methods: Procedure improvement: we add 0.05% sodium ascorbate in the preparative HPLC mobile phase and add 1 mL 5% sodium ascorbate solution in the collection bottles to prevent the radiolysis decomposition of C11 PIB. In brief, C11 methyl triflate is bubbled into a reactor containing a mixture of 1 mg precursor with 0.1 mL 2-butanone at 15 oC, maintaining at 15 oC for 3 min after bubbling. The reaction mixture is diluted with 1 mL preparative HPLC mobile phase (60% methanol : 40% (100 mM ammonium formate) : 0.05% sodium ascorbate (V/V/W)]) and purified by HPLC. The product fraction is collected into a pressure reservoir containing 50 mL sterile water for injection and 1 mL 5% sodium ascorbate. The mixture solution is passed through a light C18 Cartridge followed by 10 mL sterile water rinsing. Finally the C11 PIB in the cartridge is eluted out with 1 mL ethanol for injection and 14 mL saline sequentially into a final product vial through a Millex FG filter (0.2 μm).

Results: Radiochemical purity before ((adjacent 5 times. 93.25%, 93.27%, 91.34%, 91.19%, 93.11%) and after (adjacent 5 times. 98.19%, 98.91%, 99.12%, 99.01%, 99.10%) procedure improvement.

Conclusions: Adding sodium ascorbate in the preparative HPLC mobile phase and collection bottle can significantly improve the radiochemical purity.

STUDENT POSTER PRESENTATIONS

POSTER #67

EXPLORING AUTOBIOGRAPHICAL MEMORY IN BILINGUAL HISPANICS. Acevedo-Molina MC, Griego S, Mizell JM, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Hispanics in the United States (US) are expected to experience the greatest increase in Alzheimer's disease (AD) diagnoses in the next four decades. Unfortunately, accumulating evidence suggests that currently available cognitive tests may be less accurate at detecting cognitive decline in Hispanics. As such, there is a critical need for better cognitive tests for age- and AD related cognitive decline in Hispanics. Episodic autobiographical memory (EAM), which is our memory for personally relevant events, has the potential to be a sensitive measure of both normal and AD-risk related cognitive aging. More importantly, EAM has the potential to be a culturally appropriate measure given that individuals are asked to describe personal events, which inherently come from their own cultural framework and background knowledge. However, studies that examine autobiographical memory in Hispanics in the US are lacking. Broadly, the focus of the present study is to examine EAM in Hispanics with the purpose of contributing to the development of more sensitive and culturally appropriate cognitive tests that can be used among this population. An important feature about the population of Hispanics in the U.S. is they are commonly bilingual. Thus, as a first step we aimed to examine if bilingualism influenced EAM specificity in young bilingual Hispanics.

Methods: Twenty cognitively healthy young bilingual Hispanics narrated EAMs in English and Spanish, describing events that happened while speaking one language or the other. Using the scoring protocol of the Autobiographical Interview (Levine et al, 2002), we evaluated the narratives for episodic and non-episodic detail. We also asked young bilinguals which language they were primarily using when the memories were encoded.

Results: We found that young bilingual Hispanics retrieve more episodic than non-episodic (semantic/other) detail while describing EAMs in English or Spanish. There was no difference in overall detail for memories retrieved in English versus Spanish. Interestingly, language congruency did not influence EAM specificity either.

Conclusions: We replicated an important finding from the literature with non-Hispanic White young adults, namely that EAM tends to be described mostly with episodic details. From a feasibility standpoint, our findings suggest that we can conduct the Autobiographical Interview in bilingual Hispanics in both English and Spanish. Future directions include recruiting older monolingual and bilingual Hispanics to examine the relationship between age and EAM specificity among this population. Given the present findings, there is ample opportunity to observe age-related decline in EAM episodic specificity.

POSTER #68

EVALUATING THE IMPACT OF ALZHEIMER'S DISEASE RISK FACTORS ON REAL-WORLD AUTOBIOGRAPHICAL THOUGHT – A MIND WINDOW STUDY. Andrews EA, Grilli MD, Abraham FF, Mason DL, Raffaelli Q, Mehl MR, Allen JJB, Andrews-Hanna JR. University of Arizona; Arizona Alzheimer's Consortium.

Background: Although conscious thought is an aspect of everyday life, relatively little is known about how characteristics of thought influence us in the context that matters most: everyday life. Tracking aspects of "real-world" thought could offer important insight into cognitive and affective mechanisms that shape, or are shaped by, healthy and pathological brain aging – including that seen with Alzheimer's disease.

Methods: To better understand the relationship between real-world thought and psychological factors, we developed a freely-downloadable and cross-platform mobile application called Mind Window. Mind Window uses repeated 'check-ins' to solicit numerous characteristics of a user's mood and thoughts over an indefinite time period. In order to gather a broad description of thinking, these check-ins sample the manner of thought (intentionality, domain, and lability), content-relevant features, and associated affective qualities. In addition to longitudinal sampling, established measures are used to assess a number of trait characteristics.

Results: In this ongoing study, we surveyed 1,321 participants who each completed at least 10 Mind Window check-ins over multiple days. Current data show that older adults experience fewer real-world autobiographical thoughts when compared to younger participants. They also rated being more aware of their autobiographical thinking and that these thoughts were viewed as being more: pleasant, helpful, focused, intentional, vivid, and specific to time/place. When statistically accounting for age, a number of characteristics of real-world autobiographical thinking showed significant association with three major behavioral risk factors for Alzheimer's disease – depression, loneliness, and subjective memory impairment.

Conclusions: Tools like Mind Window provide a scalable and broadly accessible way of gathering contextually-informed, longitudinal data about various aspects of thinking. Such information can help us better understand the relationship between everyday thought and risk factors for cognitive decline. Our study demonstrates that reports of real-world thinking can provide statistics to potentially aid not only clinical trials, but also benefit treatment efforts through capabilities such as early identification, symptom clarification, and the tracking of drug effects on cognition.

POSTER #69

AGE IMPACTS THE BURDEN THAT REFERENCE MEMORY IMPARTS ON AN INCREASING WORKING MEMORY LOAD. Bernaud VE, Hiroi R, Poisson ML, Castaneda AJ, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Rodent aging research has often utilized spatial mazes, such as the water-radial arm maze (WRAM), to evaluate cognitive decline. The WRAM can simultaneously measure spatial working memory (WM) and reference memory (RM), where these two forms of spatial memory are often represented orthogonally. There is evidence, however, that these two memory domains might yield interference at a high WM load.

Methods: The current study evaluated performance on the WRAM in female rats to assess whether the presence of a RM component in the task impacted the trajectory of WM ability with an increasing WM load. To determine whether this putative relationship between memory types was age-dependent, young and aged rats were tested on either a WM-only or a WM + RM version of the WRAM.

Results: Results showed that young rats outperformed aged rats on the task testing solely WM performance, suggesting that WM ability is compromised with age. The addition of a RM component deteriorated the ability to handle an increasing WM load, where young rats performed similar to their aged counterparts. Aged rats also had challenges with the RM domain, but in a different context. Specifically, aged rats repeatedly entered both WM arms and RM arms within a day of testing, as compared to young rats. Interesting relationships between these two memory types were revealed, where aged rats that excelled in RM domains were also found to excel in WM domains when WM demand was high; this relationship was not seen in young rats.

Conclusions: Overall, the addition of a RM element to this WM task detrimentally impacted the ability to handle WM information across young and aged timepoints, especially with a high WM load. This interplay between WM and RM provides insight into the relationships between memory domains across complex maze tasks, potentially improving the understanding of complexities of age- and disease- related memory failures and optimizing their respective treatments.

POSTER #70

A LONGITUDINAL STUDY OF THE UNIQUE GUT MICROBIOTA OF 3XTG-AD MICE MODELING KEY AD PATHOLOGIES. Borsom EM, Keefe CR, Hirsch AH, Orsini GM, Conn K, Jaramillo SA, Testo G, Palma Avila M, Bolyen E, Dillon MR, Lee K, Caporaso JG, Cope EK. Northern Arizona University; Arizona Alzheimer's Consortium.

Background: The collective microbes and their genomes that inhabit the gastrointestinal tract, known as the gut microbiome, contribute to a myriad of host functions. Individuals differ widely in the composition of their gut microbiome, attributed to the effects of environment, genetics, and diet. The gut microbiota, the aggregate of microbial cells that inhabit the gastrointestinal tract, communicates bidirectionally with the brain via immune, neural, metabolic, and endocrine pathways, known collectively as the gut-brain axis. The gut-brain axis is suspected to contribute to the development of Alzheimer's disease (AD), characterized by plaque deposition, neurofibrillary tangles, and neuroinflammation. We hypothesize that altered gut microbiota composition contributes to the development of AD pathologies and neuroinflammation via the gut-brain axis.

Methods: To elucidate the role of the gut-brain axis in AD, we characterized the gut microbiota of triple transgenic (3xTg-AD) mice that model plaque deposition and neurofibrillary tangles. Fecal samples were collected fortnightly from 4 to 52 weeks of age (n=57 3xTg-AD mice, n=71 wild-type). DNA was extracted, the V4 region of the 16S rRNA gene was amplified and sequenced on the Illumina MiSeq. Taxonomic profiling, and alpha- and beta-diversity were analyzed using QIIME 2. A custom reverse transcription qPCR assay was used to assess microgliosis, astrogliosis, and Th1/Th2 inflammation in the hippocampus and colon at 8, 24, and 52 weeks of age. Fold changes were calculated using ΔΔCt.

Results: Our results show altered microbial communities in 3xTg-AD mice when compared to wild-type (p=0.001, pairwise PERMANOVA at 4, 24, and 50 weeks). Alpha diversity decreased in 3xTg-AD compared to their wild-type strains at each timepoint [(4 weeks(p=0.00083), 24 weeks (p=0.0131), and 50 weeks (p=0.0037), Kruskal Wallis)]. Using q2-longitudinal, we determined Bacteroides and Turicibacter relative abundance increased over time while Lactobacillus abundance did not significantly change over time in 3xTg-AD mice (r-squared: 0.80; p=1.744259e-76). Gene expression of GFAP (astrogliosis marker) was increased in the colon of 3xTg-AD mice at 24 weeks compared to 52 weeks (p=0.009, Mann-Whitney,) and the hippocampus of 3xTg-AD mice at 52 weeks compared to 52 week WT mice (p=0.015, Mann-Whiteney). Gene expression of Mrc1 (microgliosis marker) was increased in the hippocampus of 3xTg-AD mice at 24 weeks compared to 52 weeks (p= 0.004 , Mann-Whitney) and gene expression of IL-2 (Th1) was increased in the colon of 3xTg-AD at 52 weeks when compared to 52 week WT mice (p=0.049, Mann-Whitney).

Conclusions: We have identified changes in the gut microbiota and immune response that may be predictive of the development of AD pathologies. Future studies using a multi-omic approach will assess strain-level features and functions of the gut microbiota in AD.

POSTER #71

INFLUENCE OF FECAL MICROBIOTA TRANSPLANTATION ON GUT MICROBIOTA COMPOSITION AND NEUROINFLAMMATION OF 3XTG-AD MICE. Borsom EM, Keefe CR, Hirsch AH, Orsini GM, Conn K, Jaramillo SA, Bolyen E, Dillon MR, Lee K, Caporaso JG, Cope EK. Northern Arizona University; Arizona Alzheimer's Consortium.

Background: The gut microbiota, the aggregate of all microbial cells that inhabit the gut, bidirectionally communicates with the brain via cytokines, neurotransmitters, hormones, and secondary metabolites via the gut-brain axis. The gut microbiota is thought to contribute to the development of Alzheimer's disease (AD), characterized by plaque deposition, neurofibrillary tangles, and neuroinflammation. We hypothesize that manipulation of the gut microbiota can alter development of AD pathologies and neuroinflammation via the gut microbiota-brain axis.

Methods: To further elucidate the role of the gut-brain axis in AD, we performed fecal microbiota transplants (FMT) from 3xTg-AD mice, modeling plaques and neurofibrillary tangles (52-64 weeks), to young 3xTg-AD (n=5) or wild-type mice (n=10). Phosphate buffered saline (PBS) was gavaged into 3xTg-AD (n=5) and wild-type mice (n=10) as a control. For FMT, a fecal slurry from aged 3xTg-AD mice was prepared and given to experimental mice via oral gavage. At 8 weeks, mice were gavaged with FMT or PBS for 5 consecutive days, followed by fortnightly maintenance transplants for 24 weeks. The V4 region of the 16S rRNA gene was sequenced on the Illumina MiSeq. Data were analyzed using QIIME 2. Reverse transcriptase qPCR was used to assess microgliosis, astrocytosis, and Th1/Th2 inflammation in the hippocampus of the FMT cohort at 24 weeks of age.

Results: Our results show a shift in microbiome composition in FMT-treated mice when compared to control (PBS-treated) mice. Bacteroides were increased in 3xTg-AD and wild-type mice receiving FMT. At 24 weeks of age, there was no difference in neuroinflammation between mice treated with FMT compared to control (PBS) in 3xTg-AD or wild type mice. We observed partial engraftment of the gut microbiota from aged 3xTg-AD mice in all FMT-treated mice.

Conclusions: We demonstrate the ability to transplant an aged gut microbiome into young mice, however we did not observe changes in neuroinflammation at 24 weeks of age. Future studies will evaluate neuroinflammation and neuropathologies at later time points. These studies will contribute to our understanding of how features of the gut microbiota may contribute to AD development.

POSTER #72

BREAST CANCER THERAPIES REDUCE RISK OF ALZHEIMER'S DISEASE AND DEMENTIA: A CLAIMS-BASED RETROSPECTIVE STUDY WITH CLINIC TO BENCH IMPLICATIONS. Branigan GL, Torrandell-Haro G, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Worldwide, breast cancer is the most common non-skin cancer in women. Currently, Alzheimer's disease affects 1 in 9 persons in the US over the age of 65, two thirds of whom are women. The high global prevalence and economic impact of Alzheimer's disease presents a significant public health challenge while the identification of therapies to prevent Alzheimer's disease (AD) remains a challenge. The object of this study was to determine whether estrogen modulating therapy (EMT) exposure is associated with risk of Alzheimer's (AD) in women with breast cancer in the Symphony claims data set and identify potential mechanisms by which these drugs may impact risk.

Methods: Patients receiving EMT for breast cancer treatment were identified and survival analysis, stratified by age and by individual therapeutics, was used to determine the association between EMT exposure and diagnosis of AD. A propensity score approach was used to minimize measured and unmeasured selection bias. The impact of the impact of EMT on mitochondrial bioenergetics and dynamics were determined using Metabolic flux analysis and live cell imaging using Rat E18 hippocampal neurons.

Results: In this cohort study of propensity score matched perimenopausal to postmenopausal aged women with breast cancer, EMT exposure was associated with decrease in diagnosis of neurodegenerative disease, most specifically AD (RR, 0.85; 95% CI, 0.78-0.92; $P < 0.001$) and Dementia (RR, 0.88; 95% CI, 0.84-0.93; $P < 0.001$). The preventative effect of EMT was shown to increase with age and was associated with a 5-year shift in disease conversion rate. Mitochondrial bioenergetic data suggest that tamoxifen and the aromatase inhibitors show estrogen-like response.

Conclusions: Among female patients with breast cancer, exposure to estrogen modulating therapies was associated with a decrease in diagnosis of AD and Dementia. If tamoxifen and aromatase inhibitors are acting to increase estrogen-related actions in brain tissue, the argument for the protective association of estrogen with AD-related outcomes is strengthened.

POSTER #73

AGE-RELATED DIFFERENCES IN RESTING-STATE COGNITION: AN ADAPTED THINK-ALOUD PARADIGM. Burns H, Griffith C, Cegavske C, Andrews E, Nye P, Vega-Reid J, Strojek D, Spillman A, Raffaelli Q, Wilcox R, Ryan L, Grilli M, Andrews-Hanna J. University of Arizona; Arizona Alzheimer's Consortium.

Background: Despite cognitive and physical challenges associated with aging, numerous studies suggest that well-being paradoxically improves as part of the typical aging process. This increase in well-being has been linked to changes in mood, memory, and social relationships, yet it remains unclear how improved well-being manifests in the unprompted spontaneous thoughts of older adults. Prior work also has not clarified how deviations in the ways thoughts arise and unfold may signal abnormal aging processes such as preclinical Alzheimer's disease (AD) or AD risk factors, many of which have been linked to poor well-being. For example, prior literature has shown depression to be an important AD risk factor, as well as genetic factors such as presence of the apolipoprotein E (APOE) e4 allele. In this study, we aim to illuminate the characteristics of healthy and unhealthy cognitive aging by examining so-called "resting state" thoughts.

Methods: Fifty-five cognitively normal older and 56 younger adults completed an adapted "Think Aloud" resting state paradigm whereby participants voiced aloud their continuous stream of thought alone at rest for 7-10 minutes. Thoughts were audio recorded and rated continuously by experimenters on content characteristics such as negative valence, positive valence, internal versus external focus, and so on. Trait questionnaires assessed well-being and individual differences in AD risk factors (including depression), and these risk factors were analyzed in conjunction with the Think Aloud task.

Results: Preliminary analyses comparing objectively-assessed content ratings across age groups revealed that older adults' thoughts were more internally-oriented / imaginative and less externally-oriented / perceptual than younger adults. Older adults' thoughts were also more positive than younger adults, and they consistently scored higher than young adults on measures of well-being. In regard to depression, an important risk factor for AD, less positive thoughts were associated with greater symptoms of depression.

Conclusions: Although this study is ongoing, early findings suggest a new way to evaluate spontaneous thought processes that both illuminate the aging process and distinguish between healthy cognitive aging and AD risk. Our findings thus far suggest that in the absence of a task at hand, cognitively healthy older adults may be more comfortable being alone with their thoughts than young adults, benefitting well-being overall. How these processes relate to changing patterns of brain connectivity marks an important objective of future research.

POSTER #74

METFORMIN IR VS XR: A RETROSPECTIVE OBSERVATIONAL STUDY ON AD PROTECTION. Butler R, Hallquist A, Torrandell G, Rodgers KE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's (AD) is a debilitating disease characterized by a loss of memory and executive function, currently, with no viable therapeutic. Perhaps even more discouraging, a report by the CDC indicated that for 2018 roughly 8.2% of the total US population was diagnosed with diabetes, a high-risk factor for AD development (CDC, 2020); giving further support to the scores of studies that have been undertaken to try to find the pathological link underlying this established association. As a result, there has been a recent foray into assessing diabetic treatment in the protection of AD development - one of which, is metformin. In addition to its antidiabetic action, studies have implicated its use with slowing cognitive decline (Samaras et al, 2020), improved learning and memory (Susan et al, 2019) and strong therapeutic translation in people (Sluggett et al, 2019). However, McGovern et al, 2017 indicated that metformin had the lowest adherence rates when compared to other antidiabetics, possibly due to the digestive side effects. Thus, we hypothesized that metformin extended release (XR), formulated to be taken less and produce fewer side effects, would have higher adherence and thus prove more beneficial in decreasing incidence of AD than its predecessor, metformin immediate release (IR).

Methods: Data was gleaned from the "Mariner" claims dataset using PearlDiver (a paid online medical data repository). This dataset contained deidentified medical and treatment data via all insurance provider networks on 53 million patients from January 2007 through April 2020. We examined the efficacy of the metformin IR and XR drug formulations via stratifying by formulation, assessing GI issues and their affect on adherence rates and the overall prevention of neurodegenerative disease, including AD.

Results: Analysis of results indicated that when compared to MetIR formulations, MetXR significantly decreased GI issues after 3months, had significantly higher drug adherence rates and thus decreased the probability of developing a neurodegenerative outcome – particularly for the dementias, including AD and vascular dementia (VasDem). Confidence in this data was further solidified with a significant balance using the nearest neighbor method for propensity score matching.

Conclusions: MetXR showed significant decreases in several GI complications that may contribute to a diminished adherence over the MetIR formulation, and thus was shown to be significantly protective against the development of dementias, including AD and VasDem. Future work will focus on ensuring the null hypothesis is invalid and hopefully will reveal new insights into treatment efficacy with potential implications in research and treatment plan modifications.

POSTER #75

STRUCTURAL STUDY OF REGULATED INTRAMEMBRANE PROTEOLYSIS OF THE P75NTR BY γ-SECRETASE. Chan KY, Poh YP, Chiu PL. Arizona State University

Background: Programmed cell death (PCD) maintains the tissue size in a multicellular organism. Uncontrolled PCD in neurons has long been implicated in neurodegenerative diseases, e.g. Alzheimer's disease. p75 neurotrophin receptor (p75NTR) plays an important role in regulating neuronal growth and also involves in apoptotic signaling, which leads to morphological changes in cells in PCD. When binding to nerve growth factor (NGF), p75NTR maintains cell survival and proliferation; on the contrary, p75NTR induces apoptosis when the NGF precursor (pro-NGF) binds onto p75NTR. The complex formation of the pro-NGF, p75NTR, and sortilin initiates the apoptotic signaling. The subsequent proteolytic processing on p75NTR by γ-secretase relays the signaling to the neuronal apoptosis. p75NTR, the founding member of tumor necrosis factor (TNF) receptor superfamily, is a type I transmembrane protein, involved in the downstream cell death signaling after the release of intracellular domain (ICD) through regulated intramembrane proteolysis (RIP) executed by γ-secretase. Detailed molecular mechanism of how the γ-secretase cleaves p75NTR and releases its death domain is still unknown. To answer this question, our ultimate goal is to study the molecular mechanism of the p75NTR cleavage by γ-secretase using cryogenic electron microscopy (cryo-EM).

Methods: We generated four p75NTR mutants with various truncated mutants in Sf9 insect cells to determine the cleavage site for the γ-secretase. We characterized the bindings using size-exclusion chromatography, SDS-PAGE, and negative-stain EM.

Results: p75NTR mutants generated and characterized their bindings with γ-secretase.

Conclusions: We will stabilize the complex formation and probe the interaction between these proteins using single-particle cryo-EM. The result will gain a fundamental understanding of how p75NTR cleavage triggers the neuronal apoptosis signaling.

POSTER #76

UTILIZING TRACTOGRAPHY-GUIDED THETA BURST STIMULATION TO IMPROVE MEMORY PERFORMANCE IN MILD COGNITIVE IMPAIRMENT. Chen AY, That VT, Ugonna C, Liu Y, Nadel L, Chou Y. University of Arizona; Arizona Alzheimer's Consortium.

Background: Mild cognitive impairment (MCI) is a transitional stage between normal aging and Alzheimer's disease (AD). Studies have shown that significant degeneration of the hippocampal network is associated with MCI, especially in the memory domain. To enhance memory functions, targeting the hippocampus, which still exhibits plasticity at the stage of MCI, may be an effective strategy. Theta burst stimulation (TBS) is a non-invasive neuromodulation tool and has been closely investigated as a potential therapeutic approach for enhancement of cognitive functions in MCI. However, none of the previous studies in MCI have directly targeted the hippocampus in their stimulation protocols. In this study, we developed a personalized, image-guided hippocampal TBS protocol for individuals with MCI. Specifically, we utilized white matter tractography maps as a guide to effectively relay the modulation effects of the superficial TBS to the hippocampus.

Methods: Nine right-handed older adults aged 65 to 74 years old participated in our study. Participants were classified as MCI based on test scores derived from the Uniform Data Set version 3 (UDS3) neuropsychological battery. Diffusion-weighted MRI data were acquired at baseline for each participant to plan for an optimal superficial stimulation site. MRtrix was used to generate white matter tractography from the left hippocampal region. In this cross-over design, each participant underwent 2 sessions of each of the following TBS conditions: excitatory intermittent TBS (iTBS), inhibitory continuous TBS (cTBS), and sham TBS. Each TBS session was applied separated by at least 5 days to prevent a potential carry-over effect. Outcome measures including resting-state fMRI and the Face-Name associative memory test (FNAME) were acquired immediately before and after each TBS session.

Results: Excitatory iTBS significantly enhanced associative memory performance and increased resting-state functional connectivity along the inferior longitudinal fasciculus (ILF) to the hippocampus compared to the sham TBS. Individuals who had a larger increase in functional connectivity between subfields of the hippocampus (i.e., CA1 and hippocampal fissures) and the superficial stimulation site following active TBS had greater memory enhancement ($p < 0.05$).

Conclusions: Results of our pilot study suggest that tractography-guided TBS can be used to modulate hippocampal functional connectivity and improve associative memory in individuals with MCI. These findings provide new insight into how TBS propagates to the hippocampus from the superficial stimulation site along the inferior longitudinal fasciculus. Findings of our study may provide a useful strategy to inform the design of future TBS protocols for MCI.

POSTER #77

TOWARD MICROSTRUCTURAL MR MARKERS IN ALZHEIMER'S: A POST-MORTEM STUDY. Comrie CJ, Ahsan Z, Beach TG, Serrano GE, Hutchinson EH. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is an irreversible degenerative brain disease associated with dementia in an estimated 5.5 million Americans. However, within the medical field approximately 20% of all AD cases are misdiagnosed and it can be difficult to differentiate AD from other separate or comorbid disorders with similar symptoms and pathology such as Parkinson, benign brain tumors, or small strokes. In addition, Alzheimer's can only be confirmed upon autopsy by well accepted pathological histology markers and there is an urgent need for in-vivo non-invasive markers for the early detection of AD. To explore novel non-invasive MRI markers of AD that would meet these challenges, we developed an advanced microstructural MRI battery.

Methods: The samples used in this preliminary study were post-mortem (PM) temporal lobe blocks at the level of the hippocampus from one brain with advanced AD and one age-matched control. Fixed and rehydrated samples were received from the Brain & Body Donation Program in Sun City AZ. The samples were cut into 2.5 cm diameter circles centered on the hippocampus and then placed into a specialized air tight tube and imaged simultaneously. The microstructural MRI battery acquisition included diffusion-weighted imaging (DWI), Multi-Spin Echo (MSE) and Susceptibility Inverse Recovery (SIR). Diffusion tensor imaging (DTI) was performed using DWIs with b=100-1000 s/mm2 and mean apparent propagator MRI (MAP-MRI) used b=100-6000 s/mm2. The more conventional DTI method assumes Gaussianity and reports diffusivity with the Trace metric and anisotropy with the Fractional Anisotropy (FA) metric, while the non-Gaussian method of MAP-MRI reports information about the microstructural environment with the Non-Gaussianity (NG) and Propagator Anisotropy (PA) metrics. The values of the FA and PA maps were analyzed qualitatively and also evaluated by quantitative 2D histograms for both the healthy and AD samples. The SIR technique produces T1 and a Bound Pool Fraction (BPF) maps, where BPF is associated with the presence of macromolecules. The MSE technique produces T2 and Myelin Water Fraction (MWF) maps, where the MWF is indicative of myelin content.

Results: Several key preliminary findings emerged from this work. First, similar contrast weighting was found between the NG and PA but not other MAP-MRI metrics. This pattern indicates that in regions of high NG there is also high microscale anisotropy or highly anisotropic compartments. Next, FA was reduced in the hippocampus of the AD sample, but PA followed a distinct pattern with increases in some subfields. This indicates a geometrically complex environment with high microscale anisotropy but low macroscale or geometric anisotropy. The 2D histograms between FA and PA also showed a distinction between AD and control specimens. The PA histogram displayed 3 peaks in contrast to the 2 peaks shown in the healthy PA histogram for the same range of FA values. This is indicative of complex microstructure and also sensitivity of the PA metric to tissue features that are not detectable by FA. The T1 map showed disruption of the white/grey interface in the cortex of the brain which resembled known pathologic features of AD. Finally, BPF values were slightly greater for the AD sample which is consistent with the presence of pathologic macromolecules, although more evidence is needed.

Conclusions: This project investigated microstructural MRI methods to identify promising markers of AD pathology in patients. While this work is in the early stages, the developed MRI battery displays promising preliminary results for identifying AD in post mortem tissue using several of the approaches investigated. The research is ongoing with a larger dataset to find consistent AD biomarkers with these methods, and results will be validated by comparison with histology in the same samples.

POSTER #78

GOAL SETTING: A GLIMPSE INTO EPISODIC FUTURE THINKING IN YOUNG AND OLDER ADULTS. Cruz LE, Griffith CX, Andrews-Hanna JR, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Episodic future thinking allows one to "pre-experience" an event that may occur in their personal future, which has implications for goal success. Research has shown that, compared to young adults, cognitively normal older adults envision the future with less episodic richness. This reduction in episodic richness is exacerbated in older adults with Alzheimer's disease (AD) dementia, raising questions about the effects of higher AD risk on episodic future thinking and goal success. This project seeks to better understand the relationship between goal attainment and future thinking, as well as how episodic future thinking and self-narrative continuity are affected by AD risk in younger and older adults.

Methods: In a multi-session study, participants created four goals, and subjectively rated the personal significance and vividness with which they imagined each goal. Ten days later, they rated the degree to which they planned and made progress in their goals. They also completed the prospective and retrospective memory questionnaire (PRMQ).

Results: Analysis of these data showed a moderate positive correlation between goal vividness and goal progress, but no correlation between personal significance and goal progress. Goal planning was positively related to goal vividness, progress, and personal significance. Interestingly, older adults reported significantly more goal planning, personal significance and vividness, but did not make significantly more goal progress. Relatedly, PRMQ data showed no significant age-related differences in reported prospective memory efficiency.

Conclusions: These data reveal part of the relationship between episodic future thinking and goal follow through. Future research will shed light on how this episodic mechanism leads to individual differences in goal attainment, and how higher AD risk affects goal success and future thinking.

POSTER #79

AMYLOID-B ANALYSIS FROM MICRODISSECTED HUMAN BRAIN CELLS USING MICROFLUIDICS AND MASS SPECTROMETRY. Cruz Villarreal J, Egatz-Gomez A, Noutsios GT, Sandrin TR, Coleman PD, Ros A. Arizona State University; Arizona Alzheimer's Consortium.

Background: Soluble amyloid β (Aβ) oligomers are considered to play a major role in Alzheimer's disease (AD). Based on the Aβ hypothesis, Aβ oligomers are considered the neurotoxic species responsible for neuronal dysfunction. However, details on their chemical nature have not been elucidated mainly due to a lack of analytical methods to access the proteomic cell content. The identification of AD-related Aβ species in brain cells and their environment could provide valuable insights into the disease. Thus, here we propose to investigate the differences in Aβ species from AD and non-AD human brains. To address this interrogation, we are developing a microfluidic immunoassay for in situ mass spectrometry (MS) detection of Aβ species from microdissected human brain cells.

Methods: We have previously developed a microfluidic platform for sample preparation and immunocapture on-chip in tandem with MALDI-MS for analysis. The multiple-layer PDMS manifold reversibly bonded to a conductive substrate allowing its use as a target in the MALDI MS analysis. The immunoglobulin G (IgG) 6E10 for Aβ was used to confirm the immunocapture on-chip, which includes IgG immobilization, Aβ incubation, washing steps, and matrix for co-crystallization. By removing the PDMS manifold, crystals were exposed on the substrate for in situ MALDI-MS analysis. To collect brain cells directly into the microfluidic platform, we coupled our platform to a laser microdissection (LCM) instrument. Different Aβ species were prepared and characterized with MALDI-MS.

Results: We have shown the brain cell loading to the platform with a 70% capture efficiency and confirmed the immunocapture on-chip for synthetic Aβ. The IgG specificity was confirmed through controls. We determined the limit of detection of Aβ in our assay as 35 nM using a Bruker Microflex instrument. Moreover, different Aβ oligomeric states were observed with MALDI-MS, including oligomers up to 12-mers, showing the capability of detecting a range of oligomeric states without the need for pre-treatment procedures.

Conclusions: We have shown the functionality of our platform in combination with LCM and MALDI-MS, showing the capability of immunocapture Aβ on-chip and of detecting amyloid-beta oligomeric species with MALDI-MS without any sample treatment. The implementation of the proposed assay to study Aβ from AD brains could overcome the current limitations of studying protein content and elucidate the role of Aβ in AD.

POSTER #80

FIBRILLIN-1 DEFICIENCY ACCELERATES CEREBROVASCULAR AGING, LEAVING THE BRAIN MORE VULNERABLE TO TBI. Curry T, Bromberg CE, Saber M, Rowe RK, Gonzales R, Esfandiarei M, Currier Thomas T. University of Arizona College of Medicine-Phoenix; Midwestern University; Barrow Neurological Institute at Phoenix Children's Hospital; University of Colorado Boulder; Arizona Alzheimer's Consortium.

Background: Cerebrovascular aging (CVA) is a risk factor for cognitive decline, dementia, stroke, cerebral aneurysms, and adverse outcomes following traumatic brain injury (TBI). CVA is associated with extracellular matrix impairment, vascular wall weakening and stiffening, blood-brain barrier (BBB) permeability, and exacerbated cytokine production. However, the mechanisms contributing to the features of CVA that increase the vulnerability to TBI for the geriatric population are poorly understood. A mutation in the fibrillin-1 (Fbn1) gene leads to elevated systemic transforming growth factor-beta (TGF-beta) and matrix metalloproteinases (MMPs) -2/-9 implicated in CVA.

Methods: In this study, heterozygotes of a well-characterized transgenic mouse model (Fbn1+/-) were utilized to test the hypothesis that increased TGF-beta/MMP activity would accelerate cerebrovascular rigidity, BBB permeability, and neurological alterations associated with aging, leaving the brain more vulnerable to diffuse TBI. In 6, 9, and 12M-old Fbn1+/- and C57BL/6 wildtype (WT) male and female mice, posterior cerebral artery (PCA) rupture point (N=3-5/group), BBB permeability (N=2-3/group), injury viability (N=2-3/group), and neurobehavioral severity scale (NSS) outcomes (N=10-11/group) were assessed.

Results: Our data shows that 6-month-old Fbn1+/- mice have compromised PCA wall strength ($p<0.05$), increased BBB permeability ($p<0.05$), and elevated NSS scores ($p<0.05$) in comparison to 6M WT and similar to 12M-old WT mice. To investigate vulnerability to mild TBI (mTBI), varying pulse pressures (1.11-1.32atm) were applied to the brains of 6M-old WT (1.25-1.32atm) and Fbn1+/- (1.17-1.21atm) mice using midline fluid percussion injury, where Fbn1+/- mice required lower pressure to induce mTBI righting reflex times (4-6minutes).

Conclusions: These data support that CVA via increased TGF-beta/MMP plays a critical role in the vulnerability of the aged brain to mTBI. Using this novel approach allows for the mechanistic study of TGF-beta/MMP pathways that could serve as a therapeutic target for prevention or management of symptoms in geriatric TBI patients.

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POSTER #81

IDENTIFICATION OF RETINOBLASTOMA BINDING PROTEIN 7 (RBBP7) AS A MEDIATOR AGAINST TAU ACETYLATION AND SUBSEQUENT NEURONAL LOSS IN ALZHEIMER'S DISEASE AND RELATED TAUOPATHIES. Dave N, Vural A, Piras IS, Winslow W, Surendra L, Winstone JK, Beach TG, Huentelman MJ, Velazquez R. Arizona State University; Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Evidence indicates that tau hyper-phosphorylation and subsequent neurofibrillary tangle formation contribute to the extensive neuronal death in Alzheimer's disease (AD) and related tauopathies. Recent work has identified that increased tau acetylation can promote tau phosphorylation. Tau acetylation occurs at lysine 280 resulting from increased expression of the lysine acetyltransferase p300. The exact upstream mechanisms mediating p300 expression remain elusive. Additional work highlights the role of the epigenome in tau pathogenesis, suggesting that dysregulation of epigenetic proteins may contribute to acetylation and hyper-phosphorylation of tau. Here, we identify and focus on the histone-binding subunit of the Nucleosome Remodeling and Deacetylase (NuRD) complex: Retinoblastoma-Binding Protein 7 (Rbbp7). Rbbp7 chaperones chromatin remodeling proteins to their nuclear histone substrates, including histone acetylases and deacetylases. Notably, Rbbp7 binds to p300, suggesting that it may play a role in modulating tau acetylation.

Methods: We interrogated Rbbp7 in post-mortem brain tissue, cell lines and mouse models of AD.

Results: We found reduced Rbbp7 mRNA expression in AD cases, a significant negative correlation with CERAD (neuritic plaque density) and Braak Staging (pathogenic tau inclusions) and a significant positive correlation with post-mortem brain weight. We also found a neuron-specific downregulation of Rbbp7 mRNA in AD patients. Rbbp7 protein levels were significantly decreased in 3xTg-AD and PS19 mice compared to NonTg, but no decreases were found in APP/PS1 mice that lack tau pathology. In vitro, Rbbp7 overexpression rescued TauP301L-induced cytotoxicity in immortalized hippocampal cells and primary cortical neurons. In vivo, hippocampal Rbbp7 overexpression rescued neuronal death in the CA1 of PS19 mice. Mechanistically, we found that increased Rbbp7 reduced p300 levels, tau acetylation at lysine 280 and tau phosphorylation at AT8 and AT100 sites.

Conclusions: Collectively, these data identify a novel role of Rbbp7, protecting against tau-related pathologies, and highlight its potential as a therapeutic target in AD and related tauopathies.

POSTER #82

HIERARCHICAL BAYESIAN LEARNING FOR CEREBRAL MORPHOMETRY ANALYSIS.

Fan Y, Wang Y. Arizona State University; Arizona Alzheimer's Consortium.

Background: Three-dimensional data on Riemannian manifolds, such as triangular meshes and tetrahedral meshes, records the shape and geometric properties of the object in the form of spatial sampling points and their connections. They are widely used in precise anatomical morphometry analysis, such as the measurement of cortical pathological deformation in studies of Alzheimer's disease (AD). Extracting and aggregating geometric features is considered the key to learning the intrinsic shape information from this type of data. Recently, the Gaussian process (GP) based Bayesian learning demonstrates strong regression and classification ability in medical data analysis. However, current studies mainly focus on image-based and signal-based tasks while Bayesian learning on manifolds has been seldom investigated. Effectively and efficiently aggregating features from the irregular off-the-grid data through Bayesian inference is one of the primary goals of designing Bayesian learning methods on manifolds.

Methods: We propose a hierarchical Bayesian learning framework as an implementation of the Bayesian belief network on manifolds. We introduce a hierarchical Bayesian network with convolutional architectures to the anatomical morphometry analysis. Specifically, we concentrate on two fundamental aspects of designing the Bayesian learning method: GP kernel study and Bayesian learning framework. We discover two important characteristics of the periodic diffusion kernel (PDK) that are beneficial to the design of Bayesian learning on manifolds: geometry-awareness and intra-kernel convolution. Our contributions are summarized threefold: (1) We rigorously prove two characteristics of PDK. The PDK is implemented in two different ways based on its original definition. Eventually, we solve both the input organization and feature aggregation with a single kernel design. (2) We propose a complete framework of hierarchical Bayesian learning on manifolds, including a doubly dimension reduction scheme and a deep GP learning module. (3) We validate the hierarchical Bayesian network by applying it to the landmarking problem of brain morphometry analysis. We use the full ADNI-2 baseline cohort as the dataset. Large amount of experiments prove the effectiveness of our methods.

Results: we apply our method to the problem of tetrahedron-based cortical morphometry analysis. The task is to select landmarks and classify subjects into their diagnostic group with the features of landmarks. We use the whole ADNI-2 baseline cohort as the dataset including 105 AD patients, 289 mild cognitive impairment (MCI) patients, and 141 cognitively unimpaired (CU) subjects. The performance is evaluated by accuracy (ACC), sensitivity (SEN), and specificity (SPE). Initially, we fix the Bayesian learning model to be one layer and change the number of mixtures of PDK. We test one to five mixtures and report the results of one and five mixtures. Generally, with five mixtures, the PDK model has stable performance. More mixtures mean the model can learn more complicated structures, but the computational cost is also more. Then, we fix the number of mixtures to be five and evaluate different architectures. The layer size of the latent GP layer is 2. Results show that (1) hierarchical models generally outperform the single layer model; (2) PDK shows a better performance; (3) the Bayesian method, especially Bayesian with PDK, has a better feature aggregation capability. The experimental results demonstrate the great potential of Bayesian learning techniques in medical imaging analysis.

Conclusions: We address the challenge of applying Bayesian learning on manifold-valued tasks and propose a hierarchical Bayesian network framework. We demonstrate the great potential of Bayesian learning techniques in medical imaging analysis. Our future work will focus on designing an end-to-end deep Bayesian network. A Bayesian model integrated with feature learning or a deep kernel learning model may be even more expressive and applicable for manifold-valued applications.

POSTER #83

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

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

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

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

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

POSTER #84

PINE-TREE: PRIME INDUCED NUCLEOTIDE ENGINEERING USING A TRANSIENT REPORTER FOR EDITING ENRICHMENT. Frisch C, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: The continuous and rapid development of CRISPR technologies for genome engineering shows promise in helping to uncover the pathogenesis of Alzheimer's disease (AD). A more recent transversion mutation identified in the APOE gene known as the ApoE Christchurch (APOEch) mutation has revealed no cognitive impairment with AD pathology in post-mortem brain studies. Current base editing technologies are not able to efficiently generate engineered cell lines to study the mechanisms and potential protective effects of mutations like the APOEch mutation. Unlike base editing technologies, the most recently developed prime editing system can efficiently edit transversion mutations [1]. Conventional approaches only report on transfection efficiency of plasmid delivery but fail to address editing efficiency at the cellular level. To report on editing efficiency at the genomic level, we have engineered a dual prime editing guide RNA (pegRNA) system able to target an episomal blue fluorescent protein (BFP) and a target site (TS) at a chromosomal locus with the prime editing 2 and 3 (PE2 and PE3) systems. With this study, we discuss how PINE-TREE provides an efficient platform to introduce transversion mutations at the genomic level in HEK293 cells with hopes of creating isogenic human-induced pluripotent stem cell (hiPSC) derived models to study AD.

Methods: For the plasmid construction of dual targeting pegRNAs at the episomal BFP and chromosomal TS, pegRNAs were synthesized as oligonucleotides. Incubation of synthesized pegRNAs with T4 DNA Ligase Buffer (NEB) and T4 Polynucleotide Kinase added 5' phosphates to each oligonucleotide. Oligonucleotides were duplexed in a heating block and cloned into a modified pSB1C3 vector containing a U6 promoter and BbsI restriction enzyme digestion sites. BFP and TS pegRNAs were PCR amplified with primers adding restriction enzyme sites. PCR products were digested and ligated into a digested pUC19 vector (Addgene #50005) to contain pairs of pegRNA expression cassettes. HEK293 cells underwent a lipid-based transfection with vectors containing a BFP reporter, pegRNA expression cassettes, and a prime editor. HEK293 cells were dissociated, and populations were sorted 72hr post-transfection into a master mix containing Phire Hot Start II DNA Polymerase [2]. Sanger sequencing was performed on PCR products and editing efficiency was quantified using EditR [3].

Results: Using constructed vectors for the PE2 and PE3 systems, sorted HEK293 cell populations transfected with dual targeting pegRNAs showed an increase in editing efficiency when compared to populations previously reported by Anzalone et al.1 Specifically, sorted cell populations using the PE3 system showed almost a 2-fold increase in edited cells when compared to populations previously reported. Preliminary results suggest editing in HEK293 cells using the PE2 system at the APOEch mutation site, resulting in an amino acid substitution from an arginine to serine at amino acid 136.

Conclusions: The current PINE-TREE method shows promise in editing transversion mutations such as the APOEch mutation. We hypothesize that further optimization of reporter editing using the PE3 system is needed to determine the full potential and efficiency of the PINE-TREE system and optimal translation into hiPSCs. With optimal editing efficiency in hiPSCs, this system can be used to generate clonal isogenic hiPSC lines to study the effects of mutations involved in AD pathogenesis.

POSTER #85

GRAY MATTER VOLUMETRIC DIFFERENCES IN HEALTHY OLDER ADULTS AT RISK FOR ALZHEIMER'S DISEASE. Gallegos N, Hoscheidt S, Stickel A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: It is well-documented that gray matter volume decreases in Alzheimer's disease (AD). Gray matter volumes have been shown to be correlated with disease progression and cognitive deficits. These brain changes can be detected in some of the earlies stages of this disease, such as the preclinical stages where there are no cognitive symptoms of AD.

Methods: In this study, we investigated gray matter volume loss in individuals who are at high risk of developing AD based on several risk factors, including carrying the apolipoprotein e4 allele (APOE-4) or having a first-degree family history of AD. We analyzed the gray matter volumes in 46 cognitively healthy older adults, ages 49 to 89 with an average of 70 years, with one or both risk factors, and an additional 32 matched controls without either risk factor.

Results: Voxel-based morphometry of high-resolution MRI showed significantly smaller gray matter volumes in risk groups compared to controls in a region of the left anterior hippocampus and amygdala, as well as other brain regions including the left temporal pole and the right superior frontal gyrus.

Conclusions: This study provides evidence that these risk factors have an influence on gray matter volumes even in cognitively healthy individuals. Subsequent analyses will determine which of the risk factors are driving these differences. We also plan to correlate these volumetric measures with performance on tasks of memory and executive functions.

POSTER #86

LEGAL IMPLICATIONS OF USING ARTIFICIAL INTELLIGENCE TO PREDICT PRE-SYMPTOMATIC ALZHEIMER'S RISK. Ghaith S, Marchant GE, Lindor RA. Mayo Clinic; Arizona State University.

Background: Artificial intelligence (AI) is being applied to identify pre-symptomatic biomarkers of Alzheimer's disease. These biomarkers build upon and incorporate earlier work identifying genetic, neurologic, psychological and blood biomarkers of Alzheimer's disease. AI biomarkers have the potential to be more accurate, and predict Alzheimer's further in advance, than previous biomarkers. As such, these biomarkers are likely to have dramatic impacts on patients, the health care system, and the legal system. This presentation will explore the legal implications of AI biomarkers, including the potential for discrimination and stigmatization of at-risk patients.

Methods: This project will proceed in three stages. First, we identify the early progress of AI in predicting Alzheimer's risk in patients, and the likely capabilities, timeline, and limitations of such biomarkers. Second, we will research statutes, regulations, and case law to identify potential legal applications of AI Alzheimer's biomarkers in discrimination and litigation contexts. Third, we identify existing legal protections that will apply in these contexts, as well as the legal gaps and possible solutions to fill those gaps.

Results: AI is rapidly advancing in its ability to predict Alzheimer's, and it is likely that such biomarkers will become commercially and clinically available in the next few years. These biomarkers will create discrimination and stigmatization risks for patients in employment, various types of insurance coverage (health, life, long term care, disability), housing, and marriage and sexual relationships. In addition, we identify actual precedents in case law where AI biomarkers may be applied in litigation contexts to evaluate competency to adopt or revise wills, create or amend trusts, sell property, enter into business contracts, purchase insurance contracts, be held responsible for criminal or tortious acts, and determine damages based on life expectancy.

Conclusions: AI biomarkers of Alzheimer's will have numerous legal applications and implications. Such applications will help to protect the autonomy of Alzheimer's patients, but many will impose legal risks on individuals found to be at risk of Alzheimer's. We identify some options for policymakers to better protect Alzheimer patients from these legal risks.

POSTER #87

COLONY STIMULATING FACTOR-1 RECEPTOR INHIBITION AS A PHARMACODYNAMIC MECHANISM TO TRACK PERIPHERAL INFLAMMATION AFTER TBI. Giordano KR, Murphy SM, Saber M, Green TRF, Rojas-Valencia LM, Ortiz JB, Lifshitz J, Rowe RK. University of Arizona COM-Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Health Care System; University of Colorado–Boulder; Arizona Alzheimer's Consortium.

Background: Inflammation is a hallmark of traumatic brain injury (TBI) pathophysiology that contributes to both brain damage and repair. To investigate microglial mechanisms in central and peripheral inflammation following TBI, we inhibited the colony stimulating factor-1 receptor (CSF-1R), critical for microglial survival, with PLX5622 (PLX). We hypothesized that microglia depletion would attenuate central inflammation.

Methods: After randomization, mice (n=105) were fed PLX or control diets (21 days) and then received midline fluid percussion injury (mFPI) or sham injury. Immune cell populations (leukocytes, myeloid cells, microglia, monocytes, macrophages, neutrophils) and cytokine levels (IL-6, TNF-α, IL-1β, INF-γ, IL-10, IL-17A) were quantified in the brain and blood by flow cytometry and multiplex ELISA at 1, 3, or 7 days post-injury (DPI), respectively. Data were analyzed via Bayesian multivariate multi-level models.

Results: PLX depleted microglia (CD11b+CD45low) with no additional PLX-dependent changes in the brain. In the periphery, PLX depleted a subset of circulating monocytes (CD45+CD11b+CD115+). However, independent of mFPI, we observed a PLX-dependent increase in IL-6 and classical monocytes (CD45+CD11b+Ly6Chigh), and a PLX-dependent decrease in patrolling monocytes (CD45+CD11b+Ly6Clow). Monocyte population redistributions were sustained through 7DPI. At 3DPI, PLX prevented mFPI-induced increases in circulating myeloid cells (CD45+CD11b+) and neutrophils (CD45+CD11b+Ly6G+). Independent of PLX, mFPI-induced changes in peripheral inflammation resolved by 7DPI.

Conclusions: CSF-1R inhibition depleted a subset of central and peripheral immune cells. Although TBI-induced inflammation resolved irrespective of intervention, CSF-1R inhibition sustained peripheral inflammation. Collectively, our results indicate that CSF-1R inhibition may be a mechanism for targeting central and peripheral immune cell populations to track disease state and build a pharmacodynamic temporal profile of inflammation after TBI.

POSTER #88

TDP-43 EXPRESSION IN DEMENTIA-RELEVANT CIRCUITS CAUSES AXONAL DEGENERATION AND BEHAVIORAL DEFICITS IN DROSOPHILA. Godfrey RK, Bjork RT, Williams C, Hala'ufia G, Cowell HB, Lehmkuhl EM, Alsop E, Jensen K, Zarnescu DC. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Trans active response (TAR) DNA-Binding protein 43 (TDP-43), an evolutionarily conserved RNA/DNA binding protein that regulates RNA processing, is known to form pathological, cytoplasmic inclusions in numerous neurodegenerative diseases. First identified in ubiquitin-positive inclusions in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), TDP-43 pathology has now been detected in Alzheimer's disease (AD), with more severe hippocampal atrophy associated with TDP-43 positive inclusions.

Methods: Given the success of modeling ALS in flies with TDP-43 proteinopathy, we have developed a novel model of dementia based on TDP-43. To achieve this, we overexpress human TDP-43 in the mushroom bodies of the Drosophila brain. Mushroom bodies form an elaborate, associative network that overlaps in function and gene expression with neurons in the human hippocampus and frontal cortex. We use a combined imaging, molecular and behavioral approach to evaluate the effects of TDP-43 proteinopathy in mushroom bodies.

Results: We find that TDP-43 is mislocalized from the nucleus to the cytoplasm and forms axonal inclusions. This results in both behavioral deficits and age-dependent axonal degeneration in mushroom body neurons. Importantly, we find that the cognitive deficits in working memory and sleep appear prior to our ability to detect axonal degeneration, paralleling what is seen in human disease. Using RNA immunoprecipitations and RNAseq, we identified several candidate targets of TDP-43 in mushroom bodies, including Dally-like protein (Dlp/GPC6), a translational target that we recently reported in ALS models and patients.

Conclusions: These findings suggest that TDP-43 expression in mushroom bodies cause FTD relevant phenotypes that may help uncover novel mechanisms of disease. Future experiments are aimed at identifying additional FTD-relevant targets of TDP-43, including novel therapeutic strategies.

POSTER #89

VIRTUAL FOCUS GROUPS AND ADRD RESEARCH: NEW OPPORTUNITIES TO OVERCOME BARRIERS. Gómez-Morales A, Carll P, Cordova L, Glinka A, Gonzalez-Piles S, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: Focus groups are generally conducted in-person, challenging the participation of individuals juggling multiple responsibilities. Fewer focus groups are adapted to user-friendly technologies to help reach diverse and harder-to-reach communities, such as caregivers of adults with chronic medical conditions and the professional providers who serve them. Many of these caregivers do not participate because they work full-time, are more geographically isolated, or are housebound due to health, transportation, or other barriers. Virtual or computer-mediated focus groups via videoconference offer solutions to include these populations, learn about their needs and concerns, and hear their ideas regarding programs and services to better serve them.

Methods: Based on recent literature and our past research experience with focus groups, the team developed and implemented a series of steps unique to running focus groups virtually, including tips and considerations regarding IRB approval, recruitment, screening, and informed consent approaches, privacy, and confidentiality in virtual environments, moderator guide development and group processes.

Results: Virtual focus groups (N=47) were conducted in English or Spanish for family caregivers (83%) and separate focus groups for care recipients (17%) living in Arizona. Caregivers ranged from 18 to 90 years of age and care recipients from 34 to 85 years. A quarter (25.5%) participated in Spanish. Professional providers working with chronically ill adults and their family caregivers (N=25) participated in separate focus groups with almost half opting to participate in Spanish (48%). Their ages ranged between 18 to 80 years. These groups helped to attract diverse samples of participants including Hispanic or Latino, Caucasian, African American and participants, people working full and part-time, and individuals from rural areas.

Conclusions: Virtual focus groups offer a unique opportunity to reach more diverse populations regardless of their caregiving contexts. Additionally, virtual focus groups offer the chance to learn novel ways to break barriers to health access by providing virtual reach capabilities for caregiving populations that are housebound, geographically isolated, working full-time, or other situations that preclude attendance from research projects.

POSTER #90

MISLOCALIZED EXPRESSION OF THE NUCLEAR PORE COMPLEX PROTEINS NUP153, -93, AND -214 IN ALZHEIMER'S DISEASE BRAINS. Goras M, Brokaw D, Delvaux E, Nolz JD, Mastroeni D, Coleman P. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive, neurocognitive disorder characterized by memory dysfunction. The presence of neuropathological aberrations, namely amyloid plaques, and neurofibrillary tangles, although key characteristics of this disease, have shown to be poor prognostic indicators. As such, clinical trials targeting AD neuropathology have largely been unfruitful, necessitating new research into novel mechanisms of the underlying pathways mediating cognitive decline. Nuclear pore complexes (NPCs) are the main conduits for molecular exchange across the nuclear envelope in eukaryotic cells. The NPC contains approximately 30 distinct nucleoporins (NUPs) which form a selective channel that supports the factor mediated shuttling of cargo through the NPC. Mutations in nucleoporin genes have been linked to various human diseases including neurodegenerative diseases. Tau is the major component of neurofibrillary tangles in (AD), and a recent study has suggested a role in NPC deterioration and thus nuclear-cytoplasmic defects. This study however was not an extensive one and only investigated four nucleoproteins from one layer of the NPC structure. In this study, we have targeted all three major components of the NPC structure, by analyzing gene expression of representative NUPs from homogenate brain tissue and neuronal data in AD patients.

Methods: Three significantly differentially expressed NUPs (NUP 214, -93, -153), representing different parts of the NPC structure (cytoplasmic filaments, inner ring structure, nuclear basket), were selected for validation by immunohistochemistry and Western blotting in postmortem human hippocampal sections.

Results: Bioinformatic analysis revealed widespread differential NUP gene expression across multiple brain regions in AD. These results were reflected in immunohistochemistry and immunoblotting results, which revealed quantity and localization changes of the selected NUPs in AD. Our findings revealed mislocalization of cytoplasmic- facing nucleoporin NUP214 in the cytoplasm in AD and nuclear localization of inner ring and nuclear basket nucleoporins NUP93 and NUP153 in hippocampal CA1 neurons.

Conclusions: These results and this research, represents one of the first attempts to categorize differential changes throughout the entire structure of the NPC in AD patients. Future studies will explore the hierarchical relationship between neuropathological hallmarks of AD and NPC aberrations to better understand the etiology of impaired nucleocytoplasmic transport in neurodegeneration.

POSTER #91

AGE-RELATED DIFFERENCES IN THE EFFECTS OF AN SSRI ON COGNITION IN FEMALE RATS. Hanson TC, Hiroi R, Koebele SV, Bernaud VE, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Selective serotonin reuptake inhibitors (SSRIs) are a commonly used treatment for depression and anxiety-related symptoms. Sex and age are both factors that increase vulnerability to cognitive detriment and affective symptoms, with women and older individuals more likely in need of SSRI treatment. This vulnerability may be related to interactions between gonadal hormones, age, and the serotonergic system. Previous preclinical research studying SSRIs, particularly regarding effects on cognition, has been mostly performed in males. The current study investigates whether treatment with the SSRI citalopram affects cognition, anxiety-like, and depressive-like behaviors in female rats, including whether these SSRI-related behavioral outcomes differ by age.

Methods: Vehicle or SSRI (citalopram) was given via oral administration to both young and middle-aged ovary-intact female Fischer-344 rats. Animals were then tested on a behavioral battery to assess cognition, anxiety-like, and depressive-like behaviors.

Results: SSRI treatment impaired cognition in middle-aged female rats as compared to vehicle-treated middle-aged female rats, where there were no significant SSRI-associated cognitive impacts observed in young rats. Anxiety-like and depressive-like behavioral data are in the process of being scored and analyzed; relationships amongst affective and cognitive data will be assessed to determine if associations differ by age and/or SSRI treatment.

Conclusions: The current study indicates that the SSRI citalopram negatively impacts cognition in middle-aged, but not young adult, female rats. Additional research evaluating whether ovarian hormone milieu alters these effects will be an important next step, as menopause-related hormone and reproductive-tract alterations may further impact cognitive and affective outcomes. Moreover, other important clinically-relevant future directions include the role of sex and SSRI type in modulating cognitive and affective profiles following SSRI treatment.

POSTER #92

ANGIOTENSIN-(1-7)/MAS RECEPTOR AGONIST PROTECTS HIPPOCAMPUS NEURONS IN MOUSE MODEL OF VASCULAR DEMENTIA. Hoyer-Kimura C, Konhilas J, Mansour H, Polt R, Hay M. University of Arizona; ProNeurogen, Inc.; Arizona Alzheimer's Consortium.

Background: Decreased brain blood flow, increased inflammation, and increased reactive oxidative species (ROS) are correlated to accelerated progression of both vascular contributions to cognitive impairment and dementia (VCID) and Alzheimer's disease related dementia (ADRD). It has been previously demonstrated that VCID models with blood brain barrier dysfunction exhibit hippocampal neuronal loss and impaired cognitive function. Our novel synthetic glycosylated Angiotensin-(1-7) derivative (PNA5), has an enhanced half-life and is optimized for better blood-brain-barrier penetration. In our preclinical VCID model, PNA5 treatment inhibits brain ROS production, and reverses cognitive deficits. We hypothesized that 1) neuronal cell count in the CA1 region of the hippocampus will be decreased in our heart failure (HF) induced VCID mouse model and 2) PNA5 treatment will mitigate neuronal cell loss within the hippocampus and protect cognitive function.

Methods: VCID was induced in adult male C57BL/6J mice (10-15/group), via HF. Control mice underwent sham surgery. Following 5 weeks post coronary ligation, mice were treated with either 1) saline or 2) 50 micrograms/kg/day PNA5, via daily subcutaneous injection for 21 days. Novel-object recognition was used to measure cognitive function and is represented as a Discrimination ratio. Hippocampal neuronal cell loss was determined through analysis of free-floating formalin-fixed 16micron cryosection brains, stained with NeuN (ab177487, 1:500) and counted using ImageJ. CA1 Hippocampal regions (-1.6 to -2.0 millimeters from bregma) were imaged at 40x magnification. Data were analyzed by one-way ANOVA.

Results: VCID-Saline mice displayed cognitive impairment (Discrimination ratio mean -0.02, SE +0.07) compared to Control-Saline (Discrimination ratio 0.57+0.1). Cognitive function was rescued by PNA5 treatment (Discrimination ratio 50micrograms/kg/day 0.61+0.09). VCID-Saline mice displayed a significant decrease in neurons in the CA1 region (3.35 + 0.11 cell/ pixel linear area) compared to Control-Saline mice (3.94 + 0.12). Mice treated with PNA5 had significantly higher CA1 neuronal cell count (3.87 + 0.17) in comparison to VCID-Saline treated mice.

Conclusions: These data suggest that PNA5 protects against VCID cognitive impairment and prevents neuronal cell loss in VCID mouse models.

POSTER #93

METABOLIC PROFILING OF NEOCORTICAL TISSUE DISCRIMINATES ALZHEIMER'S DISEASE FROM MILD COGNITIVE IMPAIRMENT, HIGH PATHOLOGY CONTROLS, AND NORMAL CONTROLS. Jasbi P, Shi X, Chu P, Elliott N, Hudson H, Jones D, Serrano G, Chow B, Beach T, Liu L, Jentarra G, Gu H. Arizona State University; Yale School of Medicine; Midwestern University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common cause of dementia, accounting for an estimated 60 to 80% of cases, and is the sixth-leading cause of death in the United States. While considerable advancements have been made in the clinical care of AD, it remains a complicated disorder that can be difficult to identify definitively in its earliest stages. Recently, mass spectrometry (MS)-based metabolomics has shown significant potential for elucidation of disease mechanisms and identification of therapeutic targets as well diagnostic and prognostic markers that may be useful in resolving some of the difficulties affecting clinical AD studies, such as effective stratification.

Methods: In this study, complementary gas chromatography- and liquid chromatography-MS platforms were used to detect and monitor 2,080 metabolites and features in 48 post-mortem tissue samples harvested from the superior frontal gyrus of male and female subjects. Samples were taken from four groups: 12 normal control (NC) patients, 12 cognitively normal subjects characterized as high pathology controls (HPC), 12 subjects with non-specific mild cognitive impairment (MCI), and 12 subjects with AD.

Results: Multivariate statistics informed the construction and cross-validation ($p < 0.01$) of partial least squares-discriminant analysis (PLS-DA) models defined by a 9-metabolite panel of disease markers (lauric acid, stearic acid, myristic acid, palmitic acid, palmitoleic acid, and four unidentified mass spectral features). Receiver operating characteristic analysis showed high predictive accuracy of the resulting PLS-DA models for discrimination of NC (97%), HPC (92%), MCI (~96%), and AD (~96%) groups. Pathway analysis revealed significant disturbances in lysine degradation, fatty acid metabolism, and the degradation of branched-chain amino acids. Network analysis showed significant enrichment of 11 enzymes, predominantly within the mitochondria.

Conclusions: The results expand basic knowledge of the metabolome related to AD and reveal pathways that can be targeted therapeutically. This study also provides a promising basis for the development of larger multi-site projects to validate these candidate markers in readily available biospecimens such as blood to enable the effective screening, rapid diagnosis, accurate surveillance, and therapeutic monitoring of AD.

POSTER #94

NEUROIMAGING CORRELATES OF FINE MOTOR FUNCTION DURING FINGER TAPPING IN HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT COHORTS: A SAGE-FMRI STUDY. Keeling EG, Prigatano GP, Stokes AM. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a leading cause of death in the United States, affecting over 6 million Americans. While AD is classically defined by pathological biomarkers and memory symptoms, motor function decline has also been implicated as a potential AD-specific symptom. Previous studies have shown that fine motor ability, assessed via a simple finger tapping exam, reveals different patterns between healthy aging and mild cognitive impairment, as well as between mild cognitive impairment and Alzheimer's disease. In this preliminary study, we aim to assess the differences in functional activation during finger tapping between healthy aging and mild cognitive impairment groups, leveraging an advanced functional MRI method to sensitively assess both global and microvascular changes.

Methods: Five healthy aging controls (HC, 3 females; 75.6±4.8 years) and five subjects with mild cognitive impairment (MCI, 3 females; 73.6±5.0 years) were included in this preliminary study. Cognitive data was collected using the BNI Screen for Higher Cerebral Functions (BNIS). Finger tapping data was collected using the Modified Halstead Finger Tapping Test (HFTT), scored on 7 trials. MRI data were acquired at 3T (Ingenia, Philips); tasks were implemented using Presentation software. Multi-band SAGE-fMRI data were acquired with 2 gradient-echoes, 2 asymmetric spin-echoes, and 1 spin-echo (TE1-5=8.0/28/60/80/100 ms, acquisition matrix: 80x78; voxel size: 3.0x3.0 mm; slice thickness: 3.0 mm; TR=2500 ms; multiband factor=2). For each TE, a reverse phase-encoding acquisition was acquired to correct for EPI image distortions. The motor task was performed using the left (non-dominant) hand. A block design (10 TR per block, 4 trials per block type) was implemented with both rest and tapping blocks, during which participants tapped a response device at a rate of about one per second. SAGE-fMRI data were processed using single-echo and multi-echo combinations. Specifically, T2* and T2 SAGE maps were processed using a piecewise function. Subsequently, all SAGE-fMRI images were processed using standard procedures with FSL and AFNI. AFNI was used to calculate the statistical parametric maps of response to stimuli from all fMRI data and to run a two-sample t-test between HC and MCI groups (clusters>100 voxels).

Results: There were no significant differences between sex, age, HFTT score, or BNIS score from HC to MCI ($p>0.05$). T2* and T2 SAGE maps showed significantly greater activation for HC than MCI in the brain stem and frontal pole ($p<0.01$). T2* SAGE maps also showed significantly greater activation for HC than MCI in the right inferior frontal gyrus, right caudate, and the right thalamus ($p<0.01$). T2* and T2 SAGE maps showed significantly less activation for HC than MCI in the left postcentral gyrus ($p<0.01$). There were no significant differences between groups in the rest of the sensorimotor network, including the precentral gyrus or supplementary motor cortex.

Conclusions: Preliminary results indicate that SAGE functional activation reveals differences between HC and MCI during a finger tapping motor task. Previous literature has shown similar results, reporting decreased activation from HC to amnestic MCI in the contralateral inferior frontal gyrus. Completion of recruitment will help to confirm the groupwise differences seen in this preliminary analysis.

POSTER #95

IMPLEMENTATION OF MULTI-CONTRAST, MULTI-ECHO SAGE-FMRI IN AGING AND ALZHEIMER'S DISEASE. Keeling EG, Bergamino M, Burke AD, Steffes L, Stokes AM. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a leading cause of death in the United States, affecting over 6 million Americans. Functional MRI (fMRI) presents an opportunity by which to evaluate memory and cognitive function in patients. However, standard fMRI acquisitions suffer from signal dropout in regions highly relevant to memory and executive function, such as the medial temporal and inferior frontal lobes. To better study memory with fMRI, we propose the application of a combined spin- and gradient-echo (SAGE) acquisition; SAGE-fMRI is expected to recover much of the signal dropout seen in standard fMRI, as well as provide both global and microvascular functional data, motivating its application in AD.

Methods: Five healthy controls (HC, 4 females; 66.6±5.0 years) and four cognitively impaired subjects (CI, mild cognitive impairment or mild AD; 3 females; 77.3±4.0 years) were included in this preliminary study. MRI data were acquired at 3T (Ingenia, Philips); tasks were implemented using Presentation software. SAGE-fMRI data were acquired with 2 gradient-echoes, 2 asymmetric spin-echoes, and 1 spin-echo (TE1-5: ranged from 5.4-56 ms per task; acquisition matrix: 64×64; voxel size: 3.75x3.75 mm; slice thickness: 5.0 mm; TR=3000 ms). For each TE, a reverse phase-encoding acquisition was acquired to correct for EPI image distortions. The face-name memory encoding and recall tasks conditions were organized in alternating block designs and consisted of novel (i.e., unfamiliar faces) and repeated (i.e., one of two recurring faces) phases, with brief rest periods between conditions. SAGE-fMRI data were processed using single-echo and multi-echo combinations. Specifically, TE2 and TE5 were processed individually, where TE2 is similar to standard fMRI acquisitions; T2* and T2 SAGE maps were processed using a piecewise function. Subsequently, all SAGE-fMRI images were processed using standard procedures with FSL and AFNI. AFNI was used to calculate the statistical parametric maps of response to stimuli from all fMRI data and to run a two-sample t-test between HC and CI groups.

Results: In the face-name recall task, T2* SAGE maps detected groupwise differences in the medial temporal lobe, where HC had significantly higher activation than CI. HC also showed significantly higher activation in T2* and T2 SAGE maps in the precuneus and frontal pole. Widespread significant activation in regions not relevant to the task was observed for TE2 and may indicate that SAGE is more specific than standard fMRI in detecting true activation in response to the task. A proposed compensatory mechanism where HC has significantly less activation than CI in the middle temporal gyrus, previously reported in the context of the same task, was detected with a T2 SAGE map.

Conclusions: SAGE-fMRI enables functional characterization sensitive to both global and micro-vasculature, featuring improved acquisition in regions relevant to memory, executive function, and AD. Preliminary results exhibited sensitivity to groupwise differences in the medial temporal and inferior frontal lobes, as well as improved specificity to task-related activation. In the future, these group differences can be better assessed with an increased sample size. The improved acquisition in the medial temporal and inferior frontal lobes are critical benefits for the application of SAGE-fMRI in AD.

POSTER #96

USING DIFFUSION TENSOR IMAGING TO IDENTIFY WHITE MATTER CORRELATES OF MOTOR ACQUISITION AND VISUOSPATIAL PROCESSES IN COGNITIVELY-INTACT OLDER ADULTS. Lingo VanGilder J, Bergamino M, Hooyman A, Beeman SC, Schaefer SY.
Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Decline in visuospatial function may be an early indicator of Alzheimer's disease (AD). In a series of cross-sectional studies, we have reported that complex figure copying and recall (measured using the Rey Osterrieth Complex Figure Test (RCFT), a well-established clinical test of visuospatial function) is related to the acquisition of an upper-extremity motor task, suggesting that motor task acquisition may be a simple, affordable way to probe preclinical AD. The underlying neural mechanism of this relationship remains unclear, although white matter vasculature has been implicated in disease severity in AD and other neurodegenerative diseases, and results from recent lesion studies suggest that specific white matter tracts may play a role in motor skill performance. The purpose of this exploratory study was to identify the white matter neural correlates of the RCFT and motor task acquisition processes in older adults. Based on previous literature, we hypothesized that right hemispheric frontoparietal tract structure would be positively related to both RCFT and motor task acquisition.

Methods: Nondemented older adults (n=19, age>65 years) completed the RCFT and 50 training trials of an upper-extremity task using their nondominant hand. Participants returned one week later and completed follow-up trials; motor task acquisition was measured as the difference in performance between the average of the last five trials of the first training session and average of the first five trials of the second training session. Participant motor task acquisition and RCFT scores were entered into a principal component (PC) analysis to reduce the dimensionality of the data; only PCs greater than one were carried forward in subsequent analyses. Participants underwent diffusion magnetic resonance imaging to quantify whole-brain diffusion metrics (e.g., fractional anisotropy, etc.). Participant age and PCs were entered into a general linear model that was applied at each voxel for each diffusion map and an FDR-correction was applied to account for multiple statistical tests. Clusters were identified from contiguous voxels that were at least FDR<0.01 and greater than or equal to 100 voxels in size.

Results: Results suggest that the bilateral superior longitudinal fasciculus and corticospinal tract are related to visuospatial memory and motor task acquisition.

Conclusions: Recent work has shown that performance on this motor task is related to whole-brain amyloid and bilateral hippocampal atrophy. Future work will evaluate if these white matter regions of interest also present with elevated amyloid and/or atrophy over time in parallel with changes in visuospatial decline.

POSTER #97

SYNTHESIS OF HIGH AFFINITY DYRK1A PROTACS TOWARDS TREATMENT OF ALZHEIMER'S DISEASE AND SARS-COV-2. Maddern S, Schofield K, Chavez T, Shaw A, Hulme C. University of Arizona; Arizona Alzheimer's Consortium.

Background: The dual-specificity tyrosine phosphorylation-regulated kinase 1A is of high interest to our group. Small molecule inhibitors of DYRK1A have afforded proof-of-concept results, mitigating the formation of both amyloid plaques and neurofibrillary tangles in a triple transgenic in vivo model of AD. These compounds have now been repurposed towards high affinity DYRK-PROTACs targeting the degradation of DYRK1A, thereby knocking out both catalytic and scaffolding functions. A PROteolysis TArgeting Chimera (PROTAC) is a heterobifunctional molecule which binds both target protein (i.e. DYRK1A) and an E3-ligase.

Methods: Organic synthesis, KdELECT and KINOMEscan assays, and Schrodinger ligand-based modeling were used to design and evaluate the produced PROTAC compounds.

Results: Herein, we describe the first-of-class synthesis of Von Hippel-Lindau (VHL) and Cereblon DYRK-PROTACs and associated DYRK1A kinase affinity (Kd ~2-10nM).

Conclusions: These high affinity DYRK-PROTACs demonstrate the validity of our structure-based approach employed to drug DYRK1A toward treating Alzheimer's disease. Therapeutic relevance to both Alzheimer's and SARS-CoV-2 is discussed.

POSTER #98

THE RELATIONSHIP BETWEEN HIPPOCAMPAL VOLUME AND MEDIAL TEMPORAL LOBE WHITE MATTER TRACT INTEGRITY IN OLDER ADULTS. Matijevic S, Haaheim L, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Within aging, there is a decrease in both hippocampal volume and integrity of the white matter tracts that connect to the medial temporal lobe (MTL). Past evidence suggests that both of these factors can contribute to cognitive decline in normal aging, MCI, and Alzheimer's Disease. However, the interaction between hippocampal volume and white matter integrity losses in aging has been underexplored. In this study, we aim to investigate how the integrity of white matter connections between the MTL and other regions relates to hippocampal atrophy in normal aging.

Methods: Diffusion weighted images were acquired from 165 older adults, between the ages of 50-92. Deterministic tractography will be used to extract four different measures of white matter integrity- fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD)- from the uncinate fasciculus, fornix, and cingulum. Freesurfer's hippocampal subfield segmentation protocol will be used to extract whole hippocampal volumes from high resolution T1 weighted images.

Results: We predict that age will be associated with smaller hippocampal volumes as well as lower FA and higher MD, RD, and AD values within the uncinate fasciculus, fornix, and cingulum. We will test whether hippocampal volume interacts with age to predict FA, MD, RD, and AD values within the three tracts, hypothesizing that age will influence the relationship between hippocampal volume and white matter integrity.

Conclusions: The results of this study will help clarify the extent to which age differences in hippocampal volumes and white matter integrity are related to each other, which may provide insight into the mechanisms contributing to age related damage to the hippocampus and its associated tracts.

POSTER #99

AGE-ASSOCIATED ALTERATIONS IN LOCUS COERULEUS NEURONAL, GLIAL CELL, AND VASCULAR ELEMENTS IN COGNITIVELY ASSESSED AGED MACAQUE MONKEYS.

McDermott K, Sinakevitch I, Gray DT, Khattab S, Pyon WS, Barnes CA. University of Arizona; University of Florida, Gainesville; 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 involved in the modulation and optimization of behavioral performance in mammals. The LC is a molecularly and anatomically heterogeneous region that is densely innervated by blood vessels and glial cells. The LC appears to be especially vulnerable to age-related neurodegeneration and is one of the first regions to show evidence of pathological changes associated with Alzheimer's disease (Mather & Harley 2016). While previous work has investigated age-related changes in neurochemical markers in the LC, the impacts of normative aging on LC neuron, glial cell, and vascular characteristics in non-human primates remains an open question.

Methods: Our research utilizes coronal brainstem sections from a colony of 30 cognitively assessed rhesus macaque monkeys 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 locus coeruleus region for each immunolabeled section was imaged bilaterally at 40X on a high-resolution confocal microscope to obtain 3-dimensional volumes of the LC for the quantification of neuron, glial cell, and vascular densities using unbiased stereological techniques. These data were assessed with respect to the age and cognitive status of the monkeys.

Results: Preliminary results indicate that overall TH+ density and total neuron density remain stable in the older monkeys compared to the adults. Furthermore, vascular and reactive astrocyte density was not different between the adult and aged animals. No anatomical variable has shown a relationship with any of the three behaviors used to assess cognition in these animals. If these results hold it would indicate that cell loss, changes in vascular innervation, and increases in astrocyte reactivity do not occur in the LC region in normative aging.

Conclusions: These results support the hypothesis that LC degradation is a key component of pathological aging but is not compromised in healthy normative aging.

POSTER #100

LONELINESS AND AGING: MANIFESTATIONS OF LONELINESS IN EVERYDAY CONVERSATIONS AMONG OLDER ADULTS. McVeigh KM, Mehl MR, Wank AA, Polsinelli AJ, Moseley S, Glisky EL, Grilli MD. University of Arizona; Indiana University; Minnesota Epilepsy Group, St. Paul, MN; Arizona Alzheimer's Consortium.

Background: Loneliness is a perceived lack of social and emotional support and is related to many adverse health and cognitive outcomes. Losing a partner to death, deteriorating health, and decreasing network size may make older adults particularly susceptible to loneliness, which is further associated with risk for Alzheimer's disease, cardiovascular disease, and mortality. It is unclear how loneliness is related to everyday social interactions, despite knowing the importance of social interaction to cognitive function and overall well-being in older adults. One important function of social interaction is memory sharing. Autobiographical memory sharing (i.e., memory for personal events) in particular facilitates meaningful connections with others and is susceptible to age-related changes, but also has not yet been studied in the context of loneliness. Due to the valuable role of memory sharing in social interactions, it seems important to study the relationship between daily social interactions and loneliness also from the perspective of conversational autobiographical memory sharing. To begin to address these gaps in knowledge, we investigated whether lonelier older adults have different real-world conversations, social engagement, and autobiographical memory sharing than less lonely older adults.

Methods: Participants included 106 healthy, cognitively unimpaired older adults (age range = 65-90, M = 76.12, SD = 6.00). We used the Electronically Activated Recorder (EAR) as an unobtrusive, observational method to capture sound files of real-life, everyday instances of social interaction and conversational memory sharing over the course of four days. Sound files containing conversations were identified and scored for conversation type and memory sharing using established protocols. We measured self-reported loneliness with the loneliness scale from the National Institutes of Health (NIH) Toolbox. We examined the relationship between loneliness and different conversation types (small talk, gossip, practical conversation, substantive conversation, or personal/emotional disclosure), number of episodic and non-episodic autobiographical memories, and number of details included in episodic memories.

Results: Higher loneliness was significantly related to more time spent alone ($r = .40$, $p = .0002$). Higher loneliness was also significantly related to less small talk ($r = -.24$, $p = .016$) and less gossip ($r = -.24$, $p = .016$) in conversations. However, loneliness was not significantly related to autobiographical memory sharing ($r = 0.04$, $p = .73$), number of episodic autobiographical memories ($r = 0.004$, $p = .965$), number of non-episodic autobiographical memories ($r = .07$, $p = .516$), or number of details included in autobiographical memories ($r = .038$, $p = .708$).

Conclusions: Results showed that lonelier older adults spent more time alone and were less likely to engage in small talk and gossip, independent of how many conversations they had. However, loneliness was not significantly related to autobiographical memory sharing, indicating that among older adults, higher loneliness may not lead to fewer or greater attempts to connect through autobiographical memory sharing.

POSTER #101

STRUCTURAL AND FUNCTIONAL ANALYSIS OF P47 COFACTOR BINDING ON THE P97 DISEASE MUTANT. Nandi P, Li S, Coulumbres RC, Wang F, Williams DR, Malyutin AG, Poh Y, Chou TF, Chiu PL. Arizona State University; California Institute of Technology.

Background: Human p97/VCP (valosin-containing protein) is a hexameric AAA+ (ATPase associated with diverse cellular activities) ATPase plays a pivotal role in the regulation of multiple cellular activities by interacting with various cofactor proteins. Critical roles of p97 involve ubiquitin-dependent protein quality control and regulation of membrane fusion in the Golgi apparatus in the presence of cofactor p47. Heterozygous missense mutations of p97 have been implicated in numerous neurodegenerative diseases, such as IBMPFD (Inclusion body myopathy with early-onset Paget's disease and frontotemporal dementia) and ALS (amyotrophic lateral sclerosis). The disease mutations of the p97 are mostly clustered on the N-domain or the connection between N and D1-domain. The single amino acid mutation of R155H on the N-domain is the highest mutated sites, leading to a rare degenerative disease multisystem proteinopathy 1 (MSP1) and resulting in abnormal ATPase activity and cofactor dysregulation. Our study aims to characterize the key complex structure formed by the protein interactions between $p97^{R155H}$ and p47 cofactor to help answer its disease relevance.
Methods: We pursued biochemical characterization in combination with single-particle cryo-electron microscopy (cryo-EM) to study $p97^{R155H}$ mutant interaction with p47 in the presence or absence of nucleotides. Additionally, to understand the functional behaviors of the complexes, we performed ATPase activity assays and fluorescent labeling to detect the temperature-related intensity change signals to guide quantitative determination of their mutual binding affinities.
Results: Our results report the cryo-electron microscopy (cryo-EM) structures of the full-length $p97^{R155H}$-p47 complex for the first time in different nucleotide-binding states. In the absence of nucleotides in the D1 nucleotide binding pocket, $p97^{R155H}$ is still stable either as a hexamer or stacked as $p97^{R155H}$ dodecamer. The $p97^{R155H}$ dodecamer does not bind to p47 or nucleotides and bears close resemblance to the inhibitor bound CB-5083:p97 structure, implying that the dodecameric form is inactive. The highly symmetric dodecamer, with a highly ordered C-terminal tail, thus prohibits the $p97^{R155H}$ from participating in any downstream substrate processing. In the full-length $p97^{R155H}$-p47 complex structure, the p47 interacts through its UBX domain in an asymmetric manner to bind the $p97^{R155H}$ N-domain. In the absence of nucleotides, four N-domain densities and one p47UBX domain were identified by docking the atomic models into the density map. Consistent with previous findings, we saw that p47 does not bind to p97R155H as a trimer, instead there is a dynamic equilibrium for this $p97^{R155H}$-p47 interaction when the D1 and D2 nucleotide binding pockets are empty. We further employed deep coordinate neural network analysis to analyze data heterogeneity of the nucleotide bound states of $p97^{R155H}$-p47.The flexibility of the p47UBX bound N-domains were less for the $p97^{R155H}$|ATPγS-p47 dataset, whereas it is fragmented in $p97^{R155H}$|ADP-p47 dataset. Superimposition of the D1 and D2 domains of the three different nucleotide states revealed that the D1 domains exhibit negligible structural change, whereas the D2 HTH motifs of the complexes with nucleotides are tilted downward. The C-terminal tails of the $p97^{R155H}$|ATPγS-p47 structure points in an opposite direction than that of $p97^{R155H}$-p47 and $p97^{R155H}$|ADP-p47, hence implying the C-terminal tail conformation may influence the p97 D2 ATPase activity. The structures also established that the D1 and D2 arginine fingers play a critical role for the elevated $p97^{R155H}$ ATPase activity.

Conclusions: p97 is a crucial protein essential to ER-associated degradation and our structures of the p97-p47 complex reveal the mechanism of the protein-protein interaction initiating membrane fusion. This study highlights the possible disease mechanism caused by the R155H mutation, relevant in neurodegenerative disease multisystem proteinopathy (MSP).

POSTER #102

NEGATIVE CORRELATIONS BETWEEN GLOBAL MEAN-CORTICAL AND REGIONAL HIPPOCAMPAL AMYLOID-B PLAQUE BURDEN BASED ON PIB AND FLORBETAPIR PET MEASUREMENTS. Narnur P, Corkill B, Chen Y, Luo J, Lee W, Reiman EM, Su Y, Chen K.
University of Arizona; University of Arizona College of Medicine Phoenix; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium

Background: Several PET tracers have been developed for the assessment of amyloid-β (Aβ) plaque burden in the living human brain. One harmonization algorithm we developed using machine learning (ML) is based on the mapping of regional Aβ burden of one tracer to the global mean cortical Aβ PET measurements of another tracer. Potential challenges to harmonization include tracer-dependent differences in radiotracer binding to neuritic versus diffuse plaques, off-target binding, and non-specific binding in cerebral and reference regions. In this exploratory study, we used 18F-florbetapir (FBP) and 11C-PiB images from the same, mostly cognitively unimpaired research participants to demonstrate negative associations between regional Standard Uptake Value Ratios (SUVRs) in certain brain regions and global mean-cortical SUVR (mcSUVR) for intra-/inter-tracer pairs and to start formulating possible explanations for these findings.

Methods: For this analysis, we downloaded paired FBP and PiB PET images from 86 cognitively unimpaired and 6 cognitively impaired 63.95±8.36 year-old research participants in the Open Access Series of Imaging Studies (OASIS) Dataset. Based on the centiloid of 20.6 positivity cut-off value, 21.7% were Aβ+ using FBP PET and 23.9% were Aβ+ using PiB PET. mcSUVR of FBP and PIB were derived as the region-size weighted average over 7 bilateral regions with the cerebellum cortex reference region. An automated brain mapping algorithm (SPM12) was used to transform each image into a standardized brain atlas and characterize positive and negative global mcSUVR to regional SUVR correlations for intra-/inter-tracer pairs. Additionally, we examined negative associations of SUVRs in those regions with MMSE score post-hoc.

Results: Negative correlation of global mcSUVR with regional SUVR for between-tracer pairs and for within-PiB pair were observed in the vicinity of the hippocampus ($P<0.0007$ and 0.0025, respectively, uncorrected for multiple comparisons), thalamic and sub-thalamic regions but not for within-FBP pair.

Conclusions: This study found a negative correlation between global mcSUVR and regional SUVRs in bilateral hippocampal, and some subcortical regions for between-tracer global/regional pairs and within-PiB global/regional pair but not for the within-FBP from the same research participants. While both tracers have demonstrated value in the detection of neuritic Aβ plaques, we postulate that the negative correlations may be attributable to 1) PiB's greater sensitivity to the detection of diffuse plaques and the preferential deposition of diffuse rather than neuritic plaques in the hippocampus, 2) binding affinity or off-target binding difference, and/or 3) some preprocessing artifacts.

POSTER #103

GENOTYPIC EFFECT ON MICROBIOME DEVELOPMENT AND COLONIZATION IN A DROSOPHILA MELANOGASTER MODEL OF PARKINSON'S DISEASE. Olson SC, Call GB. Midwestern University; Arizona Alzheimer's Consortium.

Background: Parkinson's disease (PD), the second most common neurodegenerative disease in the United States, is commonly associated with predominantly motor and neurological symptoms. Recently, the development of non-motor symptoms have begun to be increasingly correlated with PD, with the most common symptoms being gastrointestinal (GI) disturbances such as gut dysbiosis and constipation. In fact, nearly all PD patients will display one or more GI symptoms, and will often do so years before any neurological symptoms develop. Due to the high prevalence of these GI symptoms in PD patients, it is thought that there is a mechanism of communication between the gut and brain. In a previous experiment by our laboratory, developmental effects were observed due to microbiome alterations in PD model (park25) Drosophila melanogaster through a fecal transfer technique which has been the driving force for all current experiments. These park25 flies are an excellent PD model as they possess many similar phenotypes to PD, such as decreased lifespan, dopaminergic neuron loss, and impaired motor function.

Methods: To test this relationship between the microbiome and its ability to affect Drosophila, we inoculated axenic (germ-free) park25 and various control Drosophila embryos with four different standard bacterial stocks including Lactobacillus brevis, Lactiplantibacillus plantarum, Acetobacter pomorum, and Acetobacter tropicalis as well as various concentrations of L. plantarum as indicated from a previous experiment. The embryos were either mono-associated with one bacterial strain or were given a combination of all four strains. Motor function was tested via climbing assay once the adult flies reached 6-7 days post-eclosion. In addition, the flies were then homogenized and plated, the subsequent colonies were counted, and the relative CFUs/fly were calculated.

Results: While no motor ability improvements were noted with the various inoculations, when comparing the bacterial colonization levels of the PD and control flies, we noted a significant increase in colonization in the park25 flies. Additionally, the park25 flies that received the combination inoculation had not only increased colonization, but A. tropicalis was found to be the predominant contributor.

Conclusions: While the park25 flies have a notable increase in the amount of bacterial colonization when compared to the control flies, the cause of this remains unknown. It seems that the development and contents of the microbiome is, to some extent, genotype-driven.

POSTER #104

INVESTIGATING HOW UTILIZING DETAILS AND HOLISTIC PIECES OF INFORMATION DIFFER BETWEEN YOUNGER AND OLDER E4 CARRIERS AND NONCARRIERS. Palmer JM, Grilli MD, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: An updated model within the medial temporal lobe (MTL) is hypothesized to carry detail and holistic pieces of information via direct and indirect pathways, respectively. Age-related changes in the MTL circuitry suggest that older adults are biased toward holistic pieces of information and away from details. Individuals with the apolipoprotein e4 allele, a genetic risk factor for Alzheimer's disease (AD), may be less biased from holistic information due to elevated pathology in the indirect pathway. A continuous object recognition paradigm provides an opportunity to behaviorally test this hypothesis.

Methods: Older and younger e4 carriers and noncarriers were given a continuous object recognition task (younger carrier, n=14; younger noncarrier, n=37; older carriers, n=24; older noncarrier, n=37). Participants indicated whether objects superimposed on either a Repeated White background, Repeated Scene, or a Novel Scene were the "same," "similar," or "new" compared to objects previously seen in the task. We measured recognition memory as the proportion of correctly identifying repeated objects. Pattern separation performance was the proportion of correctly identifying similar objects. In order to quantify the types of errors made when participants viewed similar objects, we calculated a difference score by subtracting the proportion of identifying a similar object as "same" by the proportion of identifying similar objects as "new." Finally, we analyzed pattern separation false alarms as the proportion of identifying novel objects as "similar."

Results: Analysis of recognition scores showed that the Novel Scene condition significantly lowered scores compared to all other scenes for all groups. Younger adults outperformed older adults on correctly identifying similar objects. Older adults also produced a specific kind of error, misidentifying similar objects as "old" more than "new" compared to younger adults, regardless of the scene condition. However, this error was the most pronounced in the Repeated Scene. Interestingly, APOE status interacted with scene condition and age such that in the Repeated Scene, younger e4 carriers produced less pattern separation false alarms. This trend switched in older adults such that e4 carriers made more false alarms compared to their noncarrier counterparts.

Conclusions: For recognition, older and younger adults were affected by changing the scene condition in the same way such that putting a repeated object in a unfamiliar scenes hurt memory performance for all groups. Our results also replicated an age-related deficit in identifying similar objects. Furthermore, older adults were more likely to identify a similar object as "old," particularly in familiar scenes, suggesting a possible overreliance on more hoslistic pieces of information. This supports the notion that older adults are biased away from the subtle details and toward more holistic pieces. Additionally, the unique interaction between age, scene, and APOE status in false alarms is consistent with the hypothesis that regards e4 as an antagonistic pleiotropy allele. Antagonistic pleiotropy alleles show benefits to an organism's fitness in younger adults followed by detriments in aging. Lower pattern separation false alarms among younger carriers may reveal a subtle behavioral advantage in the task. This advantage is lost in aging as older e4 carriers produced more pattern separation false alarms, suggesting a subtle memory detriment.

POSTER #105

PROGESTOGENS IMPACT COGNITION DURING THE TRANSITION TO MENOPAUSE IN THE RAT: DISSOCIATION OF PROGESTOGEN- AND MEMORY- TYPE. Peña VL, Koebele SV, Northup-Smith S, Woner VE, Melikian R, Patel S, Bulen HL, Ladwig D, Dyer CA, Mayer LP, Bimonte-Nelson HA. Arizona State University; FYXX Foundation; Arizona Alzheimer's Consortium

Background: Progestogens, such as progesterone, medroxyprogesterone acetate (MPA), and micronized progesterone (mP4), are given to ovary-intact women during the transition to menopause to attenuate heavy uterine bleeding and other symptoms. Both progesterone and MPA administration have been shown to impair cognition and effect the GABAergic system in ovariectomized (Ovx) rats compared to vehicle-treated controls. mP4, however, has yet to be investigated for cognitive effects in a preclinical setting, despite widespread clinical use. Given that preclinical menopause-related progestogen investigations have been limited thus far to models of surgical menopause via Ovx, the goal of this experiment was to investigate the cognitive impact of the three clinically-used progestogens progesterone (P4), MPA, and mP4, in an ovary-intact transitional menopause model using 4-vinylcyclohexene diepoxide (VCD).

Methods: One group of rats received vehicle injections, and the remainder of the groups received VCD to induce follicular depletion, modeling transitional menopause in women. Vehicle or hormone administration began during perimenopause to model the time period when women often take progestogens alone. Rats then underwent testing to assess spatial working and reference memory in the water radial-arm maze (WRAM) and Morris water maze (MM). At sacrifice brains were dissected for western blot protein analysis for GAD65+67.

Results: Results indicate that P4 and MPA improved learning for the working memory measure, but only MPA impaired delayed memory retention in the WRAM. mP4 showed no differences compared to vehicle controls for working memory. For the WRAM reference memory measure, rats that had undergone induced transitional menopause with no exogenous hormone administration showed impaired learning and memory retention compared to vehicle controls with no induced transitional menopause; progestogens did not impact this impairment. No treatment differences were observed on the MM. Additionally, there were no treatment differences for GAD65+67 levels for any brain regions assessed. There was, however, a significant correlation between GAD65+67 levels and working memory, such that progesterone treated rats with higher levels of GAD65+67 in the ventral hippocampus tended to make more working memory errors in the WRAM.

Conclusions: These findings indicate that while P4 and MPA have been previously shown to impair cognition in an Ovx model, giving these hormones early in an ovary-intact perimenopause model elicits divergent effects, such that these progestogens can improve cognition. Further investigation into progestogens is warranted to fully understand their impact on cognition and to detail parameters with variants of menopause type.

POSTER #106

THE ROLE OF VITAMIN B12 DEFICIENCY ON STROKE OUTCOME AND MECHANISMS IN OLD-AGED FEMALE MICE. Poole J, Pascual AS, North S, Weissig V, Gu H, Jadavji NM. Midwestern University; Arizona State University; Carleton University; Arizona Alzheimer's Consortium.

Background: The population in the US and globally is aging and the prevalence of age-related diseases, such as stroke, is predicted to increase. As people age, their ability to breakdown or absorb certain nutrients decreases. Nutrition is a modifiable risk factor for ischemic stroke. A vitamin B12 deficiency is common in old aged adults, because of changes in metabolism. Clinical studies have reported that patients with a vitamin B12 deficiency have increased risk of ischemic stroke and result in worse outcome after stroke. However, how a vitamin B12 deficiency changes the brain making it more vulnerable to stroke requires further investigation. The aim of this proposed study is to investigate the role of vitamin B12 deficiency on stroke outcome and its mechanisms using old-aged female mice.

Methods: Aged (18-month-old) female mice were placed on either a control or vitamin B12 deficient diet for a period of 4 weeks, after which an ischemic stroke was induced in the sensorimotor cortex using the photothrombosis model. Animals were continued on diets four weeks after damage when motor function was assessed using the accelerating rotarod, forepaw placement, and ladder beam walking tasks. When behavioral testing was completed, animals were euthanized. Brain, blood, cecum, and liver were collected for further analysis

Results: After ischemic damage, females on a vitamin B12 deficient diet had larger damage volume in brain tissue. Additionally, deficient females had reduced coordination and balance when tested on the accelerating rotarod, as well as a worse neurodeficit score. We are currently working through analysis of the forepaw placement and ladder beam tasks. Metabolomic analysis of the cecum showed changes in methylmalonic acid and vitamin B12 transportation. Brain tissue is currently being processed for mitochondrial metabolomics and apoptosis.

Conclusions: A dietary vitamin B12 deficiency impacts motor function outcome after stroke in aged female mice. The mechanisms through which this impaired function is driven by are under investigation.

Funding: Arizona Alzheimer's Consortium (NMJ, VW)

POSTER #107

EVALUATION OF PHOSPHO-TAU PATHOLOGY IN THE HIPPOCAMPUS AT 6 MONTHS FOLLOWING EXPERIMENTAL TRAUMATIC BRAIN INJURY IN RATS. Rajaboina B, Mian E, Hair C, Baun J, Zurhellen C, Adelson PD, Thomas TC. Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona-COM-Phoenix; Arizona State University; NeuroScience Associates, Knoxville, TN; U.S. Department of Veterans Affair, Arizona; Arizona Alzheimer's Consortium.

Background: Traumatic brain injury (TBI) chronically increases neuroinflammation, where neuroinflammation is hypothesized to increase the risk or accelerate neurological disorders by, in part, facilitating the formation of tau pathology associated with Alzheimer's disease (AD). Limited information is available regarding the formation of tau pathology at 6-months following a single experimental diffuse TBI, and sex differences have not been evaluated. The following experiments aimed to 1) assess the effect of single diffuse TBI on the accumulation of phosphorylated tau (pTau) in the DG, and 2) determine sex-specific effects at 6-months post-injury.

Methods: Adult, male and female, Sprague Dawley rats were subjected to either a midline fluid percussion injury (FPI) (n=6/sex) or sham surgery (n=5/sex). At 6-months post-injury, rat brains were extracted and immunostained for Iba-1 and AT8 (counterstained with neutral red) to identify microglia and pTau pathology, respectively. Pixel density analysis via ImageJ generated approximations of positive AT8 staining that were analyzed using a two-way ANOVA (sex and injury).

Results: Positive AT8 staining was identified at 1.78% in the DG of injured rats of both sexes compared to 1.21% in DG of shams ($p<0.05$). To evaluate if the counterstain (neutral red) influenced the outcome, adjacent brain sections were immunostained for only AT8, where differences between injured and sham were no longer detectable.

Conclusions: Therefore, we conclude that at 6-months following midline FPI in rats, levels of pTau are not detectable in the DG of male or female brain-injured or sham rats. Assessment of Iba-1 staining for morphological changes in microglia indicative of chronic neuroinflammation are ongoing. pTau pathology has been identified at earlier time points post-injury and in different locations, indicating a need for additional region and time-dependent assessments of other biomarkers to support our conclusions.

POSTER #108

SUPERVISED AND UNSUPERVISED FLOW CYTOMETRY ANALYSIS OF THE ESTROUS CYCLE INTERACTION WITH A PERIPHERAL IMMUNE CHALLENGE IN FEMALE MICE.
Rojas-Valencia LM, Giordano KR, Dudic A, Tallent BR, Saber M, Lifshitz J. University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix Veterans Affairs Health Care System; Arizona State University, Arizona Alzheimer's Consortium.

Background: TBI and other neurological diseases pathophysiology involves a CNS inflammatory response and initiates a peripheral immune response. Female hormones (estradiol, progesterone) define phases of the menstrual and estrous cycle in people and rodents, respectively. The hormones regulate reproductive cycling and have anti-inflammatory properties. As laboratory, translational, and clinical research incorporate more females, the foundational knowledge of inflammation is challenged, whether direct or initiated by disease processes (e.g., TBI, Alzheimer's). We hypothesized that the estrous cycle phase would influence the composition of peripheral immune cell populations in response to a peripheral immune challenge.

Methods: Female mice (n=12) were tracked for the estrous cycle phase by daily vaginal smears taken at the same time of day for 8 days prior to lipopolysaccharide (LPS) administration (1.2 mg/kg, intraperitoneal). Vaginal smears were stained with Hematoxylin to determine the estrous cycle phase based on observed cell types (neutrophils, cornified cells, epithelial cells). Submandibular blood collected before LPS injection (baseline) and 24 hours post-injection (terminal) was analyzed by flow cytometry to quantify myeloid cell populations. Flow cytometry results were analyzed by manual gating and then unsupervised clustering (tSNE) and dimensionality reduction (FlowSOM) approaches.

Results: Manual gating showed a significant decrease in leukocytes (CD45+) and classical monocytes (CD45+CD11b+ Ly6Chigh) and a significant increase in neutrophils (CD45+CD11b+Ly6G+) at 24 hours post-LPS. The unsupervised analysis produced 10 cell clusters, for which 8 had significant responses to LPS. One novel cluster is CD45+CD11b+CD115intermediateLy6C+ cells (monocyte subclass), which decreased post-LPS. Another CD45+CD11b+ Ly6CintermediateLy6Glow cluster significantly increased after the peripheral immune challenge.

Conclusions: Thus, tSNE and FlowSOM unsupervised analysis indicate an emerging differential inflammatory response among female mice; further quantification between cycle phases can indicate pro-inflammatory interactions with the peripheral cell population.

POSTER #109

THE DEVELOPMENT OF A HIGHLY SELECTIVE, WELL-TOLERATED AND ORALLY BIOAVAILABLE INHIBITOR OF DYRK1A FOR TREATMENT OF ALZHEIMER'S DISEASE.

Rokey S, Foley C, Velasquez R, Dunckley T, Shaw A, Meechoovet B, Hulme C. University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Targeting Alzheimer's Disease (AD) pathology at single components is likely impossible, and a successful therapeutic strategy will require pleiotropic interventions. Herein, we articulate an alternative strategy involving targeting of both amyloid and tauopathies through selective inhibition of the dual specificity tyrosine phosphorylation regulated kinase-1A (DYRK1A), thereby reducing both APP and tau phosphorylation events. We describe the transition from a proof-of-concept compound, DYR219, to a high affinity, Kinome selective and orally bioavailable inhibitor DYR533 suitable for IND enabling studies. Inhibition of DYRK1A in vivo has been shown to ameliorate amyloid plaque and NFT formation, with a concomitant increase in cognition as seen in several different behavioral tests. Although we obtained the first-in-class POC for this approach, there is now a DYRK1A inhibitor in Phase1A for FTD, known as SM07883 which in addition to our observed pathology changes, also significantly decreases neuro-inflammation. SM07883 has several liabilities relative to DYR533 which will be discussed. Its clinical entry suggests we have a high likelihood of similar success.

Methods: Methods used in this work include: synthesis, structure-based drug design, KD and IC50 determinations, KinomeScan, microsomal stability (time independent and time dependent), solubility studies, in vivo pharmacology (3xTgAD model), in vivo behavioral studies, pre-clinical toxicology studies (e.g. micronucleus, safety pharmacology panel87), and pharmacokinetic studies of DYR533 in mouse and rat.

Results: The poster describes the weaknesses in our initial proof-of-concept compound DYR219 (solubility, bioavailability, kinome selectivity) and successful efforts to address these which led to the discovery of an exquisitely selective, potent, safe, and orally bioavailable DYRK1A inhibitor DYR533. The full compound profile of DYR533 is presented, spanning DYRK1A affinity to pre-clinical toxicology studies will be revealed.

Conclusions: Studies are currently being prepared to recapitulate activity of DYR533 in vivo (AD & DS models) which will be followed by IND enabling studies.

POSTER #110

CHARACTERIZATION OF SPATIAL WORKING AND REFERENCE MEMORY ACROSS THE ADULT LIFESPAN IN A TRANSGENIC RAT MODEL OF ALZHEIMER'S DISEASE. Ruhland AM, Bulen HL, Bernaud VE, Peña VL, Koebele SV, Northup-Smith SN, Opachich Z, Manzo AA, Valenzuela Sanchez M, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: As of 2020, the Alzheimer's Association estimates that in the United States, 5.8 million individuals are living with Alzheimer's Disease (AD), and nearly two-thirds of these cases are women. The use of transgenic rodent models permits the study of specific pathological presentations associated with cognitive changes and disease progression. The TgF344-AD transgenic rat model expresses mutant human amyloid precursor protein (APPSW) and presenilin 1 (PS1ΔE9) genes. This model has been shown to exhibit Aβ plaques, tau pathology leading to neurofibrillary tangles, and neuronal loss; however, it has not been well characterized in terms of cognition and much of the work has been done in males or collapsed across sex. The current study used female rats from this model to evaluate learning and memory performance at three distinct age-points.

Methods: Thirty Wildtype (WT: n=30) and 30 Transgenic (Tg: n=30) sexually inexperienced, female rats were used. Rats were bred at Arizona State University (ASU) and protocols were in accordance with ASU's Institutional Animal Care and Use Committee, and National Institutes of Health, guidelines. The breeding schedule for this study was methodically conducted to ensure that for each genotype, rats were the ages of 6, 9, and 12 months for simultaneous behavioral evaluation in a between-subjects fashion. The behavioral battery included the Water Radial-Arm Maze (WRAM) to assess spatial working and reference memory performance as working memory load increased, the Morris Maze (MM) to assess spatial reference memory performance, and the Visible Platform (VP) task as a control task to confirm an animals ability to complete the procedural components necessary to solve a water-escape task.

Results: On the WRAM, Tg rats made more working memory errors compared to WT rats at the 6 month and 12 month time points, but not at the 9 month time point. For the MM task, Tg rats at each age exhibited greater distances and longer latencies to reach the platform than WT rats across all testing days, indicating a transgenic-induced reference memory impairment. The probe trial for the MM demonstrated spatial localization of the platform for each group; indeed, all groups had significantly greater swim distance in the NE quadrant, where the platform was previously located, as opposed to the SW/opposite quadrant. The effect of Genotype was not significant for any age on the VP control task, confirming visual and motoric capability to solve a water-escape task.

Conclusions: The current study found age-related memory changes in Tg versus WT control females using the TgF344-AD rat model, with differences demonstrated by memory type. Brain tissue was collected for later evaluation of AD-like pathology. These pathological assessments will be correlated with behavioral outcomes to evaluate putative relationships between pathology and cognition, which may differ with age.

POSTER #111

SEX, AGE, AND REGION-DEPENDENT CHANGES IN ASTROCYTE ACTIVATION IN A BEHAVIORALLY RELEVANT CIRCUIT FOLLOWING EXPERIMENTAL TBI IN RAT. Sabetta Z, Condon A, Krishna G, Adelson PD, Thomas TC. University of Arizona; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; Arizona State University; University of Bath, England; Arizona Alzheimer's Consortium.

Background: Traumatic brain injury (TBI) survivors face long-term post-TBI morbidity and increased risk for age-related neurodegenerative diseases. Clinical studies report sex differences in prevalence and severity with neuroinflammation as a primary modulator for persisting pathophysiology. Astrocytes can influence post-injury neuroprotection, neurorepair, and neuropathology, yet the longitudinal consequences in both sexes are unknown. The thalamocortical (whisker) circuit (WBC) in rodents underlies late-onset somatosensory hypersensitivity to whisker stimulation following a single TBI and serves as an in vivo model for assessing the influence for secondary pathophysiology on circuit function and morbidity.

Methods: Glial fibrillary acidic protein (GFAP) levels and soma counts were quantified in the thalamic, cortical, and inhibitory nuclei using ImageJ. Male and female Sprague Dawley rats (n=5-6/group) were subjected to sham surgery or midline fluid percussion injury (FPI). At 7, 56, and 168 days post-injury (DPI), brains were processed for GFAP or silver stain to evaluate astrocyte activation and neuropathology.

Results: GFAP density and soma increased as a function of FPI ($p>0.0001$) and DPI ($p>0.05$) with an interaction between FPI×DPI ($p>0.01$) for GFAP intensity in the thalamus. At 7DPI, GFAP was elevated by ~45% compared to sham and remained elevated at 168DPI. However, GFAP intensity increased between 56 and 168D in shams, such that GFAP levels in sham and FPI rats were similar 168D. Measures in the inhibitory nucleus mirrored the thalamus. In the cortex, GFAP intensity increased as a function of FPI ($p>0.0001$), DPI ($p<0.0001$), FPI×DPI ($p<0.0001$), and approaches significance with Sex×FPI ($p=0.06$). GFAP pixel density and soma counts increased by 82-100% in FPI at 7DPI and decreased over time, where females were more like age-matched shams at 56DPI and males at 168DPI. Amino-cupric silver stain indicated that neuropathology was increased at 7DPI and decreased over time.

Conclusions: These data indicate a single mFPI results in prolonged neurodegeneration coupled with a glial response that differs in sex, time, and region-dependent fashion, with age being a factor that influences gliosis independently over time. A longitudinal assessment of A1 and A2 astrocytes could indicate whether these sex, time, age, and region-dependent effects on astrocytes demonstrate a change in balance neurotoxic or neuroprotective function.

POSTER #112

NOVEL FRAGMENTS TARGETING DYRK1A AS PLATFORM CHEMOTYPES FOR AD DRUG DISCOVERY. Schofield K, Chavez T, Gokhale V, Shaw A, Hulme C. University of Arizona; Arizona Alzheimer's Consortium.

Background: Fragments are small molecular entities defined by the rule of 3 (MW ≤ 300, cLogP ≤ 3, #H-bond donors ≤ 3). As such, fragment-based drug discovery (FBDD1) has become a mainstay enabling technology at the onset of translational campaigns. Herein, we present a collection of novel Dual Specificity Tyrosine regulated kinase 1A fragments, with associated affinity, docking poses and an assessment of relative distances between hinge and conserved lysine H-bond acceptors, common in many DYRK1A inhibitors. The molecules represent ideal starting points for drug discovery campaigns targeting DYRK1A inhibition and effects on Alzheimer's phenotypes. Our laboratory has produced various potent DYRK1A fragments. By building off each fragment, DYRK1A picomolar inhibitors have been designed with favorable selectivity, oral bioavailability, microsomal stability, and lacking toxicity in preclinical models. Utilizing Schrödinger molecular modeling software sheds light on the DYRK1A ATP binding pocket enabling new postulates to increase potency and selectivity of Type 1 inhibitors in a synthetically expeditious manner. The viewer will receive a guided tour of the DYRK1A active site highlighting a knowledge-based de novo strategy in drug discovery.

Methods: Methods used during this work include Schrodinger ligand-based and property modeling, a variety of synthetic methods, and utilization of the KdElect® to obtain Kd values of the DYRKs, and CLKs part of the CMGC family of kinases.

Results: The Hulme laboratory has produced over 20 unique potent fragments that bind the DYRK1A catalytic site. All DYRK1A fragments have been docked and strategies to obtain optimal binding with the hinge and conserved lysine in the binding pocket have been determined.

Conclusions: Through FBDD and SAR development, new series of DYRK1A inhibitors have been discovered and the poster reveals the structure of DYR0001, the starting point on the translational path to the pre-clinical candidate DYR533.

POSTER #113

DEEP RESIDUAL INCEPTION ENCODED-DECODER NETWORK FOR AMYLOID PET HARMONIZATION. Shah J, Ghisays V, Luo J, Chen Y, Lee W, Li B, Benzinger TLS, Reiman EM, Chen K, Su Y, Wu T. Arizona State University; Mayo Clinic; Banner Alzheimer's Institute; Washington University in St Louis; Arizona Alzheimer's Consortium.

Background: Amyloid PET is an in vivo technology to visualize and quantify beta-amyloid deposition in the brain. However, the use of multiple amyloid tracers with varied characteristics compounded by processing variabilities poses significant challenges to interpret or combine results from cross-center studies, and to define common positivity threshold. In this research, we developed an encoder-decoder based deep model as a harmonization strategy to render imputed amyloid PET images of one amyloid tracer to the images of another.

Methods: 91 PiB-florbetapir (FBP) image pairs from the 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. Residual Inception Encoder-Decoder Neural Network (RIED-Net) was implemented to learn the nonlinear mappings from the image pairs in 2D using encoding-decoding architecture in conjunction with residual inception blocks and generating imputed images. A 10-fold cross-validation was implemented on axial, coronal and sagittal views separately to generate imputed PiB SUVR imaging from FBP data. The average imputed PiB image from all three views was used for performance evaluation. Correlation was evaluated between the imputed vs. real PiB SUVR image voxel-wise, and between the virtual PiB mcSUVR derived from imputed PiB vs. the real PiB mcSUVR. The trained RIED-Net model was also applied to an independent dataset with 46 subjects from www.gaain.org/centiloid-project, and the same metric was used to assess performance.

Results: The imputed PiB SUVR images were visually more similar to real PiB SUVR images than FBP. Voxel-wise correlation improved from 0.89 between PiB and FBP to 0.95 between the synthetic and real PiB SUVR image ($p<0.0001$) in the cross-validation. The agreement of mcSUVR improved from $r=0.91$ to $r=0.96$ ($p<0.0001$) in the cross-validation dataset and from $r=0.92$ to $r=0.96$ ($p<0.001$) in the independent dataset.

Conclusions: We proposed a novel encoder-decoder based deep model for synthetic imaging. The model discovered the voxel-wise nonlinear associations between the input images and the output images which significantly improved agreements of amyloid burden measurements from different tracers. The result was further confirmed in an independent dataset demonstrating the generalizability.

POSTER #114

PREVENTION OF WEIGHT GAIN AND EXPRESSION OF KEY MARKERS OF ALZHEIMER'S DISEASE IN HIGH FAT-HIGH SUCROSE-FED MALE MICE WITH GENISTEIN AND/OR EXERCISE. Shah J, Kubinski A, St Aubin C, Banayat T, Broderick TL, Shim M, Al-Nakkash L. Midwestern University; Arizona Alzheimer's Consortium.

Background: Previous studies have indicated that increased intake of a western diet (high fat with high sugar, HFHS) has harmful effects on health, increasing the risk of metabolic syndrome, obesity, insulin resistance, type 2 diabetes mellitus, cardiovascular disease, loss of bone mass, inflammation, and neurodegenerative diseases such as Alzheimer's disease (AD). Genistein is a naturally occurring isoflavonic phytoestrogen found in high concentrations in soy products and is known to improve insulin sensitivity and provide anti-inflammatory & 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 exercise (Ex), or both (Gen+Ex) would reduce the obese-diabetic phenotype while also limiting the progression of AD pathology in a HFHS-fed murine model.

Methods: C57BL/6J male mice (5-6 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. Drinking water contained sucrose and fructose. Moderate exercise was comprised of treadmill running (5 days/week) for 150 minutes/week for the 12-week study duration.

Results: The HFHS-induced increase in body weight (weight gain) was reduced by 15% with Ex ($P<0.05$) or by 36% with Gen ($P<0.05$) and reduced by 55% by Gen-Ex combined ($P<0.05$) compared to HFHS. The following data were obtained via western blot expression of proteins in brain homogenates: (1) pGSK (involved in formation of PHF-Tau) was significantly increased by HFHS diet and this was prevented by Ex, Gen or 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 Ex, Gen or Gen+Ex. We are currently evaluating additional key proteins involved in the progression of AD.

Conclusions: We conclude that genistein and exercise often in isolation, but mainly in combination have significant benefits to prevent the etiology of AD markers in the brains of HFHS-fed male mice. These benefits are associated with improvements in body weight.

POSTER #115

AGE-RELATED REGIONAL NETWORK COVARIANCE PATTERN OF GRAY TO WHITE MATTER CONTRAST IN HEALTHY MIDDLE-AGED TO OLDER ADULTS. Smith SG, Bharadwaj PK, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Reductions in gray to white matter contrast (GWC) in magnetic resonance imaging (MRI) have been shown to be an important factor related to aging. These age-related contrast differences are thought to be primarily due to changes in white matter signal intensity and have been shown to differ in those experiencing healthy versus pathological aging. Previous studies have focused on univariate analyses to evaluate GWC differences. How MRI GWC regionally covaries on a region of interest (ROI) basis in relation to age, in cognitively unimpaired older adults, has yet to be investigated.

Methods: We applied a multivariate network analysis technique, the scaled subprofile model (SSM; Alexander & Moeller, 1994), to identify a GWC covariance pattern related to age in a sample of healthy older adults. GWC was computed for each participant from 3T volumetric MRI scans for 68 ROIs using Freesurfer (v5.3) with a depth of 30% of the cortical ribbon from the GWC boundary to the gray matter-cerebrospinal fluid boundary (Kong et al., 2015). SSM network covariance analysis was performed on the GWC ROIs using Akaike Information Criteria with 10,000 bootstrap iterations to identify a linear combination of GWC patterns associated with age.

Results: A linear combination of SSM components was associated with increasing age ($R2 = .526$, $p < 2.80e\text{-}22$). The combined age-related SSM pattern was characterized by decreases in bilateral middle temporal, left (L) pars orbitalis, bilateral superior frontal, bilateral supramarginal, right (R) inferior parietal, R superior parietal, and R frontal pole areas, with relative increases in bilateral caudal anterior cingulate, L cuneus, bilateral isthmus cingulate, L lingual, L pericalcarine, bilateral posterior cingulate, bilateral transverse temporal, and R temporal pole areas. After controlling for age, sex, and years of education, greater expression of the SSM age-related GWC pattern was associated with lower Wechsler Adult Intelligence Scale-IV Working Memory Index scores ($R2$ change $= .014$, $p = .023$).

Conclusions: The results indicate a regional pattern of GWC in healthy middle-aged to older adults characterized by decreases in selective frontal and parietal brain regions as well as relative increases in distinct frontal, occipital, and temporal areas with increasing age. Given that degradation of myelin can affect differences in MRI gray-white boundary signal intensities, the observed regional differences in GWC may reflect a pattern of age-related demyelination that was also associated with poorer working memory performance. Together, our findings suggest that SSM network analyses of MRI GWC may provide an important neuroimaging biomarker, with potential applications for the evaluation of interventions for brain aging.

POSTER #116

INTERACTION OF WMH VOLUME AND SEX DIFFERENCES ON HEART RATE RESPONSE TO AEROBIC EXERCISE IN HEALTHY MIDDLE-AGED TO OLDER ADULTS. Song H, Raichlen DA, Klimentidis YC, Bharadwaj PK, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: White matter hyperintensities (WMH) on magnetic resonance imaging (MRI) scans are associated with brain aging and cerebrovascular disease (CVD), and have been suggested to occur more in women than men. Engagement in aerobic physical activity (PA) may help to slow the development of WMH; however, the extent to which PA influences WMH volume may vary depending on responsivity to exercise. Here we sought to investigate a novel risk factor for CVD and brain aging by examining whether sex-specific vulnerability to WMH is associated with differences in HR response during exercise.

Methods: Data from the UK Biobank for 813 healthy adults (56.5% women), ages 44-74 years, who completed a submaximal graded exercise test (sGXT) and brain MRI scans and were free of hypertension, diabetes, current smoking, and obesity were included. To determine HR response to exercise, we quantified the change in HR (peak - rest) during the sGXT. WMH volumes were obtained from the UK Biobank after processing with FSL-BIANCA software and were adjusted for intracranial volume. Participants with high vs. low WMH volumes were defined as those above and below the median.

Results: Analysis of covariance showed a significant WMH group by sex interaction for HR response after adjusting for age, BMI, blood pressure, smoking history, and time interval between the sGXT and MRI scans, $F(1, 803) = 4.57$, $p = .033$. The interaction effect remained significant after further adjusting for cardiorespiratory fitness and time spent in moderate-to-vigorous PA, $F(1, 801) = 4.55$, $p = .033$. Simple effects analyses revealed that women with high WMH had greater HR responses than those with low WMH ($p = .022$), whereas men showed no difference; and that among individuals with high WMH, women showed greater increases in HR responses than men ($p < .001$).

Conclusions: The results indicate that larger WMH volumes in healthy middle-aged to older women, but not men, are associated with greater increases in HR during exercise. Our findings suggest that greater chronotropic responses to exercise may be an important biomarker in women, potentially leading to a greater risk for brain aging.

POSTER #117

STATIN THERAPIES REDUCE RISK OF ALZHEIMER'S DISEASE AND DEMENTIA WITH INCREASED PROTECTIVE THERAPEUTIC EFFECT WITH INCREASING AGE. Torrandell-Haro G, Branigan GL, Vitali F, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: A previous peer-reviewed publication (Torrandell-Haro et al. 2020, Alzheimer's&Dementia: TRCI) reported that statin therapy was associated with risk reduction of Alzheimer's disease. Herein we sought to determine the replication validity of statin therapy on the incidence of Alzheimer's disease and dementia in a larger dataset with a clinical population of 15 million participants.

Methods: This retrospective cohort study used the Mariner claims dataset, which includes prescription and records of 15 million patients from private-payer and Medicare insurance from across the United States. Patient records surveyed for a diagnosis of Alzheimer's or dementia starting 1 year after statin exposure. 304,662 participants aged 45 years and older, without prior history of neurodegenerative diseases or brain surgery, were included in the study. In this study, patients with and without exposure to statins were categorized by age groups (60-65, 70-75, 80-85) to determine an association between age and Alzheimer's outcomes.

Results: Of the 304,662 participants included in the study, 152,331 patients (mean [SD] age, 61.75 [3.4] years) were exposed to statin therapy, and 152,331 patients (59.76 [2.6] years) were not treated with statins. Statin exposure was associated with a lower incidence of Alzheimer's (relative risk, 0.51; 95%CI, 0.46-0.57; $P < .001$) and dementia (relative risk, 0.61; 95%CI, 0.58-0.61; $P < .001$). The incidence of Alzheimer's and dementia was reduced by all statins with variances in individual risk profiles. Increasing age was associated with a greater risk reduction of Alzheimer's disease in patients with statin exposure compared to non-statin controls.

Conclusions: Outcomes of these analyses validated previous findings that statin therapy is associated with decreased risk of Alzheimer's and dementia using a larger database than the previously reported. Further, statin exposure was associated with age-dependent reduction in risk of Alzheimer's disease diagnosis.

POSTER #118

BODY MASS INDEX-RELATED REGIONAL COVARIANCE PATTERNS OF WHITE MATTER MICROSTRUCTURE IN HEALTHY OLDER ADULTS. Van Etten EJ, Bharadwa PK, Raichlen DA, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: Elevated body mass index (BMI) scores are related to increased risk for cerebrovascular disease and have been associated with reductions in white matter integrity (WMI), particularly in whole brain and regional tracts of fractional anisotropy (FA). However, less is known about how BMI impacts other measures of WMI, including mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). Further, previous studies have primarily utilized univariate analyses for investigating relationships between BMI and WMI. We applied a multivariate statistical method, the Scaled Subprofile Model (SSM; Alexander & Moeller, 1994), to identify regional covariance patterns associated with BMI for each WMI measure. We then examined how these BMI-related WMI patterns differed in relation to age, sex, and vascular risk factors, including white matter hyperintensity (WMH) volume, hypertension, cholesterol, history of smoking, and self-reported physical activity.

Methods: A cohort of 195 cognitively healthy adults (100F/95M, mean±sd age = 69.8±10.6, mean±sd BMI 25.4±4.0), ages 50 to 89 were included. Volumetric T1 and diffusion weighted 3T MRI scans were processed using Freesurfer (v5.3) and TRACULA (Yendiki et al, 2011) to generate FA, MD, RD, and AD values of 18 major white matter tracts. WMH volumes were measured using T1 and T2 FLAIR scans and the lesion segmentation toolbox (Schmidt et al., 2012) with SPM12. The SSM network analyses with 10,000 bootstrapped iterations were performed for each WMI measure to identify a linear combination of white matter tract patterns associated with BMI.

Results: There were significant BMI-related regional patterns for FA ($p < .001$) and RD ($p = .039$), accounting for 11.8% and 3.3% of the variance in BMI, respectively. The BMI-FA pattern was characterized by negative loadings from bilateral superior longitudinal fasciculus-parietal (SLFP) and superior longitudinal fasciculus-temporal (SLFT) and positive loadings from right cingulum-angular bundle (CAB) and left uncinate fasciculus (UNC). The BMI-RD pattern was characterized by negative loadings from bilateral CAB and positive loadings from bilateral SLFP and SLFT. Increasing age was significantly associated with greater expression of the BMI-FA ($p = .002$) and BMI-RD ($p = .026$) patterns and sex was significantly related to the BMI-FA ($p < .001$) and BMI-RD ($p = .013$) patterns, with males experiencing greater expression of the patterns than females. After controlling for age and sex, hypertension status was associated with greater expression of the BMI-FA ($p = .023$) and BMI-RD patterns ($p = .015$) and higher self-reported physical activity was related to less expression of the BMI-FA ($p < .001$) and BMI-RD ($p = .001$) patterns, whereas elevated WMH volume was associated with greater expression of the BMI-RD ($p < .001$), but not the BMI-FA pattern.

Conclusions: These findings suggest that, in cognitively healthy older adults, greater BMI is associated with regional patterns of white matter microstructural differences that are exacerbated by increasing age, male sex, and greater vascular risk. Utilizing multivariate network covariance methods, like SSM, may help to advance understanding of the influence of demographic and vascular risk factors on brain aging, with potential for evaluating the effects health and lifestyle interventions for healthy and pathological aging.

POSTER #119

INFILTRATION OF PERIPHERAL IMMUNE CELLS IN HUMAN BRAIN DURING MID-LIFE. Van Rossum H, Mishra A, Delatorre N, Padilla-Rodriguez M, Shang Y, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Inflammation is a well-documented feature of Alzheimer's disease (AD) in human brain. Two critical issues relevant to understanding the role of inflammation in AD that remain unresolved are: 1) the initiation phase of inflammation and 2) sex differences in the inflammatory cascade. Previous preclinical findings from our group indicated elevated immune transcripts including CD3, CD4, and MHCII. Herein, we extend and translate our preclinical discoveries to test the hypotheses that: 1) the inflammatory phenotype of LOAD is initiated in midlife of the human aging process and 2) the inflammatory cascade in brain is initiated by microglial activation in brain that promotes infiltration of peripheral immune cells into the brain.

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

Results: Cell phenotyping analyses indicated presense of CD3+, CD4+ and CD8+ positive cells in human brain consistent with infiltration of peripheral T cells into brain. Magnitude of T-cell indicators increased with age and was detectable in mid-life consistent with infiltration during midlife. In addition to CD3+, CD4+ and CD8+ T-cells activated and HLA+ microglia were present.

Conclusions: These results provide evidence for early midlife infiltration of T-cells into brain which is coincident with activated microglial suggestive of immune signaling between the central and peripheral immune compartments. Outcomes of these and future analyses are relevant to effective immuno-therapeutics to target the earliest stages of AD to reduce risk and or delay AD.

POSTER #120

CLOSER CORRELATIONS BETWEEN FLORBETAPIR PET MEASUREMENTS OF AMYLOID PLAQUE BURDEN USING A CEREBRAL WHITE MATTER REFERENCE REGION AND ALZHEIMER'S DISEASE-RELATED HYPOMETABOLISM. Wang MS, Bi TB, Jing NY, Ausdemore JC, Kramer HL, Chen Y, Luo J, Weiner MW, Landau SM, Jagust WJ, Su Y, Reiman EM, Chen K. University of Arizona, College of Medicine – Phoenix; Emory University; Square, Inc.; University of Southern California; Creighton University; Banner Alzheimer's Institute; San Francisco Veterans Affairs Medical Center; University of California, San Francisco; University of California Berkeley; Lawrence Berkeley National Laboratory; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is associated with amyloid-β (Aß) plaque deposition and a characteristic pattern of cerebral glucose hypometabolism. While a cerebellar reference region is commonly used to characterize cerebral Aβ burden, we demonstrated improvements in the ability of florbetapir PET to track Aβ burden using a cerebral white matter reference region (Chen, et al., 2015). Here, we compare associations between cerebral-to-reference region florbetapir PET standard value uptake ratios (SUVRs) using cerebral white matter versus cerebellar reference regions to two FDG PET indices of AD-related cerebral hypometabolism: "hypometabolic convergence index" (HCI) and "statistical region-of-interest" (sROI) (Chen et al, 2010; 2011).

Methods: We analyzed 1722 florbetapir and FDG PET scan pairs from the AD Neuroimaging Initiative, including 267 with probable AD dementia (pAD), 592 with MCI and 379 cognitively unimpaired (CU). Florbetapir SUVRs were computed using measures from the cerebral regions-of-interest with the cerebral white matter or cerebellar reference regions. HCI and sROI were generated from the FDG PET images. Pearson's correlations and the Steiger statistical test were used to characterize and compare the extent to which florbetapir SUVRs using cerebellar versus cerebral white matter reference regions were associated with HCI or sROI in the overall group, the pAD, MCI and CU sub-groups.

Results: Correlations between florbetapir SUVRs using the white matter reference region and HCI (0.59, 0.41, 0.45, and 0.40 in the overall, pAD, MCI and CU groups) were significantly stronger than those using the cerebellar reference region (0.40, 0.23, 0.26, and 0.20, P=1.1e-16, 3.6e-06, 1.3e-09, and 1.0e-11, respectively). Similarly, inverse correlations between florbetapir SUVR measurements using the white matter reference region and sROI measurements (-0.51, -0.32, -0.38, and -0.28 in the overall, pAD, MCI and CU groups) were significantly stronger than those using the cerebellar reference region (-0.34, -0.09, -0.24, and -0.13, P=2.0e-15, 3.2e-07, 1.7e-0, and 4.0e-07, respectively).

Conclusions: Florbetapir PET Aβ plaque measures are more closely associated with the AD-related pattern of cerebral hypometabolism when SUVRs are generated using a white matter rather than cerebellar reference regions. Additional research is needed to examine if our results are generalizable for other Aβ PET tracers and longitudinal change measures.

POSTER #121

A DROSOPHILA MODEL OF FTD BASED ON C9ORF72 HEXANUCLEOTIDE REPEAT EXPANSIONS. Williams C, Godfrey K, Cowell H, Hala'ufia G, Zarnescu D. University of Arizona; Arizona Alzheimer's Consortium.

Background: Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by a spectrum of symptoms that impair intellectual functions including short-term memory, reasoning, abstract thinking, and/or executive function, all of which can severely impact daily living activities FTD is the third-most common form of dementia, preceded by Alzheimer's disease, and greatly impacts an individual lives . While these are the most prominent indications of FTD, research has indicated that FTD symptoms present in many forms and at various ages, making early diagnosis problematic. Once diagnosed, the typical life expectancy ranges from 3-14 years, which is exacerbated by secondary illnesses caused by incapacity, neglect, or self-harm. Therefore, the need to research to better understand FTD and improve the quality of lives for inflicted individuals is great. Approximately, 43% of FTD patients have a family history related to dementia or associated neurodegenerative diseases, with up to 27% of individuals carrying an autosomal dominant mutation. When examining the subsets of familial FTD cases, three genetic mutations are prominent—microtubule-associated protein tau, progranulin, and C9orf72. The mechanisms underlying C9orf72 FTD include haploinsufficiency, RNA toxicity caused by G4C2 hexanucleotide repeat expansion (HRE) within the first intron and dipeptide repeats (DPRs) generated using noncanonical translation of the G4C2 HRE RNA. C9orf72 neurodegeneration has been modeled in multiple model organisms, however no Drosophila model of FTD based on C9orf72 HRE has been reported to date. Here we describe the development of a Drosophila model of FTD based on G4C2 HRE overexpression in mushroom body neurons. This model may help uncover novel molecular mechanisms underlying C9orf72 FTD and future therapeutic strategies.

Methods: 1. Drosophila genetics: To model FTD we overexpress C9orf72 HREs in mushroom body (MB) neurons using the GAL4-UAS system. 2. Immunofluorescence staining and confocal microscopy: To examine the morphological phenotypes caused by C9 HRE overexpression in mushroom body (MB) neurons we use immunofluorescence and confocal microscopy to detect FASII, an axonal membrane marker. DAPI will be used to label neuronal nuclei, which determines whether C9orf72 HREs cause neuronal loss. 3. Y-maze assay: The Y-maze assay is an evaluation of short-term memory by quantifying the number of times flies choose to explore a different arm of the maze; this assay reveals the ability of individual flies to recall which area they have already visited through a generation of a cognitive map of the maze. 4. Sleep assay: Using Drosophila activity monitors we are evaluating the effect of C9orf72 HRE overexpression in MB neurons on sleep and circadian rhythms which have been correlated with the progression of neurodegeneration in FTD.

Results: We are currently performing several phenotypic assays to determine the consequences of C9orf72 HRE overexpression in MB neurons compared to controls. We will present our progress on developing a Drosophila model of FTD based on C9orf72 HRE overexpression.

Conclusions: Based on our previous success with modeling C9orf72 HRE ALS, a related neurodegenerative disorder affecting motor neurons, we anticipate establishing several phenotypes caused by C9orf72 HRE overexpression in MB neurons, a circuit relevant involved in learning, memory and sleep, all of which are relevant to FTD.

POSTER #122

GLYPHOSATE INFILTRATES THE BRAIN AND MAY BE A RISK FACTOR FOR ALZHEIMER'S DISEASE. Winstone J, Pathak KV, Sharma S, Donnay M, White J, Huentelman M, Pirrotte P, Velazquez R. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The prevalence of Alzheimer's Disease (AD) is increasing in the US with an expected 14.8 million cases by 2050. Risk factors include both heritable and non-heritable environment-based components. Of particular concern is the exponential increase in the use of pesticides such as glyphosate, the active ingredient in the herbicide RoundUp. Notably, there is an increased prevalence of AD in agricultural communities, and the increase in glyphosate usage positively correlates with the increase in deaths due to AD and other forms of dementia. However, it has yet to be determined whether glyphosate crosses the blood-brain-barrier (BBB) in vivo or how it may affect AD-related pathologies.

Methods: Here, we examined levels of glyphosate in urine from 245 individuals TGen's MetricBio Cohort using UPLC-MS. Next, we examined whether glyphosate crosses the BBB in standard C57/bl6 laboratory mice. Mice received either 125, 250, 500mg/kg/day of glyphosate or a vehicle control via oral gavage for 14 days. UPLC-MS was used to detect glyphosate levels in brain tissue and urine. Brain homogenates were used to assess relative protein abundance via western blots.

Results: Notably, 60% of participants in the MetricBio Cohort showed detectable glyphosate levels in their urine with levels ranging from 1-130 µg/L. Post-mortem murine brain tissue analysis revealed that glyphosate infiltrated brain tissue in a dose dependent manner. Additionally, western blotting revealed dysregulation of key proteins involved in learning and memory, inflammation and cell death in the brain.

Conclusions: Our results highlight the need for further exploration into the long-term consequences of glyphosate exposure and its potential as a risk factor for AD. Future designs will plan to test whether glyphosate exposure increases AD-like pathology in a mouse model of AD. The implications of the current study are highly relevant given the rising glyphosate application rate and its correlation with the increase in AD.

POSTER #123

FEDERATED MORPHOMETRY FEATURE SELECTION FOR HIPPOCAMPAL MORPHOMETRY ASSOCIATED BETA-AMYLOID AND TAU PATHOLOGY. Wu J, Dong Q, Zhang J, Su Y, Wu T, Reiman EM, Ye J, Lepore N, Chen K, Thompson PM, Wang Y. Arizona State University; Beijing Institute of Technology; Banner Alzheimer's Institute; Children's Hospital Los Angeles; University of Michigan; University of Southern California; Arizona Alzheimer's Consortium.

Background: Amyloid-β (Aβ) deposition and Tau protein tangles in the brain are the well-known supportive biomarker at the earliest and mildest stages of Alzheimer's Disease (AD), followed by structure deformation detectable on brain magnetic resonance imaging (MRI) scans. In particular, the hippocampus is a primary target region in AD research. However, the influence of Aβ/Tau metabolic dysfunction on general hippocampal morphology in pathophysiological progress is still elusive. This work proposes a novel framework, Federated Morphometry Feature Selection (FMFS) model, to detect the Aβ/Tau burden associated with hippocampal morphometry markers. An exclusive innovation of FMFS is that it has an outstanding computing efficiency on ROI identification compared to the state-of-the-art methods.

Methods: FMFS include hippocampal surface-based feature calculation, patch-based feature selection, Federated Group LASSO Regression, federated screening rule-based stability selection, regions of interest (ROI) identification. The hippocampal structures are segmented from registered brain MR images and smoothed hippocampal surface are further generated. After the surface parameterization and fluid registration, the hippocampal radial distance (RD) and tensor-based morphometry (TBM) features are calculated at each surface point. Each institution selects patches on each hippocampal surface and reshape the grouped features of each subject to a vector. Next, taking Aβ/Tau measurements as dependent variables, these institutions perform the federate model on the patches of features to generate hippocampal local ROIs related to each Aβ/Tau measurement.

Results: From ADNI 1, ADNI 2, ADNI Go, and ADNI 3, we acquire two sets of scans for the study of Aβ deposition (1127 MRI and 1127 PET) and Tau deposition (925 MRI and 925 PET). ADNI florbetapir PET data are processed using AVID pipeline, which are converted to the Centiloid scales according to their respective conversion equations. For flortaucipir tau-PET, we analyze three measurements of Tau deposition, HEMIWM, Braak12, and Braak34, which are all standardized by SUVR. We perform our FMFS model to these measurements separately and acquire 4 types of ROIs related to the four measurements. Compared to the distributed alternating direction method of multipliers algorithm (DAMM), our FMFS achieve a speedup up to 89 folds under the same experimental setups. In addition, the ROIs selected by our model show a stronger predictive power in predicting MMSE than the measurements of Amyloid and Tau deposition. We also test the ROIs by predicting clinical decline in MCI patients with Cox model. The features on ROIs associated to Aβ/Tau measurements also have a superior performance in survival analysis than the hippocampal volume.

Conclusions: This work proposes a novel high-dimensional federated feature selection framework, FMFS, to study the Aβ/Tau burden associated with hippocampal subregions on two datasets. To the best of our knowledge, this is the first feature selection model to study hippocampal morphometric changes with Aβ/Tau burden across AD spectrum. More importantly, this model can visualize brain structural abnormalities affected by AD proteinopathies. Beyond brain MRI, our framework can also be applied to any other kinds of medical data for feature selection.

POSTER #124

PREDICTING BRAIN AMYLOID USING MULTIVARIATE MORPHOMETRY, SPARSE CODING AND CORRENTROPY. Wu J, Dong Q, Gui J, Zhang J, Su Y, Chen K, Ye J, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Beijing Institute of Technology; Banner Alzheimer's Institute; Mayo Clinic Arizona; University of Michigan; Arizona Alzheimer's Consortium.

Background: Biomarker-assisted early detection and intervention in Alzheimer's disease (AD) may be the key to therapeutic breakthroughs. One of the presymptomatic hallmarks of AD is the accumulation of beta-amyloid (Aβ) plaques in the human brain. However, current methods to detect Aβ pathology are either invasive (lumbar puncture) or quite costly and not widely available (amyloid PET). Our prior studies show that MRI-based hippocampal multivariate morphometry statistics (MMS) are an effective neurodegenerative biomarker for preclinical AD. Here we attempt to use MRI-MMS with a sparse coding algorithm, Patch Analysis-based Surface Correntropy-induced Sparse coding and max-pooling (PASCS-MP), to make inferences regarding brain amyloid burden at the individual subject level.

Methods: Firstly, hippocampal structures are segmented from registered brain MR images with FIRST from the FMRIB Software Library (FSL). Hippocampal surface meshes are constructed with the marching cubes algorithm. Hippocampal surfaces are parameterized with the holomorphic flow segmentation method. After the surface fluid registration algorithm, the hippocampal MMS features are calculated at each surface point. We propose a PASCS-MP and classification system to refine and classify MMS patches in individuals with different Aβ status. We randomly select patches on each hippocampal surface and generate a sparse code for each patch with our novel PASCS. Next, we adopt a max-pooling operation on the learned sparse codes of these patches to generate a new representation (a vector) for each subject. Finally, we train binary random forest classifiers on the representations of people with different Aβ status and validate them with 10-fold cross-validation.

Results: We test our method in two independent cohorts, Alzheimer's Disease Neuroimaging Initiative (ADNI) and Open Access Series of Imaging Studies (OASIS). We leverage the PASCS-MP on MMS to explore hippocampal morphometry differences for the following contrasts at the individual subject level: (1) Aβ positive individuals with MCI (Aβ+ MCI, n=171) vs. Aβ negative individuals with MCI (Aβ- MCI, n=171) from ADNI, and (2) Aβ positive CU subjects (Aβ+ CU from ADNI (n=116) and OASIS (n=52)) vs. Aβ negative CU subjects (Aβ- CU from ADNI (n=116) and OASIS (n=208)). Experimental results suggest that our proposed PASCS-MP method and MMS can discriminate Aβ positivity in people with MCI (Accuracy (ACC)=0.89 (ADNI)) and in CU individuals (ACC=0.79 (ADNI) and ACC=0.82 (OASIS)). We also train the random forest classifiers with the same experiment settings on other traditional measures including hippocampal volume and surface area, SPHARM and the sparse codes generated by PASS-MP.

Conclusions: Compared to traditional measures, MMS have superior performance for predicting Aβ positivity in the AD continuum. Besides, the proposed PASCS-MP outperforms our previous PASS-MP on refining MMS features. Compared to similar studies, this work achieves state-of-the-art performance when predicting Aβ positivity based on MRI biomarkers.

POSTER #125

PREDICTION OF BRAIN AMYLOID BURDENS WITH SIGNED DISTANCE FIELD-BASED GEOMETRIC DEEP LEARNING. Yang Z, Su Y, Chen K, Thompson PM, Reiman EM, Wang Y.
Arizona State University; Banner Alzheimer's Institute; University of Southern California; Arizona Alzheimer's Consortium.

Background: Recently, prediction of brain amyloid with structural MRI received growing interest because of its wide availability and non-invasive nature. Traditionally, brain sMRI image biomarkers use cortical or subcortical structure volume. Recent works demonstrate that surface-based brain imaging biomarkers outperforms such volume measures because it overcomes partial volume effects. However, due to different structure, regular grid based conventional CNN is hard to be directly applied to surface manifold. Most of pioneering work are designed on point cloud. This data format provides efficiency while it loses some intrinsic geometry information which is demanded in discovering subtle brain shape features.

Methods: We take the hippocampus as a composition of two 2D manifolds. Our work is to extract features on the signed distance field (SDF) of the hippocampus with sparse convolution to classify it. We first propose our SDF sparse convolution and the network architecture that could learn features on a field instead of a 2D manifold. Finally, we compare with two baselines including hippocampal volume, and PointNet++, a popular 3D object recognition deep learning approach.

Results: We recognize two important aspects of the network design, the input data formats, and network operations. When using PointNet++ to analyze SDF, we randomly sample 2500 points from 250000 points in SDF to feed into the network. When using sparse convolution to analyze a point cloud, we sample 10000 points from vertices of a mesh to feed into the network. The results show that PointNet++ could not exploit SDF information comparing to the point cloud even SDF could provide more information than a point cloud. And the performance of sparse convolution drops from 77.2% to 70.9% when only takes a point cloud is the input to the network. The combination between SDF and sparse convolution performs best in all combination settings.

Conclusions: Our work has two contributions. (1) To our knowledge, this is the first paper using SNF-based deep neural network to classify brain amyloid burdens; (2) We propose and demonstrate an effective and standard schedule for using deep learning for 3D manifold data.

POSTER #126

EFFECTS OF CHRONIC, HIGH-DOSE MINOCYCLINE TREATMENT ON COGNITIVE PERFORMANCE IN AGING RATS. Young KF, Zempare MA, Dalmendray AL, Gregolynskyj A, Chawla MK, Guzowski JF, Barnes CA. University of Arizona; University of California at Irvine; Arizona Alzheimer's Consortium.

Background: The antibiotic minocycline is a promising therapeutic intervention in multiple age-associated diseases that share inflammation as a symptom. Its neuroprotective effects have been attributed to anti-inflammatory properties exerted through interaction with T-cells and microglia. Minocycline crosses the blood-brain-barrier and can ameliorate cognitive deficits in experimental models of ischemic stroke, traumatic brain injury, and neurodegenerative conditions like Alzheimer's, Parkinson's, and Huntington's diseases.

Methods: To address the lack of research into the effects of minocycline on normative aging in the absence of brain trauma or disease, we investigated whether minocycline might affect age-related cognitive decline in rats. Middle-aged (16mo) male Fischer rats were divided into control and treatment groups, with treated rats receiving 70mg/kg/day of minocycline via drinking water (a high dose chosen for its minimal effect on water consumption). After 8 weeks of treatment, rats (18 mo) were administered a behavior test battery, with a retest 10 weeks later (20mo) to assess the impact of continued minocycline treatment on cognitive performance. The battery includes spatial and cued versions of the Morris watermaze, a spontaneous object recognition (SOR) task, and a delayed matching-to-place working memory task.

Results: Analysis of the 1st battery shows that while treated rats trend towards learning the spatial watermaze slower than controls (2WAY RM ANOVA: treatment: $F(1, 21) = 4.049$, $p = 0.057$), both groups perform similarly at the end of the task, and did equally well on the perirhinal cortex-dependent SOR task and prefrontal cortex-dependent working memory task. When retested 10 weeks later, treated rats learn the spatial watermaze at the same rate as controls, and both groups display age-related decline in performance on the SOR task. On the working memory retest, both treated and control rats achieve a shorter pathlength on the retention trial.

Conclusions: The present data suggest minocycline is not effective for modifying cognition in normative aging. While minocycline has been successful treating cases of severe brain injury or neurodegenerative disease, the degree of neuroinflammation in the aging brain may be below threshold for such beneficial effects.

Institutional Information
Research Summaries and Key Personnel
From Each Participating Institution

ARIZONA STATE UNIVERISTY
Institutional Abstract

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 six years (2015-2020). With Alzheimer's disease affecting roughly one in nine people 65 years old and over, and one in three people 85 years old and over, research on Alzheimer's disease exemplifies the type of endeavor that ASU seeks to promote, and a focus on innovative approaches is most certainly critical to research and treatment efforts.

For the Arizona Alzheimer's Consortium, ASU provides the Outreach and Recruitment Core and Research Education Component. These serve researchers throughout the state as part of the Consortium's NIA-sponsored Arizona Alzheimer's Disease Center. The ASU team includes leaders in the development of novel models to: establish a causative link between traumatic brain injury (TBI), neuroinflammation, and Alzheimer's disease (Brafman laboratory); explore injury-induced neuroinflammation as a contributor to Alzheimer's Disease (Stabenfeldt laboratory); characterize the microbiome of post-mortem brain tissue in subjects affected by Alzheimer's disease (Readhead laboratory); evaluate sex differences and gonadal hormone contributions to the trajectory of behavioral and neuropathological change across aging (Bimonte-Nelson laboratory); conduct computational image analysis and implement biomathematical techniques to increase the power to detect and track Alzheimer's disease progression (Wang laboratory); investigate the relationships between sex, age, ADRD family history, and cognitive scores and motor-cognitive game performance (Schaefer laboratory); and, develop and test multicomponent interventions for individuals with MCI or ADRD and their family caregivers (Coon laboratory). It is noteworthy that ASU has numerous scientific research domains that are being further developed and strengthened to bolster the impact on Alzheimer's disease and aging research, with a focus on discovery and action to move trajectories, diagnosis, and treatment forward. These include, but are not limited to, the neurosciences, health outcomes research, and focused translational research realms that pose hypothesis-driven questions approached from a systems and interdisciplinary perspective. Collectively, ASU has a solid framework and wide-ranging strengths that are poised to make great strides in the scientific fight against Alzheimer's disease, as well as to optimize the trajectory of brain aging, using both preclinical and clinical approaches. Moreover, it is noteworthy that the assets in the research programs at ASU within the Arizona Alzheimer's Consortium represent a range of colleges, institutes, and centers across ASU.

ASU and Phoenix-based Banner Health, one of the nation's largest nonprofit health systems, have launched a research alliance to advance the scientific study, treatment and prevention of Alzheimer's, Parkinson's and other neurodegenerative diseases. The partnership includes the establishment of the Neurodegenerative Disease Research Center (NDRC)[1]. The center is an extension of the partners' work with the Arizona Alzheimer's Consortium and is envisioned to become one of the world's largest basic science centers for the study of Alzheimer's and other neurodegenerative diseases. Researchers in the Center have already made major contributions to the study of AD and Parkinson's disease-related risk factors, mechanisms, and targets at which to aim new treatments, and they have been capitalizing on data from experimental studies, post-mortem human brain omics data, and big data analyses to help in this endeavor. The Center expected to grow to include about 20 new laboratories and additional affiliated laboratories. It will

[1] https://science.asu.edu/neurodegenerative-disease-research-center

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. We are delighted to report that Jeffrey Kordower, PhD, an internationally recognized leader in neurodegenerative disease research has joined ASU to become Founding Director of the ASU-Banner ADRC.

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's Research Education Component is led by two nationally recognized research mentors, Dr. Roberta Brinton, Regents Professor at the University of Arizona and Heather Bimonte-Nelson, University Professor at ASU, reflecting extensive commitments to research education, training and collaboration. Notably, ASU offers graduate degrees in Statistics and Biomedical Informatics, the Behavioral Neuroscience Program[2] within the Department of Psychology, as well as the Interdisciplinary Graduate Program in Neuroscience[3]. 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.

[2] https://psychology.clas.asu.edu/content/psychology-behavioral-neuroscience-phd
[3] https://neuroscience.asu.edu

ARIZONA STATE UNIVERSITY
Key Personnel

Name (last, first)	Degree	Role on project
Kordower, Jeffrey	PhD	Director, ASU-Banner Neurodegenerative Disease Research Center (NDRC)
LaBaer, Joshua	MD, PhD	Executive Director, Biodesign Institute
Coleman, Paul	PhD	Research Professor, NDRC
Dunckley, Travis	PhD	Assistant Research Professor, NDRC
Mastroeni, Diego	PhD	Associate Research Professor, NDRC
Readhead, Benjamin	MBBS	Assistant Research Professor, NDRC
Velazquez, Ramon	PhD	Assistant Research Professor, NDRC
Wang, Qi	PhD	Assistant Research Professor, NDRC
Huseby, Huseby	PhD	Postdoctoral Research Scholar, NDRC
Judd, Jessica	PhD	Postdoctoral Research Scholar, NDRC
Nolz, Jennifer	MS	Research Technologist, NDRC
Delvaux, Elaine		Research Technologist, NDRC
Bimonte-Nelson, Heather	PhD	President's Professor, Department of Psychology
Koebele, Stephanie	PhD	Postdoctoral Researcher
Pena, Veronica		Graduate Student
Bernaud, Victoria		Graduate Student
Ruhland, Ashley		Graduate Student
Hanson, Teena		Graduate Student
Northup-Smith, Stephen		Lab Manager
Logan-Robledo, Santiago		Undergraduate Research Assistant
Johnson, Raena		Undergraduate Research Assistant
Manzo, Alyssa		Undergraduate Research Assistant
Opachich, Zorana		Undergraduate Research Assistant
Christian, Jordan		Undergraduate Research Assistant
Arroyo, Ana		Undergraduate Research Assistant
Bandin, Eric		Undergraduate Research Assistant
Andrew, Kieran		Undergraduate Research Assistant
Mitbander, Avantika		Undergraduate Research Assistant
Attias, Valeria		High School Student
Braden, Blair	PhD	Assistant Professor, College of Health Solutions
Walsh, Melissa		Graduate Researcher

Name (last, first)	Degree	Role on project
Pagni, Broc		Graduate Researcher
Wilson, Melissa	PhD	Associate Professor, School of Life Sciences
Berisha, Visar	PhD	Associate Professor, School of ECEE and College of Health Solutions
Liu, Li	MD	Associate Professor, College of Health Solutions & Director, Bioinformatics Core Facility
Brafman, David	PhD	Assistant Professor, School of Biological and Health Systems Engineering
Raman, Sreedevi	PhD	Postdoctoral Fellow
Knittel, Jacob	BS	Research Technician
Essuman, Albert	BS	Graduate Researcher
Frisch, Carlye	BS	Graduate Researcher
Kostes, William	BS	Graduate Researcher
Srinivasan, Gayathri	MS	Graduate Researcher
Coon, David	PhD	Associate Dean & Professor, Edson College of Nursing and Health Innovation
Argulo, Aylin	BS	Research Specialist
Carll, Phil	MSW	Research Specialist
Glinka, Allison	MS	Research Specialist
Gomez Morales, Abi	MS	PhD Student
Maxfield, Molly	PhD	Associate Professor, College of Nursing and Health innovation
Rice, Gabe	MS	Program Coordinator
Weatherall, Zenya		Project Coordinator
Yu, Fang	PhD	Professor and Edson Chair in Dementia Translational Nursing Science
Ofori, Edward	PhD	Assistant Professor, College of Health Solutions
Schaefer, Sydney	PhD	Assistant Professor, School of Biological and Health Systems Engineering
Hooyman, Andrew	PhD	Postdoctoral Scholar
Stabenfeldt, Sarah	PhD	Associate Professor, School of Biological and Health Systems Engineering
Wang, Yalin	PhD	Associate Professor, School of Computing, Informatics, and Decision Systems Engineering
Dong, Qunxi	PhD	Postdoctoral Fellow
Fan, Yonghui	MS	Graduate Researcher
Farazi, Mohammad	MS	Graduate Researcher
Tu, Yanshuai	MS	Graduate Researcher
Wu, Jianfeng	BS	Graduate Researcher

Name (last, first)	Degree	Role on project
Yang, Zhangsihao	MS	Graduate Researcher
Pan, Rong	PhD	Associate Professor, School of Computing, Informatics, and Decision Systems Engineering
Wu, Teresa	PhD	Professor & Co-Director, ASU-Mayo Center for Innovative Imaging
Sierks, Michael	PhD	Professor, Department of Chemical Engineering
Gu, Haiwei	PhD	Assistant Professor, College of Health Solutions
Snyder-Mackler, Noah	PhD	Assistant Professor, Center for Evolution and Medicine

BANNER ALZHEIMER'S INSTITUTE
Institutional Abstract

The Banner Alzheimer's Institute (BAI) has three goals: To find treatments to prevent Alzheimer's disease (AD) without losing a generation, to set a new standard of care for patients and families, and to promote a model of multi-institutional collaboration in biomedical research. BAI is intended to accelerate the evaluation, approval and availability of treatments to postpone, reduce or completely prevent the clinical onset of AD as quickly as possible; leverage its brain imaging resources and expertise to advance the scientific study, early detection, tracking, diagnosis, treatment and prevention of AD and related disorders; address the medical and nonmedical needs of affected persons and families to the fullest extent possible, and help to establish a new standard of dementia care in the emerging population-based healthcare financing system. Finally, it is intended to complement, enhance, and benefit from close working relationships with its organizational partners inside and outside of the Arizona Alzheimer's Consortium (AAC).

BAI's Stead Family Memory Center includes a Memory Clinic, Family and Community Services Program and Clinical Trials Program. It offers a wide range of services for the evaluation and care of affected persons and family caregivers, helping to address their medical and non-medical needs throughout the illness. It provides educational, outreach and research enrollment programs for Arizona's Native American and Latino communities, evaluates and follows Native Americans in the NIA-sponsored Arizona AD Center's Clinical Core, and oversees an Annual Conference on AD and Dementia in Native Americans. Its Banner Dementia Care Initiative is seeking to demonstrate ways in which to optimize the identification and evaluation of cognitive problems, address a broad range of the affected person's and family's medical and non-medical needs, reduce unnecessary hospitalizations, and is affordable to payers in the emerging healthcare financing system. BAI conducts numerous clinical trials of investigational treatments, including those in the Alzheimer's Prevention Initiative (API). Its researchers also help oversee prospective an NIA-sponsored cohort study of cognitively unimpaired persons with two, one and no copies of the APOE4 allele, which has helped to conceptualize the preclinical stages of AD, an NINDS-sponsored study of chronic traumatic encephalopathy (CTE) in former National Football League and college football players, and one of the Precision Medicine Initiative's (PMI's) first healthcare provider-led cohort programs in a partnership between University of Arizona and Banner Health.

Its state-of-the-art NIH-supported Imaging Center includes two PET/CT systems, a 3T MRI, cyclotron, radiochemistry laboratory, and computational image analysis laboratory. It provides imaging resources and expertise, research PET tracers, image-analysis methods, data and biological samples for researchers inside and outside of Arizona. In collaboration with Mayo Clinic, it includes a longitudinal brain imaging study of cognitively unimpaired persons with two copies, one copy, and no copies of the APOE4 allele, reflecting three levels of genetic risk for late-onset AD, and image-analysis techniques with improved power to characterize subtle brain changes over time. In collaboration with the University of Antioquia and a Harvard post-doctoral student, it also includes a study of PSEN1 E280A mutation carriers and non-carriers from the world's largest autosomal dominant AD kindred in Colombia. It is a member of the AD Neuroimaging Initiative (ADNI) PET Core, where it is responsible for the development, testing and use of voxel-based image analysis techniques with improved power to detect and track AD. It has played pioneering roles in the study of preclinical AD.

AARC funds complement research activities supported by competitive grant awards from several NIA-sponsored research grants, private foundation grants, and clinical trials. In conjunction with our NIA-sponsored ADCC, subjects, images, other data, and image-analysis techniques from our

study of cognitively normal APOE ε4 carriers and non-carriers provide a core resource for interested investigators inside and outside of Arizona.

In the next few years, BAI, BSHRI, and their partners will place a growing emphasis on the acquisition of antemortem brain-imaging, CSF, and blood-based biomarkers for AD and related disorders in their longitudinal cohorts, and help to find and support the use of promising amyloid and other blood tests for AD and related disorders. These organizations, TGen, and ASU (e.g., at the ASU-Banner Neurodegenerative Disease Research Center [NDRC]) are also developing a shared resource of DNA and RNA sequencing data from different brain cell types and regions in high-quality brain samples from AD cases and controls and are using big data analytical techniques to characterize networks and drivers at which to target in the discovery of new treatments. They and their organizational partners will also be exploring targets at which to aim APOE modifying treatments. Meantime, BAI has been working with colleagues from the University of Arizona to establish a BAI facility in Tucson, Arizona. Several staff members have been hired, programs are being initiated, a facility will be constructed, and BAI Tucson is expected to officially open sometime in 2020.

With several hundred million dollars in NIH, philanthropic and industry support, API has helped to launch a new era in AD prevention research, accelerate the evaluation of prevention therapies, and help to find and support the approval, availability and affordability of prevention therapies as soon as possible. It includes a growing number of preclinical AD / theragnostic biomarker development trials in persons who, based on their genetic or biomarker findings, are at increased AD risk, including the API ADAD Colombia Study in the world's largest autosomal dominant AD (ADAD) kindred, the recently discontinued international API Generation Studies 1 and 2 in persons at particularly high risk for the clinical onset of late-onset AD, a developing NIA- and industry supported AP"I/A4 prevention trial of an amyloid-β plaque-reducing antibody therapy in cognitively unimpaired amyloid-β positive adults, and other prevention and early-phase APOE and AD-modifying drug and gene therapy trials TBD. These and other trials are intended to evaluate the investigational treatments in potentially license-enabling prevention trials; to provide a better test of the amyloid hypothesis than trials in the later preclinical or clinical stages of AD; establish the extent to which a treatment's different biomarker effects are associated with a clinical benefit and provide evidence to support their use as reasonably likely surrogate endpoints in future 24-month prevention trials; provide a shared resource of data and biological fluids for the research community after the trial is over; complement, support and providing a foundation for other prevention trials; to help clarify the benefits, risks and role of APOE genetic test disclosure in the era of Alzheimer's prevention trials; support the advancement of Alzheimer's prevention research in the Collaboration for Alzheimer's Prevention CAP); empower persons at highest risk in the scientific fight against AD; and provide a fighting chance to find and support approval of an AD prevention therapy by 2025, a primary goal of the National Plan to Address AD.

API also includes exceptionally large registries to support interest and possible enrollment in prevention studies. In partnership with the University of Antioquia, the API Colombian Registry, in collaboration now includes ~6,000 members of the PSEN1 E280A mutation kindred, including nearly 1,200 mutation carriers, who have provided their DNA and had clinical and neuropsychological evaluations. The web-based Alzheimer's Prevention Registry (www.endALZnow.org) now provides information about advances in prevention research and opportunities to enroll in prevention trials to >337,000 people and continues to grow rapidly; our GeneMatch Program (www.endALZnow.org/genematch) has enrolled >85,000 persons and aims to enroll >100,000 persons 55-75 years of age, match interested participants in API and other prevention trials and to begin to clarify what it means to learn about one's APOE test results; and these programs continue to grow. It continues to champion new ways to identify and support

enrollment in prevention trials (e.g., using an amyloid-β blood tests), and to address the logistical, ethical, and scientific issues involved in this endeavor.

BAI has several specific aims:

1. To leverage our imaging resources in the early detection, tracking, and diagnosis of AD, the clarification of genetic and non-genetic risk factors, and other collaborative research studies inside and outside of Arizona.

2. To leverage our imaging resources in the early detection and tracking of related diseases (e.g., chronic traumatic encephalopathy [CTE].

3. To implement, test and use PET radiotracer techniques (e.g., for the assessment of amyloid and tau pathology) in the study of AD and related disorders.

4. To develop image analysis techniques and composite cognitive test scores with improved power to detect and track AD and evaluate AD-modifying and prevention therapies.

5. To accelerate the evaluation of AD prevention therapies through API's preclinical AD trials and enrollment registries.

6. To introduce a new approach for the early phase evaluation of APOE and other AD-modifying drug and gene therapies using CSF and blood-based biomarkers in biomarker positive persons.

7. To support the evaluation of non-medication prevention therapies that are intended to promote cognitive health.

8. To advance the science of research participant engagement and AD study participation, including in under-represented groups.

9. To share data and biological fluid samples with the research community, establish a public resource of blood samples from thousands of well characterized persons, help the field develop and test find blood tests for AD and related disorders as soon as possible, advance the roles of blood-based biomarkers in research, treatment evaluation and clinical care, and advance the complementary research goals of our partners inside and outside Arizona.

10. To provide a care model that more fully address the needs of patients and families and BAI, and to develop and test the cost-effectiveness of a dementia care program that better addresses the needs of patients and family caregivers in the Banner Health Accountable Care Organization in the Banner Dementia Care Initiative.

11. To support the clinical research and Native American outreach, education and enrollment goals of the Arizona ADCC.

12. To promote the further development, productivity, and close working relationships of research programs involved in the fight against AD and related disorders.

BANNER ALZHEIMER'S INSTITUTE
Key Personnel

Name	Degree	Project Role
Reiman, Eric	MD	Executive Director, BAI Director, Arizona Alzheimer's Consortium (AAC) and NIA-supported Arizona ADCC
Tariot, Pierre	MD	Director, BAI
Langbaum, Jessica	PhD	Director, Alzheimer's Prevention Initiative (API)
Alexander, Robert	MD	Sr. Director, Chief Scientific Officer, API
Anderson, Allan	MD	Director, BAI Tucson
Amador, Ricardo	MS	ADCC Data Coordinator
Autry, Lynn	BS,BA	Psychometrist
Bandy, Dan	MS, CNMT	PET Technical Director and Sr. Scientist
Bauer III, Robert	BS	IT Systems Analyst
Boker, Connie	BS, MBA	Director, BAI Imaging Center
Chen, Kewei	PhD	Sr. Scientist, Computational Image Analysis
Chen, Yinghua	MS	Bioinformatics Analyst, Computational Image Analysis
Copeland, Jacquelynn	PhD	Neuropsychologist
Craig-Muller, Jennifer	BS	Clinical Research Program Senior Manager Director, All of Us Research Program
DiLise-Russo, Marjorie	MA	Senior Psychometrist
DeMarco Kathryn	BS	Clinical Research Program Manager
Devadas, Vivek	BS	Information Analyst, Computational Image Analysis
Ghisays, Valentina	PhD	Bioinformatics Scientist
Gonzalez-Green, Ricquee	BS	Clinical Research Assistant
Gopalakrishna, Ganesh	MD	Associate Director, Stead Family Memory Center
Goradia, Dhruman	PhD	Bioinformatics Scientist
Guarneri, Briley	BS	Clinical Research Assistant
High, Nellie	M.Ed	Clinical Research Program Mgr, API
Jaeger, Chad	BS	Senior Director, COO BAI
Jakimovich, Laura	RN	Multi-Center Clinical Trials Manager
James, Michelle	PsyD	Neuropsychologist
Jansen, Willemijn	PhD	Post-Doctoral Fellow (Part-Time)
Koren, Andrei	PhD	Senior Scientist, Lab Head Radiochemistry Research
Langbaum, Jessica	PhD	Director, Alzheimer's Prevention Initiative

Name	Degree	Project Role
Langlois, Carolyn	MA	Clinical Research Program Manager
Lee, Wendy	MS	Senior Manager, Research Bioinformatics
Lomay, Nicole	BS	Native American Outreach Representative
Luo, Ji	MS	Bioinformatics Analyst, Computational Image Analysis
Patel, Roma	MS	Clinical Trials Senior Manager
Pruzin, Jeremy	MD	Physician
Madrid, Mayra	BS	Clinical Research Coordinator
Malek-Ahmadi, Michael	PhD	Bioinformatics Scientist
Martinez, Laura	BS	Phlebotomist
Nisson, Lori	MSW, LCSW	Director, Family & Community Services
Ochoa, Cassandra	RDN	Clinical Research Program Mgr, API
Pandya, Sachin	BS	Clinical Research Coordinator
Parkhurst, David	BS	Clinical Research Coordinator
Perrin, Allison	MD	Physician Dementia Specialist
Protas, Hillary	PhD	Bioinformatics Scientist
Rainey, Charlie	BS	Phlebotomist, BAI Tucson
Saner, Don	MS	Senior Director, Data Science; Director, ADCC Data Management and Statistics Program
Sipes, Joshua	BS	Clinical Research Program Mgr, BAI Tucson
Su, Yi	PhD	Director, Computational Brain Imaging Analysis Program; Co-Director, ADCC Data Management and Statistics Program
Taha, Basel	BS	Clinical Research Assistant
Tsai, Po-Heng	MD	Physician Dementia Specialist, Memory Center
Vadovicky, Sheila	MSW	Senior Psychometrist
Ward, Alison	BS	Clinical Research Coordinator
Weidman, David	MD	Associate Director, BAI Clinical Trials

BARROW NEUROLOGICAL INSTITUTE
at St. Joseph's Hospital and Medical Center
Institutional Abstract

Barrow Neurological Institute (BNI) researchers conduct human, animal and other laboratory research studies that can be translated into clinical care. Its researchers continue to advance the study of Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and related neurodegenerative diseases like frontotemporal dementia (FTD). It has placed emphases on the study of AD and related disease mechanisms, including those that could be targeted by new treatments, the early detection and prevention of AD, and the evaluation of promising AD treatments in clinical trials. They have capitalized on the use of innovative brain imaging methods to advance some of its goals in people and laboratory animals, and they have developed innovative ways in which to engage and support the participation of research participants from the Latino community and other underserved groups in the fight against AD. They have sought to discover, confirm or refute hypothesized cellular and molecular mechanisms underlying AD and other neurodegenerative diseases, help detect, track and support the diagnosis of these disorders in their earliest preclinical and clinical stages, and help find effective treatments for these diseases as soon as possible.

In the past few years, neurodegenerative disease research at BNI has benefitted from the addition of accomplished senior and promising junior investigators. The number of researchers, and the laboratory and clinical resources needed to support them, will continue to grow.

Arizona Alzheimer's Consortium (AAC) funds have been used by BNI to develop the **H**ispanic **E**nrollment in **A**lzheimer's **R**esearch **T**rials (the **HEART** Program at BNI) 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 relevant studies. Matching funds from the Barrow Neurological Foundation have been used to support pilot research project awards, including those related to the validation of synapse loss by immunohistochemistry in FTD, the assessment of diagnostic and potential prognostic value of finger tapping abnormalities in adults with memory complaints, the comparison of gene expression profiles of the blood-brain barrier in AD, FTD, and a form of ALS with associated FTD (ALS-FTD), and collaborations with researchers from BNI and other AAC institutions.

Dr. Rita Sattler's laboratory is focused on the elucidation of neurodegenerative disease mechanisms in ALS, FTD and other Alzheimer's disease related dementias. Based on a strong translational research background, including time spent working for a small biotech startup company, Dr. Sattler uses patient-derived induced pluripotent stem cell (iPSC) models of varying subtypes of neurons and glia cells to study cellular and molecular changes that occur during disease manifestation and progression with the ultimate goal of identifying novel therapeutic targets. Recent studies are focused on the role of RNA binding proteins ADAR2 and TDP-43 and their contribution to aberrant disease-mediated RNA editing and splicing, respectively. In addition, the Sattler laboratory has established iPSC microglia-neuron co-culture models to study the impact of the neuro-immune axis on cortical neuronal degeneration observed in dementias, including FTD and AD. Finally, Dr. Sattler is greatly interested in the mechanisms of synapse damage and loss which is observed in AD and FTD, but also other neurodegenerative disease accompanied by cognitive impairments, such as ALS and PD. The lab is modeling these pathologies using patient-derived iPSC neuronal cultures and is testing novel spine regenerating agents in collaboration with a small biotech

company to generate preclinical data sets for future clinical trials. These studies are accompanied with the development and use of a PET tracer to image spine loss and damage in cognitively impaired patients.

Dr. Elliott Mufson is an Institutional Professor in the Division of Neurobiology at Barrow Neurological Institute. Dr. Mufson is the director of several active grants, including a National Institute on Aging-supported Program Project grant entitled the "Neurobiology of Mild Cognitive Impairment (MCI) in the Elderly" and a Department of Defense grant to study brain trauma. Dr. Mufson is a pioneer in the application of single cell gene array technology to study the genetic signature of neurons during the progression of AD. He has published 257 peer-reviewed articles and more than 40 book chapters. In 2010, the Information Sciences Institute recognized Dr. Mufson as one of the 100 most highly cited researchers in neuroscience.

Dr. Fredric Manfredsson also recently joined BNI. His work focuses on the application of viral vectors in the study of and treatment of Parkinson's disease and related neurodegenerative disorders. A significant portion of Dr. Manfredsson's research program focuses on the protein alpha-synuclein and its role in disease and normal brain function. His lab has focused on engineering and characterizing recombinant Adeno-Associated Virus (rAAV) and Lentiviral vectors for the delivery to both the central and peripheral nervous system or cells in vitro. This includes the rational engineering of novel viral capsids and expression cassettes, or the use of molecular evolution to generate large AAV libraries. The Manfredsson laboratory then utilizes these engineered vectors to study, and treat, pathological molecular processes in neurodegenerative disease, such as Parkinson's disease and Alzheimer's disease.

BARROW NEUROLOGICAL INSTITUTE
at St. Joseph's Hospital and Medical Center
Key Personnel

Name	Degree	Project Role
Burke, Anna	MD	Karsten Solheim Chair for Dementia & Director of Neuropsychiatry
Wicklund, Meredith	MD	Neurologist
Geda, Yonas	MD	Behavioral Neurologist, Psychiatrist
Baena, Elsa	PhD	Neuropsychologist
Prigatano, George	PhD	Neuropsychologist
Elliott, Carol	BS	Manager, Biobank Core Facility
Neylon, Lizzi	BS	Coordinator, Biobank Core Facility
Bakkar, Nadine	PhD	Neuroscientist
Quarles, Chad	PhD	Professor, Neuroimaging Research
Garcia, Angelica	MS	Study Coordinator
Al-Asmer, Jamileh	MBS	Study Coordinator
Batchuluun, Dawn	BS	Program Administrator
Snell, Margeaux	MD	Study Coordinator
Hanson, Krista	PhD	Neuropsychologist
Vadovicky, Sheila	BS	Psychometrist
Heimerl, Shaina	BS	Psychometrist
Prigatano, George	PhD	Neuropsychologist
Stokes, Ashley	PhD	Assistant Professor, Neuroimaging Research
Bergamino, Mauricio	PhD	MR Research, Keller Center for Imaging Innovation
Steffes, Lori	--	Study Coordinator
Sattler, Rita	PhD	Neuroscientist
Bowser, Robert	PhD	Professor and Chair of the Department of Translational Neuroscience
Mufson, Elliot	PhD	Professor, Neurobiology
Perez, Sylvia	PhD	Associate Professor, Neurobiology
Manfredsson, Fredric	PhD	Associate Professor, Neurobiology

BANNER SUN HEALTH RESEARCH INSTITUTE
Institutional Abstract

Banner Sun Health Research Institute (BSHRI) was established in 1986 in the heart of Sun City, Arizona, the nation's first planned retirement community, including more than 100,000 older adult residents in the area, and intended to make a profound difference in the scientific study of Alzheimer's disease (AD) and Related Dementias (ADRD), Parkinson's disease (PD), other age-related brain disorders, and healthy aging.

BSHRI includes: **a)** A world-renowned **Brain and Body Donation Program (BBDP)** for the study of AD/ADRD, PD, related disorders, cancer and aging; **b) Comprehensive, multidisciplinary and integrated clinical centers and programs** in cognitive, memory and movement disorders that provide coordinated world-class care and services that include subspecialist clinicians and staff from The Cleo Roberts Cognitive & Memory and Movement Centers, The Division of Neuropsychology, Family and Community Services, and the Neuro Wellness Program; **c)** More than 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 nearly 1,489 research participants (641 active), including 242 individuals of age 85 or older and 124 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 (>430 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 >130 education programs per year (nationally, internationally, regionally and locally) and leadership in world-renowned continuing education programs; training in neuropsychology for students and post-doctoral fellows; neurology residents; a highly productive summer research internship program for under-represented and other college and high school students, and partnerships with Sun Health Foundation and other stakeholders in this highly concentrated community of active older adults; **f)** Leadership roles and close working collaborations and relationships with AD/ADRD and movement disorders consortia, clinicians, scientists, educators, public health advocacy groups and organizations throughout Arizona and around the world; and **g)** Where historically, the state's largest number of productive basic scientists in the fight against AD, who are 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; these basic science programs have now completed 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.

The world renowned BBDP, directed by Thomas Beach, MD, PhD, includes ~ 900 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-hour post-mortem interval allowing unusually high tissue quality, optimizing post-mortem discovery research on the >2,000 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 >700 expired

donors since 2005, and the opportunity to relate brain pathology to biological features of other body organs; and **d)** approximately 200 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 of 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, previously at Banner Alzheimer's Institute, now full-time at BSHRI; Dr. Alireza Atri, Co-I) of an ultrasound lumbar puncture (LP) program (58 LPs performed as part of the program since July 2019); **d)** Successful launch and expansion of the Brain Health Check-In (BHCI) community service program at the Center for Health Aging; since December 2018 these walk-in or scheduled BHCIs have provided > 430 individuals with free brain health concern status assessments along with feedback, information, education, resources and referrals; (Featured in 2019 on Channel 10 Fox News; see link: http://www.fox10phoenix.com/news/arizona-news/free-test-at-banner-can-let-you-see-how-healthy-your-brain-is); **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 2019-20, 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 >130 international, national, regional, and community presentations per year; BSHRI staff provided >12,000 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 2019 see link: https://cmeregistration.hms.harvard.edu/events/dementia-a-comprehensive-update/event-summary-ff22ba91677f4bc8b0df67daffb28240.aspx?dvce=1; and **g)** Expanding the BBDP in impactful ways, including achieving an increase of enrollment to ~900 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).

BANNER SUN HEALTH RESEARCH INSTITUTE
Key Personnel

Name	Degree	Project Role
Adams, Debra	--	Research Scheduler, Center for Healthy Aging
Arce, Richard	--	BBDP Pathology Technician
Arch, Autumn	--	Post-Doctoral Fellow, Neuropsychology
Atri, Alireza	MD, PhD	Director, Banner Sun Health Research Institute
Auman, Briana	PysD	Neuropsychologist
Beach, Thomas	MD, PhD	BBDP & Neuropathology Core Director, Neuropathologist
Beh, Suet Theng	PhD	Postdoctoral Fellow
Belden, Christine	PsyD	Director, Neuropsychology
Borja, Claryssa	--	BBDP Pathology Technician
Brown, Victoria	--	Clinical Research Assistant
Bunkley, Latasha	--	Clinical Research Assistant
Choudhury, Parichita	MD	Physician - Dementia
Cipriani, Dana	--	Clinical Research Rep
Cline, Carol	--	Psychometrist Coord
Cline, Madison	--	BBDP Pathology Technician
Davis, Kathryn	--	Psychometrist
De Santiago, Stephanie	DNP	Nurse Practitioner
Dhanani, Sara	MD	Movement Disorders Neurologist
Evans, Brittani		Neuropsychology Assistant
Glass, Michael	--	BBDP Pathology Technician; Psychometrist
Goldfarb, Danielle	MD	Neuropsychiatrist (dual Neurologist/Psychiatrist)
Intorcia, Anthony	--	Associate Manager, BBDP Pathology
Keane, Marissa	--	Clinical Research Assistant
Kemperman, Marissa	--	Psychometrist
Kuramoto, Angela	RT, MHA	Senior Manager, BBDP & Center for Healthy Aging
Liebsack, Carolyn	RN, BSN	Clinical Trials Program Operations Director Center for Health Aging
Long, Kathy	--	Clinical Research Rep
Lue, Lih-Fen	PhD	Senior Scientist, Human Cells Core for Translational Research, BBDP
MinerRose, Daneva	--	Clinical Research Coordinator
Moorley, Naudia	PsyD	Neuropsychologist

Name	Degree	Project Role
Nelson, Courtney	--	BBDP Pathology Technician
O'Connor, Kathy	MS	Outreach Program Manager/Longevity Program Coordinator
Oliver, Javon	--	BBDP Pathology Technician
Papa, Jaclyn	--	BBDP Pathology Technician
Powell, Jessica	PsyD	Neuropsychologist
Quinones, Patricia	--	Research Scheduler
Rangel, Amy	--	Phlebotomist
Reade, Marina	FNP	Nurse Practitioner
Roye, Lisa	--	Psychometrist
Sahagun, Anela	--	Research Scheduler
Schmitt, Andrea	BS, CRA	ADCC Administrative Director
Serrano, Geidy	PhD	Director, Civin Laboratory for Neuropathology, BBDP
Shaikh, Farah	--	Clinical Research Assistant
Shprecher, David	DO	Movement Disorders Program Director; Neurologist
Sue, Lucia	BS	Coordinator and Tissue Donation Manager, BBDP
Suszczewicz, Katie	--	BBDP Pathology Technician
Teran, Marlene	--	Clinical Research Assistant
Vargas, Daisy	--	BBDP Pathology Technician
Walker, Jessica	--	BBDP Pathology Technician

CRITICAL PATH INSTITUTE
Institutional Abstract

Critical Path Institute (C-Path) is a nonprofit, public-private partnership with the U.S. Food and Drug Administration (FDA) created under the auspices of the FDA's Critical Path Initiative program in 2005. C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies. These pre-competitive standards and approaches have been termed "drug development tools" (DDTs) by the FDA, which established a process for official review and confirmation of their validity for a given context of use. C-Path orchestrates the development of DDTs through an innovative, collaborative approach to the sharing of data and expertise. We build consensus among participating scientists from industry and academia with FDA participation and iterative feedback. The process culminates in a formal application to FDA for official "qualification" of the DDT for a given use in product development. Qualified DDTs then become open standards for the scientific community which, in turn, may be assured both of the scientific rigor under which they were developed and of the FDA's understanding and acceptance of their validity.

The Critical Path for Alzheimer's Disease (CPAD) consortium accelerates drug development for patients with chronic neurodegenerative disease leading to dementia, primarily Alzheimer disease, by advancing Drug Development Tools (DDTs) for evaluating drug efficacy and safety, working with industry and advocacy organizations to optimize novel clinical trial designs, and aggregating anonymized patient-level data using CDISC consensus standards to facilitate the regulatory review process.

CPAD is collaborating with industry, regulators, academia and philanthropic donors to leverage the wealth of drug development knowledge that the consortium members (industry members as well as academic researchers) possess, by enabling pre-competitive widespread data sharing from clinical trials in AD and contribute directly to the availability of new effective treatments for AD by focusing on the tools and knowledge needed to support successful drug development. By expanding CPAD's existing database and by enabling a rich clinical trial repository, CPAD will contribute directly to the generation of actionable solutions for drug development across the AD continuum. This database will drive the potential for scientific discovery provided by aggregated and standardized primary clinical trial data and resulting quantitative tools will, in turn, provide solutions to optimize the design of clinical trials of AD drugs intended for regulatory review in support of marketing approval.

CRITICAL PATH INSTITUTE
Key Personnel

Name	Degree	Project Role
Sivakumaran, Sudhir	PhD	PI, Executive Director, Critical Path for Alzheimer's Disease
Burton, Jackson	PhD	Executive Director, Quantitative Medicine
Hanan, Nathan	PharmD	
Karten, Yashmin	PhD	
Romero, Klaus	MD	
Molnar, Vanda	--	
Priest, Eileen	--	

MAYO CLINIC ARIZONA
Institutional Abstract

The main goal of this research program is to determine the correlation between genetic risk for Alzheimer's disease (apolipoprotein E [APOE] genotype) and the effect of normal aging on certain measures of cognitive function, brain volume, brain metabolism, cerebral amyloid deposition, and potential plasma biomarkers (APOE fragments and others). It supports and extends our goals and efforts in our NIA funded Alzheimer's Disease Research Center in which Dr. Caselli serves as the Associate Director as well as Clinical Core Director. The principal institutions involved in this collaborative research effort are Mayo Clinic Arizona (primary site), Banner Alzheimer Institute, Barrow Neurological Institute, Arizona State University, The University of Arizona, and Translational Genomics Research Institute though as the program has matured, it has evolved into a core resource for investigators from these and other institutions as well. Our research program capitalizes on the clinical and neuropsychological expertise of the Behavioral Neurologists and Neuropsychologists at Mayo Clinic Arizona, in conjunction with the genetic expertise of Drs. Rosa Rademakers and Matthew Baker at Mayo Clinic Jacksonville. We have extended our efforts into the basic neuroscience realm through the addition our first bench neuroscientist, Dr. John Fryer who joined us from Mayo Clinic Jacksonville. Over the past year through additional philanthropic support we have performed whole genome sequencing on the 527 members of this cohort for who we had stored DNA further fostering collaboration and extending our range of scientific inquiry.

Our longitudinal study design is a unique strength with our longest participants having been followed for nearly 25 years. Cognitive and related behavioral data are analyzed with regard to demographic and health related factors (e.g., hypertension), APOE genetic status, physical and psychological stressors, cognition, and brain imaging measures. We have shown the neuropsychologically defined onset of Alzheimer's disease begins during our 50's in APOE e4 carriers, is confined to memory during the early preclinical phase but there is an increase in self-awareness of decline that is not mirrored by informant observation. In later stages of preclinical Alzheimer's disease, as patients get within a few years of incident MCI conversion, executive measures begin to decline and informant observations begin to parallel self-reports of decline. Finally, by the time MCI emerges, memory, executive skills, and in some cases visuospatial skills begin to decline; and subtle personality changes begin characterized by increased proneness to stress and reduced openness to new ideas and experiences. Missing from the preclinical profile is any indication of depression, but the development of personality changes lays the groundwork for behavioral manifestations which begin to emerge during the MCI stage.

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

To date we have:

1. Analyzed the longitudinal trajectories of all our measures, identified those showing significantly greater acceleration of decline in APOE e4 carriers relative to noncarriers, and developed a cognitive profile of APOE e4 driven pathological aging that defines the cognitive profile of preclinical Alzheimer's disease.
2. Compared our incident cases of mild cognitive impairment (MCI) to a clinical (prevalent) group of matched patients to further define an early and late preclinical/early clinical phase in which we begin to see decline in non-memory measures, especially those sensitive to executive functions.

3. Characterized the significance of subjective impairment as voiced by one's self as well as by one's informant and showed that both reflect an early stage of decline in a small subset, but that stress related symptoms overshadow the cognitive changes so that subjective impairment alone is an unreliable indicator of imminent decline.
4. Showed that personality traits that increase one's proneness to stress further speed up age-related memory decline, and this effect is more apparent in APOE e4 carriers reflecting their inherent predilection for Alzheimer's disease. In contrast we found that the developmental sex-based cognitive advantages of women over men regarding verbal memory and men over women regarding visual memory do not buffer the rate of decline associated with APOE e4.
5. Explored several computer-based cognitive tasks, but we have not yet found any to be more sensitive than conventional neuropsychological measures of declarative memory.
6. Completed a survey both online as well as among members of our cohort examining attitudes about predictive testing for Alzheimer's disease (genetic and biomarker based) and found there is considerable interest in having such testing even in the absence of definitive therapy, but that roughly 12% and 6% respectively envision suicidal ideation should they be found at high risk for Alzheimer's disease. These results are informing the design of test disclosure methods in forthcoming trials.
7. Temporarily paused all in-person testing during the COVID pandemic until we received institutional clearance with appropriate safety precautions following CDC and Mayo Clinic guidelines and policies.

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 predictive model based on genomic and other presymptomatic parameters for the timing of symptomatic conversion
4. Informing the design of primary and secondary AD prevention clinical trials in cognitively unimpaired persons at genetic and/or biomarker risk
5. Providing a core resource to all our collaborative partners
6. Correlating nontraditional measures of neuropsychiatric status such as intellectual achievement, sleep patterns, and personality factors with presymptomatic cerebral amyloid levels
7. Determining the relative 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

This research proposal has been peer reviewed and approved by the Mayo Clinic Institutional Review Board (IRB #259-99).

MAYO CLINIC ARIZONA
Key Personnel

Name	Degree	Project Role
Caselli, Richard	MD	Principal Investigator, Clinical Core Director, Associate Director, Behavioral Neurologist
Woodruff, Bryan	MD	Co-Investigator, Behavioral Neurologist
Locke, Dona	PhD	Co-Investigator, Neuropsychologist
Stonnington, Cynthia	MD	Co-Investigator, Psychiatrist
Ezenne, Adaeze	NP	Nurse Practitioner
Henslin, Bruce	BA	Study Coordinator
Brostrom, Debra	BA	Study Coordinator
Baxter, Leslie	PhD	Neuroimaging Scientist
Fryer, John	PhD	Neuroscientist

MIDWESTERN UNIVERSITY
Institutional Abstract

Midwestern University is a university of health sciences dedicated to the education of future health professionals. Midwestern has Colleges of Osteopathic Medicine, Graduate Studies, Optometry, Dental Medicine, Podiatry, Pharmacy, Veterinary Medicine, and Health Sciences. There are also 13 additional programs including new Precision Medicine and Master of Public Health Programs. We have multiple university-based clinics including the Multispecialty Clinic, the Eye Institute, the Dental Institute, and the Companion Animal Clinic. Midwestern has a rapidly growing and diverse research community focused on disease-specific research as well as basic science research. Our scientists and clinicians (both human and veterinary) are involved in many different research efforts, with collaborations throughout Arizona and the US. Midwestern supports a broad range of research, from neurological disorders and cancer to infectious diseases and anatomical studies. The research environment at Midwestern is highly collaborative and designed to use the collective expertise of our colleagues to achieve common goals.

Multiple interdisciplinary research programs have been developed in the last few years and are thriving. The MWU Institute for Healthcare Innovation (IHI) 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.

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 test a drug which may be useful for modifying the cognitive outcome in patients.
3) Developing and validating new pharmacological treatments, such as norclozapine, that could have a positive impact on Alzheimer's disease and other neurological conditions, and support research on the cellular- and subcellular-targeted delivery of relevant treatments.
4) Evaluating the dysfunction within and contribution of various neurotransmitter systems in Alzheimer's disease and related disorders, such as Parkinson's disease, prominently including the nicotinic and muscarinic receptor systems of the brain.
5) 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.
6) Examining the involvement of inflammatory molecules in the pathophysiology of Alzheimer's disease, related disorders, and CNS injury.
7) Determining whether elevated APOE4 expression is linked to cerebrovascular dysfunction in in young and aged APOE4 mice, by measuring middle cerebral artery (MCA) function in APOE3 and APOE4 mice.
8) Studying exercise induced mitigation of cellular senescence as a peripheral control mechanism for Alzheimer's disease using a senescence-accelerated SAMP8 mouse model.
9) Studying the role of vitamin B12 deficiency in creating vulnerability to neurological disease using stroke outcome as a measure in aged mice.

MIDWESTERN UNIVERSITY
Key Personnel

Name	Degree	Project Role
Jentarra, Garilyn	PhD	Administrative PI, Project Principal Investigator
Abel, Kelsey	BS	Technician
Al-Nakkash, Layla	PhD	Principal Investigator
Anderson, Sarah	MOT/OTR	MAAC Investigator
Bae, Nancy	PhD	Principal Investigator
Broderick, Thomas	PhD	Principal Investigator
Call, Gerald	PhD	MAAC Investigator
Castro, Monica	BS	Technician
Christensen, Stephanie	PhD	MAAC Investigator
Chu, Ping	BS	Technician
Delgado Flint, Melissa	PsyD	MAAC Investigator
Eckman, Delrae	PhD	MAAC Investigator
Esfandiarei, Mitra	PhD	MAAC Investigator
Fitzgerald, Nancy	DDS	MAAC Investigator
Gonzalez, Fernando	PhD	Principal Investigator
Haley, Nick	PhD	MAAC Investigator
Halket, Christine	DDS	MAAC Investigator
Hernandez, Jose	PhD	MAAC Investigator
Huang, Vanthida	PharmD	Co-Investigator
Jadavji, Nafisa	PhD	Principal Investigator
Jones, Carleton	PhD	MAAC Investigator
Jones, Douglas	PhD	Co-Investigator
Jones, T. Bucky	PhD	Principal Investigator
Kaufman, Jason	PhD	MAAC Investigator
Knudsen Gerber, Dawn	PharmD	MAAC Investigator
Kozlowski, Michael	OD, PhD	MAAC Investigator
Lawson, Kathy	PhD	Co-Investigator
Li, Weidang	PhD	MAAC Investigator
Mody, Aaron	BS	Technician
Murthy, Ashlesh	PhD	MAAC Investigator
Olsen, Mark	PhD	MAAC Investigator

Name	Degree	Project Role
Pagan, Misty	DNP, APRN	MAAC Investigator
Potter, Pamela	PhD	Co-Investigator
Potter, Ross	PhD	Laboratory Manager
Powell, Jessica	PsyD	MAAC Investigator
Ratiu, Ileana	PhD	MAAC Investigator
Revill, Ann	PhD	MAAC Investigator
Rogers, Alexandra	BS	Technician
Shim, Minsub	PhD	Principal Investigator
Storjohann, Tara	PharmD	MAAC Investigator
Swanson, Mark	PhD	Principal Investigator
Tullot, Tony	MD	MAAC Investigator
Turner, Tamara	EdD, OTR	Principal Investigator
Vallejo-Elias, Johana	PhD	MAAC Investigator
Veltri, Charles	PhD	MAAC Investigator
Weissig, Volkmar	PhD	Principal Investigator
Yevseyenkov, Vladimir	OD, PhD	MAAC Investigator

NORTHERN ARIZONA UNIVERSITY
Institutional Abstract

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 colonies of multiple murine models of single and 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). NAU and TGen North, located approximately one mile apart, share a sequencing core comprising three Illumina MiSeq machines, an Illumina MiniSeq, an Illumina NextSeq, and a MinION (Oxford Nanopore). The Joint 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 microbiome research[1,2], 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 [3], and on exploring the potential of features of the human oral microbiota for early cancer detection[4,5]. 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;[6]), a microbiome bioinformatics platform. Key features of QIIME 2 are that this platform is specifically designed for analysis of the type of data being generated in this project, and the platform is focused on ensuring reproducibility and transparency of microbiome analysis. 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
Key Personnel

Name	Degree	Project Role
Cope, Emily	PhD	PI and Project Director
Caporaso, J Gregory	PhD	PI
Keim, Paul	PhD	Executive Director, PMI
Bolyen, Evan	BS	Research Software Engineer
Borsom, Emily	BS	Graduate Student
Conn, Kathryn	BS	Undergraduate Researcher
Testo, George	--	Undergraduate Researcher
Jaramillo, Sierra	MS	Graduate Student
Keefe, Chris	BS	Student Research Software Engineer
Lee, Keehoon	PhD	Postdoctoral Scholar
Gu, Haiwei	PhD	Consultant (metabolomics)

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
Institutional Abstract

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.

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
Key Personnel

Name	Degree	Project Role
Alsop, Eric	PhD	Computational Scientist
Antone, Jerry	BS	Research Associate
Bonfitto, Anna	MS	Research Associate
DeBoth, Matthew	BS	Bioinformatician
Elyaderani, Amir	BS	Bioinformatician
Hutchins, Elizabeth	PhD	Computational Scientist
Huentelman, Matthew	PhD	Principal Investigator
Jepsen, Wayne	MS	Graduate Student
Lechuga, Cynthia	MBA	Sr. Grants & Contract Administrator
Lewis, Candace	PhD	Postdoctoral Fellow
Moore, Bethine	BA	
Meechovet, Bessie	BS, BSN	Research Associate
Naymik, Marcus	MS	Bioinformatician
Piras, Ignazio	PhD	Research Assistant Professor
Reiman, Rebecca	BA	Research Associate
Robles, Laura	MBA	Project Accountant
Talboom, Joshua	PhD	Postdoctoral Fellow
Van Keuren-Jensen, Kendall	PhD	Co-Investigator

UNIVERSITY OF ARIZONA
Institutional Abstract

Researchers at the University of Arizona (UA) are engaged in collaborative, multi-disciplinary programs of research focused on advancing our understanding of the major risk factors for brain aging and age-related neurodegenerative disease, their underlying neural substrates, and ways to prevent, delay, or treat cognitive aging and dementia. To accomplish these goals, UA investigators representing 12 departments and institutes that encompass the fields of neuroimaging, engineering, cognitive and behavioral neurosciences, neuropsychology, psychiatry, neurology, pharmacology, physiology, and statistical analysis are involved in these research programs. Projects apply a range of scientific approaches from basic neuroscience to cognitive science to clinical intervention in studies that translate across human and non-human animal models of aging and age-related disease. A major component of this research uses magnetic resonance imaging (MRI) as a cross-cutting method to measure brain function, structure, and connectivity in aging and age-related neurodegenerative disease.

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 new behavioral and neuroimaging methods 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 6) creating libraries and repositories for data sharing.

This program of research is complemented by our close ties to other research units at UA including the **Evelyn F. McKnight Brain Institute**, studying the longitudinal effects of aging on memory processes in older adults with and without increased risk for AD, and the **Center for Innovation in Brain Sciences,** focusing on the development of pharmacological interventions for degenerative brain diseases. UA researchers participate in complementary efforts to support the Arizona ADC 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:

New method development: MRI, biomarkers, and shared resources. Over the past few years, we continue to build the resources required for sharing standardized measurements that are be made available to all AAC researchers, utilizing XNAT, a shared online repository for neuroimaging data that is funded by the NIH. The complexity and high cost of collecting large-scale datasets highlights the importance of sharing data across laboratories. The database will include neuropsychological, neuroimaging, and biospecimen data obtained from well-characterized older adults. Standardized pipelines for MRI data analysis and protocols for collection of biomarkers from blood and CSF have also been successfully established.

Our researchers continue to develop and implement new MRI techniques and statistical analysis methods that may prove useful in examining brain structure, function, connectivity, and pathology in both human and non-human animal models of aging and age-related disease. MRI methods

including high-resolution structural imaging, fMRI, diffusion, perfusion, and resting state connectivity are being utilized to better understand the neural basis of memory and other cognitive changes across the normal adult lifespan, and compensatory or adaptive strategies that lead to better memory function. Over the past year, relevant pilot studies have:

- explored MRI-guided transcranial magnetic stimulation to ameliorate memory impairment in patients with MCI,
- employed new algorithms for identifying cognitively significant silent brain infarcts (CS-SBIs) on MRI, identifying the characteristics of SBIs that affect cognition and determining the impact of cerebral blood flow and patterns of brain connectivity on SBIs and cognitive changes,
- optimized a quantitative MRI microscopy acquisition battery and analysis pipeline that uses diffusion MRI and relaxometry techniques to quantify brain microstructure in fixed brains from a colony of behaviorally-characterized aged macaque monkeys,
- performed regional assessments of brain microstructure in aged macaques to characterize each individual animal's unique anatomical pattern of age-associated microstructural change,
- completed the processing and analysis of anatomical and diffusion MRI data of 114 rats collected within two NIH R01 grants, comparing behavior with regional brain volumes and diffusion parameters within white matter tracts relevant for memory and AD, and
- developed behavioral biomarkers of brain aging and AD from wearable technologies to assess sleep quality and physical activity, in order to determine how these measures related to cognitive functioning as well as postmortem brain pathology.

Early detection and risk factors for AD. A major theme of our research continues to focus on the early detection, diagnosis, and tracking of cognitive and psychological impairments associated with aging and Alzheimer's disease (AD). Several novel targets include subtle memory changes associated with hippocampal and perirhinal cortical functions, disturbances in patterns of daily thought, positive emotion, sleep quality and physical activity, and preclinical changes in MRI connectivity that may signal the effects of AD pathology prior to the onset of significant cognitive symptoms and changes in activities of daily living. Over the past year, multiple projects focused on identifying and understanding the factors that increase risk for age-related cognitive impairment and AD, including:

- understanding how positive emotional memories relate to mood and depression among older adults, and how e4 may increase risk for poor emotional regulation,
- exploring the qualities and themes that are retrieved by Hispanic/Latinos and non-Hispanic whites while creating autobiographical past narratives, and whether the qualities of future thinking may be differentially related to risk for AD in these two race/ethnic groups,
- recruiting a large cohort of individuals who have experienced COVID-19, confirmed by seropositivity and establishing baseline measures of cognitive and immune functioning to begin longitudinal follow-up in order to determine the impact of COVID-19 on trajectories of cognitive aging, and
- determining whether selective decreases in the fidelity of PRC-hippocampal connectivity and increases in PHC-hippocampal connectivity underlie age-related impairments in object and scene processing using high-resolution hippocampal imaging.

Neural mechanisms and interventions. Researchers at UA are studying various potential targets for intervention and neuroprotective mechanisms. Each study has the potential to lead to novel interventions that may decrease risk for AD, slow the progression of the disease, and ameliorate cognitive impairments associated with normal aging and AD. These include:

- development of a Drosophila model co-expressing two AD relevant proteins: TDP-43 and Tau, in order to phenotypically characterize Tau/TDP-43 co-expressing Drosophila flies and test the hypothesis that TDP-43 and Tau directly interacts to promote AD pathology, and

- performing an ELISA assay for tau on 40 CSF postmortem patient samples from patients with varying degrees of AD severity, compared to a technique known as FLOWER (frequency locked optical whispering evanescent resonator) which is capable of ultra-sensitive and label-free detection of analytes down to the single molecule level

Additional Progress in the fight against AD. In addition to these efforts, UA researchers continue to generate important findings, publications, and NIH grants related to the evaluation of AD mechanisms, risk factors, and molecular mechanisms, the detection and tracking of AD using brain imaging, biological fluid and digital biomarkers, and the evaluation of interventions that may impact risk of AD or age-related cognitive decline. UA has also established close working relationship with Banner Alzheimer's Institute—Tucson (BAI-T) to help in the clinical and biomarker characterization of research participants in relevant AD and normal brain aging studies and support the evaluation of promising AD-modifying treatments.

UNIVERSITY OF ARIZONA
Key Personnel

Name	Degree	Project Role
Ahern, Geoffrey	MD	Investigator; Neurology, Psychology, Psychiatry, Evelyn F. McKnight Brain Institute
Alexander, Gene	PhD	Investigator; Psychology, Psychiatry, Neuroscience, Evelyn F. McKnight Brain Institute
Andrews-Hanna, Jessica	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Barnes, Carol	PhD	Investigator; Psychology, Neurology, Neuroscience, Evelyn F. McKnight Brain Institute
Brinton, Robbie	PhD	Investigator, Center for Innovation in Brain Science, Pharmacology, Neurology, Psychology, Evelyn F. McKnight Brain Institute
Chen, Nan-Kuei	PhD	Investigator, Biomedical Engineering
Chou, Ying-hui	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Edgin, Jamie	PhD	Investigator; Psychology
Ekstrom, Arne	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute Investigator
Fernandez, Fabian	PhD	Investigator; Psychology, Neurology, Psychology, Evelyn F. McKnight Brain Institute
Gaffney, Kevin	PhD	Investigator, Pharmacology
Glisky, Elizabeth	PhD	Investigator Emeritus; Psychology, Evelyn F. McKnight Brain Institute
Grilli, Matthew	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Guzmán- Pérez Carrillo, Gloria	PhD	Investigator, Biomedical Engineers
Hay, Meredith	PhD	Investigator; Physiology, Psychology, Evelyn F. McKnight Brain Institute
Hishaw, G. Alex	MD	Investigator; Neurology, Psychiatry
Khanna, May	PhD	Investigator, Center for Innovation in Brain Science
Koshy, Anita	MD	Investigator; Neurology, Immunobiology, Evelyn F. McKnight Brain Institute
Matsunaga, Terry	PhD	Investigator, Medical Imaging
Mehl, Matthias	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Nikolich-Zurich, Janko	PhD	Investigator, Immunobiology, Arizona Center on Aging

Name	Degree	Project Role
Raichlen, David	PhD	Investigator; Anthropology
Rapcsak, Steven	MD	Investigator; Neurology, Psychology, Speech/Language and Hearing, Evelyn F. McKnight Brain Institute
Rodgers, Kathleen	PhD	Investigator, Center for Innovation in Brain Science
Ryan, Lee	PhD	Investigator; Psychology, Neurology, Neuroscience Program, Evelyn F. McKnight Brain Institute
Saranathan, Manojkumar	PhD	Investigator, Medical Imaging
Su, Judith	PhD	Investigator, Optical Sciences, Chemistry and Biochemistry
Trouard, Theodore	PhD	Investigator; Biomedical Engineering, Medical Imaging, Evelyn F. McKnight Brain Institute
Watts, George	PhD	Investigator, Pharmacology, Cancer Center
Weinkauf, Craig	MD, PhD	Investigator, Surgery
Wilson, Robert	PhD	Investigator, Psychology
Yin, Fei	PhD	Investigator, Center for Innovation in Brain Science
Zarnescu, Daniela	PhD	Investigator, Molecular & Cellular Biology, Neuroscience, Neurology
Zhou, Wei	MD	Investigator, Vascular Surgery

UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE – PHOENIX
Institutional Abstract

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 Biomedical Campus (PBC). The UA College of Medicine – Phoenix shares the PBC campus with the UA College of Pharmacy, UA 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 100 new allopathic doctors each year, with a class goal total of 120 students per class. 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 by the university with physicians and translational scientists to complete projects that cumulate 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 Translational Neurotrauma Research Program, a collaboration between the UA College of Medicine – Phoenix, Barrow Neurological Institute at Phoenix Children's Hospital, and the Phoenix VA Health Care System. The Translational Neurotrauma Research Program sets the goal to be the premiere destination for neurotrauma research, training, and collaboration. The program has attracted scientist trainees and physicians from multiple world-renowned institutes and will continue to grow and prosper under these strong collaborations. More recently, this program has engaged with partners from the Maricopa County Attorney's Office, Mesa Police Department, Tempe Police Department, HonorHealth Family Advocacy Center, Sojourner Center, and the CACTIS Foundation to establish the Maricopa County Collaboration on Concussion in Domestic Violence (MC3DV). Primary research directions for the program include inflammation, rehabilitation, and practical therapies for traumatic brain injury as a causative factor in challenging healthy aging and promoting neurodegenerative disease.

UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE – PHOENIX
Key Personnel

Name	Degree	Project Role
Giordano, Katherine R.	BS	CTS Graduate student
Griffiths, Daniel R.	BS	Research Specialist, Senior
Law, L. Matthew	PhD	Co-investigator, Lecturer
Lifshitz, Jonathan	PhD	PI, Professor, Director
Rojas Valencia, Luisa M.	MS	CTS Graduate student
Rowe, Rachel K.	PhD	Assistant Professor, Collaborator
Saber, Maha	PhD	Co-investigator, Post-doctoral fellow
Tallent, Bret R.	LATG	Laboratory manager

Project Progress Reports

Project Progress Reports
Arizona State University

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

An evaluation of the cognitive and neurobiological effects of the highly selective progestin segesterone acetate in a rat model of surgical menopause. Heather Bimonte-Nelson, PhD.
Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:
The specific aim of this project is to determine the effects of the progestin segesterone acetate on cognition and insulin-like growth factor-1 receptor brain profiles in a rat model of surgical menopause.

Background and Significance:
Synthetic progestogens, called progestins, are created to mimic the effects of endogenous progesterone and can be prescribed to women for various reasons. Our laboratory has demonstrated that progestogens can have varying cognitive effects, with some showing cognitive deficits, some show benefits, and some having a neutral effect. This variation has been shown in other labs as well. It has been shown that progestogens with strong progesterone receptor (PR) affinity are highly involved in neurogenesis and neuroprotection and may be cognitively beneficial. The progestin segesterone acetate is one such progestin that has a high affinity for the PR. The current project aims to cognitive effects of chronic administration of segesterone acetate (NES) in a rodent model of surgical menopause and to elucidate the relationship between behavioral outcomes and neurobiological markers of healthy cognitive aging including insulin-like growth factor-1 receptor (IGF-1R), which plays an important role in regulating neurogenesis in learning- and memory-related brain regions.

Preliminary Data, Experimental Design and Methods:
Fifty 12-month old virgin female Fisher344-CDF rats underwent ovariectomy (OVX) or sham surgery and two days later began randomly-assigned subcutaneous injection of either sesame oil Vehicle, MPA, NES low dose, or NES high dose. After 32 days of injections, animals were tested on a behavioral battery including Water Radial-Arm Maze (WRAM) to test spatial working and reference memory, Morris Maze to test spatial reference memory, and the Visible Platform task to test visual and motor acuity. Preliminary data are described below.

Proposed One-Year and Long-Term Outcomes:
Surgeries, progestin treatment, and behavior testing will be completed by the middle of the one-year project period. We expect to be scoring, analyzing, and writing the data into manuscript form soon after this time period, as well as completing brain assessments to correlate with behavioral data. Expected deliverables in a more long-term context include a manuscript submitted within two years from study initiation.

Year End Progress Summary:
The behavioral proportion of the proposed aims were completed. We found that OVX animals given NES exhibited impaired spatial memory on the WRAM task relative to OVX animals given Vehicle, and we replicated our memory impairment of the MPA treatment. Western blot analyses to determine differences in IGF-1R expression in the dorsal hippocampus are near complete, and analyses in the entorhinal cortex and frontal cortex are underway. The manuscript for this study has been started for the behavior portion of the work. When the western blot analyses are complete, they will be added to the paper, and the manuscript will be submitted. The aims are expected to be completed in the proposed time frame.

Using hiPSCs to investigate the protective mechanisms of the ApoEch mutation. David Brafman, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Use a TREE-based genome editing approach to introduce the ApoEch mutation into isogenic hiPSC lines with various ApoE genotypes. Recently, we reported the use of TREE-based editing approaches for the highly efficient generation of isogenic hiPSC lines from NDC and AD patients that only differ with respect to their ApoE genotype and not genetic background[1]. In this aim, we will use these gene editing strategies to introduce the ApoEch mutation into these isogenic hiPSCs. Engineered hiPSC lines will be extensively characterized to ensure a normal euploid karyotype, high expression of key pluripotency markers, tri-lineage differentiation potential, and absence of off-target edits.

Specific Aim 2: Examine the specific effect of ApoEch mutation on the mitigation of AD-related phenotypes in hiPSC-derived 3-D co-cultures. In this aim, the isogenic hiPSC lines generated in **Specific Aim 1** will be differentiated to establish 3-D cortical neural cultures. In turn, biochemical, cellular, and genetic methods will be used to determine the effect of the ApoEch mutation on the presence of AD-related phenotypes. Specifically, we will test if the ApoEch mutation exerts its AD-risk modifying effects through: (i) modulation of Aβ processing, secretion, or uptake, (ii) alteration in tau hyperphosphorylation and uptake, (iii) regulation of synaptic integrity, and (iv) protection against oxidative and neurotoxic stimuli.

Background and Significance:

Genome-wide association studies (GWAS) studies have identified several risk factors associated with altered probability of sporadic AD (SAD) onset[2]. Of these risk factors, polymorphism in the Apolipoprotein E (ApoE) gene, a lipoprotein transporter involved in cholesterol metabolism, is the strongest and most prevalent[3]. Compared to individuals with an ApoE ε3/ ε3 genotype, heterozygosity for the ε4 allele increases AD risk by 3 fold, and homozygosity for the ε4 allele increases risk up to 12 fold [4-6]. On the other hand, individuals with the ε2 allele are 40 percent less likely to develop AD[4-6]. Mechanistically, several amyloid-dependent and -independent mechanisms have been postulated to explain the risk-inducing ApoE4 effect[7,8] as well as the protective effects of ApoE2[9-12,13-17]. Recently, a rare variant of APOE previously associated with type III hyperlipoproteinemia[18]—the ApoE3 Christchurch (ApoEch) mutation (R136S)—was implicated in limiting neurodegeneration in a PSEN1 mutation carrier[19]. Preliminary analysis suggests that the protective effect of the ApoEch mutation might be mediated through HSPG-dependent pathways that limit the neuronal uptake of extracellular tau. Moving forward, precise understanding of the molecular mechanisms by which the ApoEch variant mitigates AD onset will be critical for developing targeted therapeutic interventions.

Preliminary Data, Experimental Design and Methods:

Generation of 3-D hiPSC-based cortical cultures. We have extensive experience in the manipulation of hiPSCs and development of protocols for their large-scale and reproducible directed differentiation towards neural and astroglial lineages[20-23]. Briefly, these optimized differentiation protocols lead to the generation of cells which express high levels of canonical astrocytic markers as well as display properties characteristic of functionally mature cells including production of APOE, responsiveness to inflammatory stimuli such as lipopolysaccharide, ability to uptake amyloid-β (Aβ), and appearance of robust slow-decaying calcium transients. In parallel, our optimized neuronal differentiation protocols result in populations that express high levels

mature neuronal-, neurotransmitter-, and cortical-related markers. In addition, these neuronal cultures display abundant rapid spontaneous calcium spikes indicative of functional maturation and synaptogenesis. Finally, RNA-seq analysis confirms that these differentiation protocols result in distinct neuronal and astrocyte populations free from contaminated hNPC populations. Together, our ability to generate pure populations of neurons and astrocytes that can subsequently be dissociated and re-cultured in defined ratios provides a unique ability for control and reproducibility.

Rapid and highly efficient generation of isogenic hiPSC lines. Current methods to generate isogenic hiPSC lines rely on the introduction of CRISPR-induced double stranded DNA breaks (DSBs) followed by homology directed repair (HDR). However, such approaches are challenging in hPSCs with efficiencies reported in the range of 1-10% depending on the gene targeted[24-27]. To that end, we have recently developed a series of methods that employ transient reporters of editing enrichment (TREE) to facilitate highly efficient single base pair editing of human cells at precise genomic loci[28]. 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. We have demonstrated that these TREE-based strategies can be used for the generation of isogenic hPSC lines with clonal homozygous editing approaching 90%. In particular, we have previously used these TREE-based methods to generate isogenic hiPSCs with various ApoE genotypes[1]. In this proposal, we will use similar strategies for the **highly efficient** introduction of the ApoEch mutation (a C→A base pair conversion at the APOE(R136) locus) into our isogenic hiPSC lines with various ApoE genotypes.

Experimental Designs and Methods

Specific Aim 1: Using our TREE approach, we will generate isogenic sets of hiPSCs that have been modified with the ApoEch mutation. For this proposal, we will focus on the generation of such sets from NDC and FAD hiPSCs that we have previously used TREE-based genome engineering to generate isogenic lines with various ApoE genotypes. As such, we will not only be able to investigate the contribution of the ApoEch mutation on the modulation of AD-related phenotypes but also the association that such a contribution has with each ApoE genotype. HiPSC lines will be analyzed as we have previously described[1,29-31] for (i) characteristic hiPSC cell morphology, (ii) expression of pluripotency markers OCT4, NANOG, and SOX2 (iii) ability to differentiate in vitro into populations representative of the three main germ layers, and (iv) a normal complement of 46 chromosomes. In addition, using a prediction program[32] we will sequence the most likely off-target sites to ensure no off-target mutagenesis.

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 p-tau and subsequent synaptic and neuronal loss. To that end, several studies have suggested that the AD-risk modulating effects of ApoE occurs at multiple levels this amyloid cascade, although several-independent mechanisms have been postulated to explain the risk-inducing ApoE effect as well[7,8]. Specifically, ApoE has been shown to modulate the following cell-intrinsic and extrinsic phenotypes: (i) Aβ production, degradation, deposition and clearance, (ii) sensitivity to excitotoxic injury, (iii) protection against oxidative stress, (iv) modulation of inflammatory response, and (v) regulation of synaptic plasticity and integrity[33]. Interestingly, it has been speculated that the effect of the ApoEch mutation might be induced through mechanisms that limit tau pathology and neurodegeneration independent of amyloid deposition[19]. In this aim, we will use the isogenic lines generated in **Specific Aim 1** to begin to probe some of these potential mechanisms. First, we will differentiate these isogenic line to 3-D cortical cultures. In addition, to elucidate if observed ApoEch phenotypes are mediated through neurons, astrocytes, or both, we will also generate 3-D cultures that consist exclusively of neurons or astrocytes. Subsequently, we will examine these

cultures to test the hypothesis that ApoEch exerts its protective effect through modulation and release of toxic species by measuring levels of Aβ production, secretion, and oligomerization as well as tau phosphorylation and aggregation in the cultures. In parallel, we will test the hypothesis that the ApoEch mutation results in cell intrinsic changes that make cell populations less susceptible to AD-related toxic stimuli. Specifically, we will measure the following cell intrinsic properties: (i) cellular uptake of exogenous Aβ and tau, (ii) inflammatory response to administration of LPS, (iii) sensitivity to oxidative (i.e. hydrogen peroxide) and excititoxic (i.e. glutamate), and (iv) electrophysiological robustness and synaptic integrity.

Proposed One-Year and Long-Term Outcomes:

Through directly comparing neural cultures that only differ with respect to only ApoE genotype and the presence of the ApoEch mutation, we will be able to determine the extent to which ApoEch interaction with ApoE genotype modulates specific AD-related phenotypes. Although the proposed studies will not interrogate all the potential hypothesized mechanisms by which ApoEch modulates AD-risk, we will uncover clues that will set the stage for future more detailed studies. In this vein, the preliminary data and models that will be generated as part of this proposal will allow us to apply for more comprehensive grants to funding agencies (e.g. NIH, Alzheimer's Association, American Federation for Aging Research) to further mechanistically probe these links.

Year End Progress Summary:

We have recently developed a series of methods that employ transient reporters of editing enrichment (TREE) to facilitate highly efficient (>80%) single base pair editing of human cells at precise genomic loci[1,34-36]. As it relates to this project, we recently developed a new method called prime-induced nucleotide editing using a transient reporter for editing enrichment (PINE-TREE) employs a prime editor[37] for the targeted editing of an episomal blue fluorescent protein (BFP), which is converted to green fluorescent protein upon a C-to-T edit. More specifically, this BFP mutant contains a histidine at the 66th amino acid position encoded by a 'CAC' codon. The C-to-T conversion of that codon to a 'TAC' or 'TAT' will cause an amino acid change from a histidine to a tyrosine as well as a shift in the emission spectra of the modified protein resulting in a GFP variant. Thus, co-transfection of cells with this BFP construct (pEF-BFP), a prime editor (pEF-PE2), and a pegRNA targeting the 'CAC' codon in BFP will result in a BFP-to-GFP conversion in cells which the base editor machinery is present and actively functioning. Moreover, we showed that when cells were also transfected with a pegRNA for a genomic target site that the transient expression of GFP is highly correlative with editing at that genomic loci. When used in conjunction with flow cytometry, this strategy can be used to efficiently purify base-edited cell populations. In addition, PINE-TREE can facilitate gene knockout through the A-to-G or T-to-C conversion of the ATG start codon to ACG (encoding threonine) or CTG (encoding leucine), respectively. To facilitate the design of PINE-TREE based strategies we have recently published a software tool, Prime Induced Nucleotide Engineering Creator of New Edits (PINE-CONE), that enables high-throughput automated design of pegRNAs and prime editing strategies[38]. We are currently using these PINE-TREE based methods to generate isogenic ApoEch hiPSC lines. In the near future, we will differentiate these lines to cortical cultures and perform a series of biochemical, cellular, and genetic assays to determine the mechanisms by which the ApoEch mutation affects disease-related phenotypes.

In terms of funding, we submitted an R21 proposal to the NIH that was reviewed in March 2021. The proposal received an Impact Score of 28 and Percentile Score of 10. Based upon the NIA payline as it relates to AD-related applications, we expect this proposal to be fully funded with a start date of July 2021.

ADRD Family Caregiving during a Pandemic: Outcomes and Intervention. David W. Coon, PhD, Molly Maxfield, PhD, Dona Locke, PhD. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

a) Drawing from assessment batteries in the NIH REACH trials, conduct telephone assessments with family caregivers of people with Alzheimer's disease and related dementias (ADRD) to examine key outcomes of caregiver stress and distress (mood, stress, social support) and coping during the COVID-19 pandemic. Expand the assessment to include social isolation and dementia worry.
b) Conduct focus groups (either face-to-face, via video-conferencing, or telephone) of family caregivers for people with ADRD regarding their experience of caregiving, social isolation, dementia worry, and coping during COVID-19 pandemic.
c) Convene a series of meetings, focused interviews, and focus groups across the year to integrating findings from Aims a & b and examine the feasibility of adapting an evidence-based intervention (e.g., CarePRO) for implementation into Mayo Clinic Arizona via face-to-face and/or video conferencing platforms.
d) Disseminate findings through presentations at national conferences such as the Gerontological Society of America and the American Psychological Association.

Background and Significance:

Between now and 2025, Arizona is projected to have the greatest increase in its proportion of both people living with ADRD and their family or informal (family and friends) caregivers (Alzheimer Association, 2020). Family caregiving for people with dementia leads to a host of negative outcomes including poorer emotional well-being and new or exacerbated physical health problems as well as lowered income and financial health (see Alzheimer's Association 2020 for a review). These negative outcomes increase the likelihood of caregiver need for and use of health and social services (Kasper et al., 2015; Stall et al., 2019). When the normal daily routine of older adults who need the help of a caregiver is disrupted, adjusting to the new routine can be difficult. During unusual circumstances—such as pandemics or other situations that limit otherwise normal daily routines—caregiver outcomes are likely to be impacted further and new, innovative models of intervention needed. The COVID pandemic provides a unique opportunity to investigate the impact and identify opportunities for intervention to help family caregivers.

Preliminary Data, Experimental Design and Methods:

Recruit and interview up to 25 family caregivers of individuals with ADRD into a 2-wave telephone assessment of their caregiving experience (mood, stress, coping strategies) approximately 4 weeks apart during the COVID-19 pandemic. In addition, recruit and enroll up to 25 family caregivers of people with ADRD to gather qualitative data through focus groups about their experience of caregiving, social isolation, dementia worry, and coping during COVID-19. Conduct analyses to integrate the data collected from panel assessments and the focus groups to explore the feasibility of adapting an evidence-based intervention (e.g., CarePRO) for implementation into health-related systems via video conferencing platforms.

Proposed One-Year and Long-Term Outcomes:

The outputs in the Methods sections describe the short-term outcomes. Data analyses from this mixed methods project would yield (a) professional presentations at meetings such as the Gerontological Society of America, the American Society on Aging, and/or the American

Psychological Association and (b) manuscripts submitted to *The Gerontologist, Aging & Mental Health, Alzheimer's & Dementia, the Clinical Gerontologist,* and/or *Dementia*. Subsequently, the PIs would submit either an R21, R34, or an R01 in 2022, based on these initial findings.

Year-End Progress Summary:

We made great progress despite COVID-10. The pandemic combined with the explosion of Zoom and other video platforms required us (with fervent requests from community providers) to refocus and pivot our focus group activities to Zoom. Twenty-six participants were recruited for focus groups with 24 caregiver participants from a variety of backgrounds sharing of caregiving during COVID. Caregivers in focus groups were on average just over 60 years of age (M = 62.2 years; SD = 10.7); 79.2% were women; and either spouses (66.7%) or adult children caring for a parent (33.3%). Although the majority were non-Hispanic White, 25% did self-identify as Hispanic or Latino. They varied in terms of education including those without a college degree (29.2%), those with a bachelor's degree (29.2%), and those with advanced degrees (41.7%). Over half were employed full or part-time (54.2%) and in terms of geographic area of residence came from rural (8.3%), suburban (50%) and urban areas (41.7%). We also recruited and interviewed 32 participants for our panel study with 31 of those participants completing T2 follow-ups. Participants were more diverse than our focus groups enrolling 87.5% female and 12.5% male participants who described themselves as Latino/Hispanic (40.6%) and as Black/African American (9.4%), Native American (3.1%), no primary group or other (21.9%) and White/Caucasian (65.6%). Participants reported different levels of education including less than a college education (34.4%), college graduate (31.3%), or an advanced degree (34.4%). They were spouses (59.4%), adult children (34.4%), or another type of relationship (6.2%); 35.3% worked; and resided in urban (34.4%), suburban (62.5%) and rural (5.9%) areas. Two of our participants identified themselves as members of the LGBT community. Data analyses are still underway but the pandemic's impact on caregivers and participant feedback suggested our team quickly revamp evidence programs (e.g., CarePRO) for Zoom-based delivery and testing.

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Characterizing the impact of mitochondrial genomics on molecular and neuropathological networks in late onset Alzheimer's disease and aged subjects. Ben Readhead, MBBS, Jennifer Nolz, Diego Mastroeni, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Construct multiomic mitochondrial brain networks in AD and aging subjects

Specific Aim 1a) Utilize WGS data available on 1,642 subjects within the NOMIS study and AMP-AD consortium to identify MT DNA variants, MT haplogroups, MT heteroplasmy, and MT copy number. **Specific Aim 1b)** Integrate available multiomic data (i.e gene expression, protein abundance, DNA methylation, miRNA abundance) to perform comparative multiomics as a function of MT variables, including identification of MT variants associated with molecular traits (MT-QTL) and association analysis to link AD-relevant clinical and neuropathological traits with MT variables. **Specific Aim 1c)** Utilize MT-QTL relationships to construct causal networks linking MT genomic features with molecular, clinical and neuropathological traits of relevance to AD and ageing. **Specific Aim 1d)** Experimental validation of top molecular traits and associated MT variants. Perform RT-PCR on select brain tissue samples to validate top MT loci of interest, and qPCR to quantify molecular traits (e.g. top genes with expression linked to loci of interest). If indicated by the data, we will also perform laser capture microdissection in a subset of samples (n=8) to verify cell-type specific associations of interest.

Background and Significance:

The dysregulation of cellular bioenergetics represents a common feature across multiple neurodegenerative diseases, including AD, Parkinson's disease (PD), and progressive supranuclear palsy(1). Multiple lines of evidence suggest mitochondrial dysfunction in AD, including regional hypometabolism in AD indicated by FDG-PET studies(2), alteration of energy sources toward amino acids and fatty acids(3), increased oxidative stress and ROS production(4), reduced intact MT in AD brains(5), and reports of reduced MT copy number and impaired base excision repair capacity in AD(6).

The generation of large amounts of high quality next generation sequences (NGS) from large patient cohorts offers novel opportunities to characterize complex interactions between MT function and cell biology, and contextualize their role in disease and aging states. The utilization of WGS data allows us to identify multiple MT variables, including the estimation of MT heteroplasmy, MT copy number, MT genotypes, and haplogroups. Further, these data may then be integrated with other layers of available omic data, to study interactions between MT variables and AD risk factors, as well as molecular, clinical and neuropathological networks.

Preliminary Data, Experimental Design and Methods:

We have performed initial MT variant calling on 1,642 subjects within the NOMIS and AMP-AD cohorts from available WGS. Initial QC demonstrated a high quality of variant calling, across approximately 2,000 MT variants. We have also characterized instances of MT heteroplasmy across all samples, and estimated MT copy number. Our initial analyses have indicated rich, complex interactions between MT variants and multiple AD relevant factors, including the modification of APOE-E4 allele dosage risk effects on AD diagnosis and molecular networks. A full summary of current findings are beyond the scope of this proposal, but as a demonstrative

Index	Name	P-value	Adjusted p-value	Odds Ratio
1	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile (GO:0000377)	4.738e-14	2.418e-10	13.56
2	RNA 3'-end processing (GO:0031123)	2.209e-8	0.00002254	22.95
3	mRNA processing (GO:0006397)	5.241e-14	1.337e-10	12.01
4	RNA export from nucleus (GO:0006405)	4.181e-10	5.334e-7	16.81
5	mRNA splicing, via spliceosome (GO:0000398)	2.259e-13	3.843e-10	12.26
6	termination of RNA polymerase II transcription (GO:0006369)	4.770e-8	0.00003477	20.59
7	regulation of SNARE complex assembly (GO:0035542)	0.0008709	0.2222	44.44
8	mRNA 3'-end processing (GO:0031124)	8.640e-8	0.00004409	18.92
9	mRNA-containing ribonucleoprotein complex export from nucleus (GO:0071427)	3.746e-8	0.00003186	16.00
10	mRNA transport (GO:0051028)	5.101e-8	0.00003254	15.38

Figure 1. Identification of cis-eQTL for MT-ND3 indicates neuropathology-associated molecular networks

example, one of the strongest cis-MT-QTL identified within the ROSMAP cohort (**Figure 1**) is chrM:10398_A/G, with alternative (G) allele associated with lower expression of core subunit MT-ND3 (**Figure 1A-B**). chrM:10398_A/G is a common polymorphism within MT-ND3 that has been extensively studied as a protective variant in PD(7), amygdala volume(8), bipolar affective disorder(9), non insulin dependent diabetes mellitus(10), and also AD(11). Our analyses are ongoing to determine whether chrM:10398_A/G is also associated with AD or related traits in our data. To our knowledge, ours is the first study that has identified chrM:10398_A/G as a cis-eQTL for MT-ND3, indicating the utility of combining multiple data modalities to explore complex associations. Integration of available brain RNA-seq and proteomics data from these same subjects has allowed us to further explore the impact of this variant on molecular networks within the brain. **Figure 1C** illustrates the genes and proteins that are regulated by MT-ND3, as a consequence of variation at the chrM:10398_A/G locus. This subnetwork includes several genes linked with a variety of neurodegenerative diseases, including AD risk-loci harboring gene *CELF1*(12), and *TARDBP/TDP-43*, the major constituent of the ubiquitinated neuronal inclusions in patients with frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Molecular function enrichments of genes and proteins within this network indicate the perturbation of mRNA processing and splicing associated with chrM:10398_A/G. Whether this association will remain as the highest priority for further experimental validation after all planned analyses have been completed is not yet clear, however the emergence of this well studied loci from the current data, is encouraging that the further investigation of multiomic MT networks is likely to be a fruitful area for additional inquiry.

Proposed One-Year and Long-Term Outcomes:

(1) Summarized genetic association between MT-DNA loci and AD-relevant traits
(2) Summarized eQTL networks linking MT-DNA loci with molecular, clinical and neuropathological networks
(3) RT-PCR results to validate key MT-DNA loci of interest, and associated top molecules that emerge from analyses.

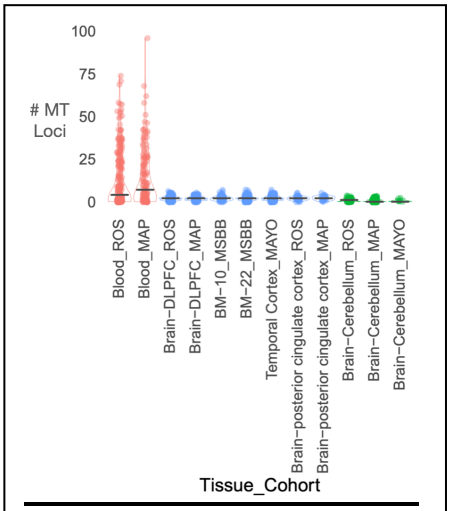

Figure. 2 Number of MT loci with detected heteroplasmy from blood and

Year End Progress Summary:

Mitochondrial heteroplasmy We have continued our investigation of MT heteroplasmy, including an examination of baseline rates of detected heteroplasmy derived from 1,642 WGS samples obtained from several tissues types and cohorts that have been profiled as part of the AMP-AD consortium efforts. Consistent with expectations, we observe the highest rates of MT heteroplasmy in samples derived from blood, compared with brain tissue derived samples (**Figure 2**). The brain tissue samples are collectively derived from five cortical regions and cerebellum across four independent clinical cohorts. Overall we observed consistent MT heteroplasmy rates across cortical regions (including

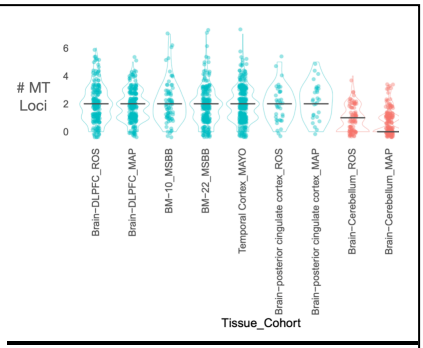

Figure. 3 Number of MT loci with detected heteroplasmy brain tissue

between and within cohorts), with approximately two MT heteroplasmy sites detected per sample (**Figure 3**). This was lower in cerebellum samples, where approximately 0-1 sites were detected per sample.

Mitochondrial copy number We have estimated MT copy number (MT-CN) across all samples, and continue to investigate how this variable associated with AD associated genetics, as well as clinical and neuropathological traits. As might be expected based on bioenergetics requirements, we see the lowest MT-CN in samples derived from blood, and intermediate levels in cerebellar samples, with the highest MT-CN observed in cortical samples (**Figure 4**), with substantial differences observed across cohorts. We have integrated out MT-CN with molecular estimates of AD pseudotime (Mukherjee, 2020) that were generated on the same cohorts described here, and observe a significant, inverse correlation between disease pseudotime and MT-CN (Corr: -0.38, P: 5e-5).

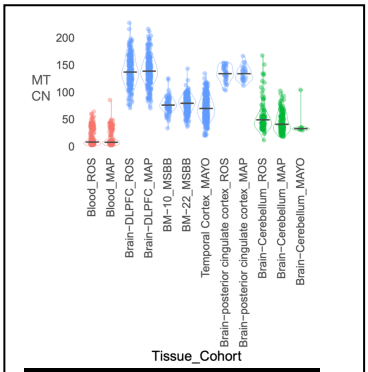

Figure. 4 MT Copy number estimates across blood and brain tissue derived WGS

Profiling the transcriptomic impact of chrM:10398G>A In complementary data generation efforts, and motivated by the preliminary results obtained here, we have collaborated with Dr. Elaine Lim and Dr. Rigel Chan (UMass Medical School) to generate RNA-seq from 60 subjects based on genotype of a mitochondrially encoded neurodegenerative protective allele, chrM:10398G>A (A114T). This variant has been studied in the context of AD, Parkinson's disease, breast cancer, and NIDDM, and has been further identified by us as associated with mitochondrial heteroplasmy and viral networks in ongoing work. To this end, we explored the effect of this allele on overall gene expression in a population of cell lines from different individuals. We explored the Harvard Personal Genome Project (PGP) cell lines, and selected 60 individuals (G n=30, A n=30) and passaged their LCLs for RNA extraction. We extracted RNA and performed whole transcriptomic RNA sequence profiling. Prior to doing so, we also confirmed their genotypes using Sanger sequencing. We have very recently received RNA-seq, and are performing ongoing analyses. Preliminary differential expression (**Figure 6**) shows informative transcriptomic effects

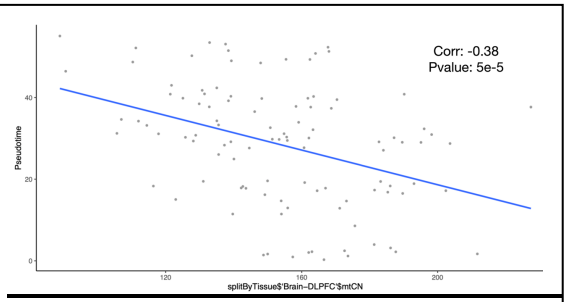

Figure. 5 Cortical MT Copy number vs.

	logFC	logCPM	F	PValue
SNORA54	-0.5311148	6.275038	19.35489	4.56E-05
ND4	-0.4423354	7.832859	17.65937	8.97E-05
ATP8	-0.4296396	7.757883	16.20506	1.63E-04
HNRNPA2B1	-0.1889789	6.502153	15.44354	2.24E-04
IGKJ5	-2.6739128	8.889848	15.42173	2.26E-04
RN7SKP80	-0.308517	10.031526	13.6444	4.82E-04
TIMM10	-0.2400641	5.729237	12.05698	9.67E-04
ND2	-0.3296876	6.35749	12.04174	9.73E-04
SNORA49	-0.29682	4.957752	11.85073	1.06E-03
EIF5B	-0.3841431	3.997096	68.95641	1.42E-03

Figure. 6 Top 10 most differentially expressed genes from RNA-seq of

of this genotype, including perturbation of several genes encoded by, or impacting on mitochondrial function (ND4, ND2, ATP8, TIMM10), including ND4, which is 400 bp downstream of chrM:10398G>A and may indicate a cis-eQTL relationship.

Validation of mitochondrial heteroplasmy sites We experienced several COVID-19 related delays throughout 2020, which affected our experimental validations, though which are now resolving. Following an integrative analysis of our computational results, we are currently selecting and prioritizing our top MT loci for RT-PCRvalidation on brain tissue samples from BSHRI. We expect that this will be completed within the coming three months.

Relating Online Motor-Cognitive Game Performance with AD Risk Factors using the MindCrowd Electronic Cohort. Sydney Schaefer, PhD, Matthew Huentelman, PhD. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to test the extent to which sex, age, cognitive scores, and family history of AD relate to performance of an online motor-cognitive game.

Background and Significance:

Earlier disease diagnosis and better symptom monitoring remain a high priority within AD research and clinical practice. In 2020, the National Institute on Aging released a Notice of Special Interest entitled, "Digital Technology for Early Detection of Alzheimer's Disease and Related Dementias" to promote research on the use of digital technology for early detection and monitoring of cognitive and functional decline in persons with Alzheimer's disease (AD) and AD-related dementias (ADRD). This AAC application directly aligns with this NOSI on the premise that video games have the potential to capture relevant digital signals for AD research. Video games may not only be sensitive to differences in cognition, but are also surprisingly popular among older populations based on reports of high satisfaction in game play among elderly adults. However, the precise elements of a game that are best suited to assess cognition are not well defined, and many of these games still require an administrator, special equipment (e.g., VR headset or a Kinect controller) or a significant amount of game time (>1 hour).

To resolve these limitations within the field, this proposal leverages our expertise in motor learning to develop an online video game in the context of AD research, since motor learning has been shown be age-dependent and more recently, sensitive and specific to AD. However, motor learning research in the context of cognitive aging has been done almost exclusively in face-to-face settings. We seek to change this using Super G, an online motor-cognitive video game we have developed. No study to date has been positioned with a large enough sample to relate motor learning with other cognitive, demographic, and health factors that are known to be associated with elevated AD risk. In this respect, Super G is unique as it may not only relate to cognition and known AD risk factors, but could, in the future, serve as a quick, easy approach to screen for different forms of dementia remotely, which would be vital for enriching AD clinical trials. Super G may also be very suitable for longitudinal studies to track changes in motor learning over time in at-risk individuals. Thus, the aim of this project was to leverage the MindCrowd electronic cohort to test the extent to which sex, age, cognitive scores, and family history of AD relate to performance of an online motor-cognitive game.

Preliminary Data, Experimental Design and Methods:

Super G was modeled after seminal psychophysical work that analyzes complex processes of learning a motor skill. Briefly, this game requires participants to learn how to apply 'accelerations' (using the left and right arrow keys on a computer keyboard) to an astronaut (named Super G) to move her from one planet to another. This precise application of the acceleration is known as the *task rule*, whereby one must learn the rule to be successful. This type of rule-based motor learning can reveal different learning curves and outcomes compared to more traditional motor tasks.

The MindCrowd dataset contains over 40,000 participants who have previously consented to being contacted for future research. We will disperse game e-mails to all consenting MindCrowd participants in an iterative fashion to better track response rate, prevent any server overloads, etc. Participants will register for the game with the e-mail they previously used in

MindCrowd. All data collected through the game are encrypted and stored on a password protected server.

Data Analysis: We will use linear mixed effects models to determine the relationship of task performance on cognitive scores, sex, age and family history of AD, all of which were collected previously via MindCrowd. Our outcome variable will be game performance, fixed effects will be trial, sex, age, and previous family history of AD, and random effects will be on participant.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes include 2-3 manuscript submissions, an initial submission of a collaborative R01 to PAR-18-596 under NOT-AG-20-017 to track participants annually, secondary analyses of race/ethnicity as a relevant biological variable, and an AAC meeting presentation as well as at a national conference. Long-term outcomes include pursuing the use of Super G as simple, easy, and affordable method to enrich AD clinical trial enrollment.

Year End Progress Summary:

Full Implementation of the motor-cognitive game onto an online platform: We successfully converted the in-lab version of our motor-cognitive game (Super G) into an online game. To do this successfully we had to hone the front-end user experience (i.e., the look, feel, and new narrative of the game) and complete the back-end software implementation (i.e., how the game stores and protects individual data). The in-lab version of Super G contained no narrative and only required a participant to achieve the task goal of landing a cursor from one target to another. Now, the game Super G, uses a narrative where users are controlling an astronaut, Super G, to explore the different planets within the solar system. We also created a tutorial video on how to play the game, which is embedded within the game site, as well as inclusive instructions informing users on the purpose of the experiment and the objective of the game. We made these updates to provide a more engaging experience for users to encourage continuous and focused gameplay. For the back-end implementation, we developed scripts to securely encrypt and store game data into a password protected relational database. This was done to ensure that all collected data would be protected from potential hackers.

Alpha Testing: Examine the reliability of data collection between an online and computer based server: Once the game was fully implemented online, we then performed alpha testing to ensure that the data collected from online participants would be equivalent to data collected in a lab based setting. For our alpha testing we set up the game to simultaneously send data to both the online and computer server where we could gauge how game play data may differ dependent upon factors related to interconnectivity and back-end implementation. We performed 100 trials of the game and then analyzed how comparable data between the two data storage methods compared. We demonstrated that data collected between each data stream was nearly identical in every way. This provided with a critical proof of concept that our in-lab task had been successfully and reliably implemented into the online platform. Results of this alpha testing were submitted and accepted as a conference abstract to the 2021 American Society of Neurorehabilitation Annual Meeting.

Beta Testing, Stage 1: Examine the similarity of performance profiles among young adults who played the game online versus in-lab: Following successful alpha testing, we then began piloting the task among younger adults who were lab members of the Schaefer and Huentelman labs. Previous research using this task was conducted *in lab* with 32 non-disabled young adults. We then piloted the game *online* with 15 non-disabled young adults. We then compared the performance profiles (i.e. the changes in performance as a function of practice) between the in-lab and online groups to examine group level similarities. Overall, we determined that there was a similar heterogeneity in performance profiles (i.e., individuals who both performed well and

struggled at the game) between groups. This suggested that the difficulty and playability of the online game is identical to that of what we previously measured in the lab.

Beta Testing, Stage 2: Examine the feasibility of online game performance among a small group of older adults: The original motor-cognitive task was designed for younger adult participants and thus had a level of difficulty that might deter older adults from continued play due to low levels of success and high levels of frustration. We therefore piloted the game in 12 older adults (mean age 70±6.7 years) at the original difficulty and then again with a decreased difficulty (i.e. increased time to complete the task goal). All game play was performed online and unsupervised. We found that indeed, at the original difficult, our older adult cohort were less inclined to play several trials most likely due to poor performance/no trial success. When we had participants play the game again at the reduced difficulty we observed a near 5-fold increase in voluntary game play (50 trials to 250 trials) and an increased number of successful trials across all participants. This stage of Beta testing allowed us to sufficiently tune the task difficulty to increase older adult engagement in the task and avoid unnecessary floor or ceiling effects that dilute the true performance profiles among all eligible participants.

Motor Task Concordance between MindCrowd and In-Lab Participants: Prior to the proposal of using our motor-cognitive game in MindCrowd, the Schaefer Lab implemented an at-home motor task assessment in MindCrowd as well. This was part of an experiment to observe if there were consistent behavioral patterns among older adults who completed a complex motor task either supervised, in the lab or unsupervised, at-home. This task varies from our online motor-cognitive task in that it is a physical task that is mailed to the home and is focused on upper extremity reaching performance. However, any evidence that suggests that performance is consistent regardless of the format of data collection (unsupervised at-home vs. supervised in-lab) will further support our initial rationale that motor-cognitive tasks performed unsupervised at home are reliable assessments of performance that we would see in the lab. Thus far, the Schaefer motor task has been delivered to 500 MindCrowd participants between the ages of 40 – 80 who have previously submitted a dried blood spot to the Huentelman lab for genetic sequencing. To date, 193 of the 500 initial MindCrowd users have completed the motor task and comparisons with our older adult in-lab sample have determined that performance on this motor task is very similar in how it relates to age and overall rate of learning. Results from this initial collection are being prepared for submission to a peer-reviewed academic journal.

International Review Board Approval and MindCrowd Participant Selection – Data Collection Wave 1: With all preliminary testing completed, we have recently received approval through both the Arizona State University and Translational Genomics Research Institute International Review Board. This approval allows us to fully integrate the task in MindCrowd as we now prepare for our first wave of data collection, scheduled for the week of April 5th. The first wave of collection will focus on the same 500 participants that the Schaefer motor task previously contacted. This will allow us to compare overall response rates between the two tasks and inter-relatedness of the performance between the two tasks. This will also serve as a critical first step to determine any bug-fixes or game updates that may be necessary to further engage MindCrowd participants as we continue to progress to future waves of data collection.

Additional deliverables: In addition to the accepted conference abstract and the first manuscript in preparation (to be submitted to the Journal of Applied Gerontology by May 15, 2021), this project was submitted by Dr. Schaefer's postdoc as a NIH F32 application (award pending).

Injury-induced inflammation as a contributor to neurodegeneration and Alzheimer's Disease. Sarah Stabenfeldt, PhD, David Brafman, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: *Evaluate acute neuroinflammation following traumatic brain injury.* We will characterize neuroinflammation in adult mice over the course of 7 days following a focal brain injury (controlled cortical impact; CCI) using protein analysis (cytokine profile and immunohistochemistry). The results from this study will provide unique insight into injury induced inflammation on potentially priming the brain for neurodegenerative pathology.

Specific Aim 2: *Evaluate chronic neuroinflammation and markers of AD pathology following traumatic brain injury.* We will characterize neuroinflammatory and hallmark AD pathology in adult mice at 1, 3, and 6 months following a focal brain injury (CCI) using protein (immunohistochemistry) and transcriptomics (RNA-seq). The results from this study will provide unique insight into whether injury-induce neuroinflammation has a pronounced effect on AD pathology progression.

Background and Significance:

An increased risk for Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) following documented TBIs has been identified in the clinic (1,2) and AD-like pathology has been observed in preclinical TBI models (3–5). Commonalities exist between TBI and AD/ADRD pathologies including a dysfunctional blood-brain barrier (BBB) (6–8) and neuroinflammation (9–12). Yet, the direct connection and potential contribution of TBI to AD/ADRD pathologies remains elusive. Notably, one hypothesis for AD/ADRD is the two hit vascular hypothesis postulating that an initial "insult" to the vascular system initiates BBB dysfunction to directly cause neuronal death. Continued BBB dysfunction then contributes to dysregulated clearance and subsequent deposition of amyloid-β (Aβ) leading to further neurodegeneration (7). One could speculate that a TBI event could serve as the first vascular "insult" contributing to neuroinflammation and ultimately neurodegenerative sequelae. Therefore, elucidating key mechanisms following TBI, particularly neuroinflammatory sequalae, that contribute to AD/ADRD will not only provide insight into basic pathological progression, but also spark novel therapeutic strategies to significantly impact both TBI and AD/ADRD.

Here, we aim to characterize neuroinflammation and neurodegeneration following TBI in the mouse. Our analysis will focus on characterizing key aspects of the neuroinflammation (cytokine profiles, necroptosis) and neurodegeneration (TDP-43, Aβ deposition, tau-phosphorylation).

Preliminary Data, Experimental Design and Methods:

Dr. Stabenfeldt is an established leader in evaluating BBB dysfunction and neuroinflammation following TBI in the proposed preclinical TBI model. She has recent publications that thoroughly characterized temporal BBB disruption profiles and also ability to exploit these windows of BBB disruption for localized nanoparticle deposition (13–15). As an extension of this foundational work, Dr. Stabenfeldt received an AD/ADRD NIH supplement on her DP2 NIH award to extend her work in TBI AD/ADRD. Moreover, the initial AAC funding provided to Dr. Stabenfeldt facilitated preliminary pilot studies to investigate initial BBB permeability in aged and 3xTg-AD mice following TBI with complementary IHC and proteomic analysis. This preliminary work is ongoing, but notably, we have observed upregulation of critical cytokines related to inflammatory-mediated

necroptosis linked to AD acutely after injury in our CCI mouse model. Additionally, we have observed aberrant TAR DNA binding protein 43 (TDP-43) pathology in frontal cortex of injured mice (one-month post-injury), with classical TDP-43 neurodegenerative pathology observed with TDP-43 translocated from the nucleus to cytoplasm in aggregates (discovered via IHC). TDP-43 pathology contributes to a number of neurodegenerative diseases, including AD. Further studies such as the one proposed in this proposal will contribute to further understanding the link between TBI and AD.

Proposed One-Year and Long-Term Outcomes:

The results from this study will provide unique insight into the contribution of inflammation following TBI on AD pathology (i.e., the contribution of TBI on AD pathology progression as relating to neuroinflammation). Data and findings from this proposal will be disseminated at the appropriate national conferences and journal publications. One compelling and exciting aspect of the team is that it includes Dr. David Brafman, who is working with Dr. Stabenfeldt to develop a complementary in vitro study to probe the relation of injury-induced neuroinflammation and AD using hiPSCs. Coupling this in vitro and in vivo study will be very attractive for external funding agencies such as NIH, Alzheimer's Association, and American Federation for Aging Research.

Year End Progress Summary:

Specific Aim 1: Our team has assessed an evaluated the cytokine profile via multiplex flow cytometry kit to compare the expression of 15 cytokines in the cortical injury penumbra of mice sustaining a TBI. We compared wild-type mice and the AD 3xTg mice (females) that sustained a TBI at six months of age, just prior to the 3xTg mice expressing substantial AD neuropathology. The profiles for both cohorts demonstrated comparable injury induced cytokine expression regardless of genetic predisposition. Subsequent immunohistochemistry data corroborated comparable microglial activation at 3d post-injury. We are currently assessing inflammatory related (TNF-a) stimulation of necroptosis via western blotting and IHC key intracellular indicators of necroptosis after TBI in the mouse model. We aim to elucidate and potentially link AD-neuropathology (i.e. necroptosis) to TBI event.

Specific Aim 2: We have completed the tissue collection for the chronic assessment of neurodegeneration in adult mice at 1, 3, and 6 months following a focal brain injury (CCI). Moreover, we have begun the immunohistochemistry (IHC) assessment for TDP-43 translocation to cytoplasm along the cortical spinal tract. Thus far, we have observed prominent TDP-43 translocation in motor neurons of spinal cord at 1 month and sustained to 6 months post-injury that may contributed to the loss of NeuN+ cells at 6months. The results are very compelling and one of the first to assess long-term neurodegenerative consequences of TBI in wild-type mice.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Developing A Univariate Neurodegeneration Imaging Biomarker with Low-Rank and Sparse Subspace Decomposition. Yalin Wang, PhD, Richard J. Caselli, MD, Kewei Chen, PhD. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Cognitive decline due to Alzheimer's disease (AD) is closely associated with brain structure alterations captured by structural magnetic resonance imaging (sMRI). It would be highly desirable for clinical applications to develop sMRI-based univariate neurodegeneration biomarkers (UNB). However, existing UNB work either fails to model strong group variances or does not capture structural changes induced by AD dementia (ADD). Our current project's **objective** is to build and deliver a novel and highly sensitive univariate morphometry index (UMI) that is clinically useful and able to improve AD diagnosis accuracy and expedite AD drug development by reducing clinical trial costs. **Hypothesis:** we hypothesize that this technique will better facilitate the identification of ADD and empower AD enrichment than hippocampal volumes, AD signature, and structural abnormality index (STAND)-scores, thus providing new imaging biomarkers as important outcome measures in clinical trials or for enrichment of individuals expected to progress within a particular time frame.

Specific Aim(s): To develop a novel low-rank and sparse subspace decomposition method capable of stably quantifying the morphological changes induced by ADD and apply it to MRI brain scans of the ADNI cohort and AZ APOE cohort.
(a). Develop new low-rank and sparse subspace decomposition methods to compute UMI; **(b).** Validate the index by 1) correlation with AD genetic risk/AD severity; 2) progression prediction to AD or its prodromal stage via the Cox model; 3) sample size estimation for clinical trials.

Background and Significance:

AD is the most common type of dementia. It is generally agreed that effective presymptomatic diagnosis and treatment of AD could have enormous public health benefits. Neuroimaging research is currently focused on the development of accurate diagnostic markers that reflect the presymptomatic changes before the clinical onset of AD and can sensitively detect AD treatment effects in a sufficiently rapid and rigorous way.

While much AD imaging biomarker research has been devoted to group difference-based analyses, UNB based on an individual patient's brain scans with high diagnostic accuracy would be highly desirable for clinical use. Such a personalized measure may overcome inflated Type I error due to multivariate comparisons with patient-specific clinical analyses. However, A recent work reported that that the currently available UNB, including hippocampal volume, cortical signature of AD and optimal mass transportation-based global index, were poorly correlated both in the whole sample and along the AD continuum. Therefore, to advance computational neuroanatomy to clinical usage, developing a robust method to quantify brain sMRI difference using a statistically powerful UNB will be highly advantageous for clinical diagnosis and prognosis. We made the first strides into developing UNB systems. We are uniquely positioned to develop a UNI system to quantify brain MR images for clinical research. The Arizona Alzheimer Consortium (AAC) grant, once available, will be leveraged to produce more exciting preliminary results. Our proposed project will make the planned R01 proposal submission more competitive.

Preliminary Data, Experimental Design and Methods:

Preliminary data We discovered a variational principle for efficiently computing Euclidean optimal mass transportation (OMT). The framework reduces the computational cost and enables applications to high-dimensional WI computation. Our preliminary results demonstrate the promise of our univariate neuroimaging index to distinguish AD patients from cognitively unimpaired (CU) subjects and to evaluate AD burden.

Experimental design and methods We propose to take a subspace decomposition approach and improve the robust principal component analysis (RPCA) method by adopting a low-rank matrix factorization mechanism, imposing regularization constraints into the sparse component to encode spatial connectivity in the original 3D morphometry features and proposing an efficient numerical scheme to solve the formulated optimization problem. With the obtained ROIs, we summarize the image information on new subjects. 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 2021.

Year End Progress Summary:

Developing univariate neurodegeneration biomarkers with low-rank and sparse subspace decomposition. In collaboration with Drs. Caselli, Reiman, Chen, and Su, we propose a novel low-rank and sparse subspace decomposition method capable of stably quantifying the morphological changes induced by ADD. Specifically, we propose a numerically efficient rank minimization mechanism to extract group common structure and impose regularization constraints to encode the original 3D morphometry connectivity. Further, we generate regions-of-interest (ROI) with group difference study between common subspaces of Aβ+AD and Aβ-cognitively unimpaired (CU) groups. A univariate morphometry index (UMI) is constructed from these ROIs by summarizing individual morphological characteristics weighted by normalized difference between Aβ+AD and Aβ-CU groups. We use hippocampal surface radial distance feature to compute the UMIs and validate our work in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. With hippocampal UMIs, the estimated minimum sample sizes needed to detect a 25% reduction in the mean annual change with 80% power and two-tailed P=0.05are 116, 279 and 387 for the longitudinal Aβ+AD, Aβ+mild cognitive impairment (MCI) and Aβ+CU groups, respectively. Additionally, for MCI patients, UMIs well correlate with hazard ratio of conversion to AD (4.3, 95% CI = 2.3-8.2) within 18 months. Our experimental results outperform traditional hippocampal volume measures and suggest the application of UMI as a potential UNB. This work has been published by Medical Image Analysis (impact factor = 11.148).

Predicting future cognitive decline with hyperbolic stochastic coding. In collaboration with Drs. Caselli, Reiman, Stonnington, and Chen, we propose a novel framework termed as hyperbolic stochastic coding (HSC). We first compute diffeomorphic maps between general topological surfaces by mapping them to a canonical hyperbolic parameter space with consistent boundary conditions and extracts critical shape features. Secondly, in the hyperbolic parameter space, we introduce a farthest point sampling with breadth-first search method to obtain ring-shaped patches. Thirdly, stochastic coordinate coding and max-pooling algorithms are adopted for feature dimension reduction. We further validate the proposed system by comparing its classification accuracy with some other methods on two brain imaging datasets for Alzheimer's disease (AD) progression studies. Our preliminary experimental results show that our algorithm achieves superior results on various classification tasks. Our work may enrich surface-based brain imaging research tools and potentially result in a diagnostic and prognostic valuable indicator in

individualized treatment strategies. This work has been published by Medical Image Analysis (impact factor = 11.148).

Multi-Resemblance Multi-Target Low-Rank Coding for Prediction of Cognitive Decline with Longitudinal Brain Images. In collaboration with Dr. Caselli, we propose a novel incomplete longitudinal brain imaging processing method, which encourages that sparse codes of neighboring longitudinal time points are resemblant to each other, favors sparse code low-rankness to reduce the computational cost and is resilient to both source and target data incompleteness. In stage one, we propose an online multi-resemblant low-rank SC method to utilize the common and task-specific dictionaries in different time points to immune to incomplete source data and capture the longitudinal correlation. In stage two, supported by a rigorous theoretical analysis, we develop a multi-target learning method to address the missing clinical label issue. To solve such a multi-task low-rank sparse optimization problem, we propose multi-task stochastic coordinate coding with a sequence of closed-form update steps which reduces the computational costs guaranteed by a theoretical convergence proofWe validated our work on ADNI dataset to predict two clinical measures and compared it with six other methods. Our experimental results showed that our proposed method achieved superior results on both computational efficiency and predictive accuracy and has great potential to assist the AD prevention. This work has been published by IEEE Transactions on Medical Imaging (impact factor = 6.685).

Improved Prediction of Imminent Progression to Clinically Significant Memory Decline Using Surface Multivariate Morphometry Statistics and Sparse Coding. In collaboration with Drs. Stonnington, Reiman, Caselli, Su, and Chen, we study the potential of using brain imaging to inform a cognitively unimpaired (CU) person's likelihood of progression to mild cognitive impairment (MCI) and benefit subject selection when evaluating promising prevention therapies. In our work, patch-based sparse coding algorithms were applied to hippocampal surface features of baseline TI-MRIs from 78 CU adults who subsequently progressed to amnestic MCI in approximately 2 years ("progressors") and 80 matched adults who remained CU for at least 4 years ("nonprogressors"). Nonprogressors and progressors were matched for age, sex, education, and apolipoprotein E4 allele dose. We achieved 92%prediction accuracy in the Arizona cohort, 92%prediction accuracy in the ADNI cohort, and 90%prediction accuracy when combining the two demographically distinct cohorts, as compared to 79%(Arizona) and 72%(ADNI) prediction accuracy using hippocampal volume. This work has been published by Journal of Alzheimer's Disease (impact factor = 3.909).

Integrating Multimodal and Longitudinal Neuroimaging Data with Multi-Source Network Representation Learning. In collaboration with Dr. Braden, we studied psychometric prediction research by integrating longitudinal and multimodal neuroimaging data. We proposed a general fusion framework for multi-source learning of brain networks -- multimodal brain network fusion with longitudinal coupling. In our work, three layers of information were considered, including cross-sectional similarity, multimodal coupling, and longitudinal consistency. Specifically, we jointly factorized multimodal networks and construct a rotation-based constraint to couple network variance across time. We also adopted the consensus factorization as the group consistent pattern. Using two publicly available brain imaging datasets, we demonstrated that MMLC may better predict psychometric scores than some other state-of-the-art brain network representation learning algorithms. Additionally, the discovered significant brain regions are synergistic with previous literature. This work has been published by Neuroinformatics (impact factor = 3.803).

Project Progress Reports
Banner Alzheimer's Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Alzheimer's Prevention Initiative. Eric M. Reiman, MD, Pierre N. Tariot, MD, Jessica B. Langbaum, PhD. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims

1. To continue to conduct a preclinical Alzheimer's disease (AD) trial/surrogate marker development program in cognitively unimpaired autosomal dominant (ADAD) mutation carriers within 15 years of their estimated age at clinical onset (i.e., the API ADAD Colombia Trial), analyze and share baseline trial data.
2. To support efforts to analyze data and samples from the recently discontinued API Generation Study 1 and Generation Study 2 trials.
3. To support efforts to share data and samples from the recently discontinued API Generation Study 1 and Generation Study 2 trials with the scientific community.
4. To plan and secure funding for other preclinical treatment trials programs/surrogate marker development programs in cognitively unimpaired individuals who are at risk for ADAD or LOAD (e.g., our proposed API A4 Trial).
5. To continue to support registries designed to assist with participant recruitment.

Background and Significance:

The Alzheimer's Prevention Initiative (API) was established to help advance this new era in Alzheimer's prevention research. It includes several complementary preclinical treatment trial programs/surrogate marker development programs in cognitively normal individuals who (1) are autosomal dominant AD (ADAD) mutation carriers ages 30-60 (API ADAD Trial; NCT01998841), (2) are apolipoprotein E (APOE) ε4 homozygotes ages 60-75 (API Generation Study 1; NCT02565511), (3) are APOE carriers (homozygotes and heterozygotes, heterozygotes must have elevated brain amyloid) ages 60-75 (API Generation Study 2; NCT03131453), (4) have elevated brain amyloid (our proposed API A4 prevention trial). It also includes the Alzheimer's Prevention Registry to help inform stakeholders and support their enrollment in these and other prevention trials, GeneMatch to help identify and support the enrollment of APOE4 homozygotes, heterozygotes and non-carriers in prevention trials, programs to disclose and assess the impact of a person's genetic or biomarker risk, future prevention trials (TBD), and other efforts to find and support the approval and availability of AD prevention therapies. Non-overlapping state and institutional funds are used to support these and related efforts, complement our NIH, philanthropic, and industry suppport, and help to find and support the approval of a prevention therapy as soon as possible.

Preliminary Data:

We and our colleagues have reported cross-sectional evidence of biomarker changes in cognitively healthy PSEN1 E280A mutation carriers compared to kindred non-carriers (1-3) and are currently exploring the longituidnal trajectory of these biomarkers. We have published manuscripts describing the API ADAD trial(4), the API Generation Program(5), the Generation Program risk disclosure process(6), and GeneMatch(7). We and our colleagues are currently analyzing API ADAD baseline (i.e., pre-randomization) trial data for publication and developing a data sharing mechanism for the scientific community. We are also analyzing data and samples from the API Generation Program and establishing a data and sample sharing mechanism.

Experimental Designs and Methods:

To help "launch the era of AD prevention research" by helping to establish the biomarker and, hopefully, "reasonably likely surrogate" endpoints needed for the field to rapidly evaluate promising preclinical treatments, provide needed infrastructure and data, and find effective treatments to reduce the risk of symptomatic AD, or prevent it completely. To accomplish these overall goals and Aim 1, we will continue to follow participant randomized into the API ADAD trial until the last participant enrolled completes 5 years of blinded treatment (a "common close" design), continue to collect tau PET, plan for disclosure of ADAD mutation carrier status at the appropriate time after the trial is completed in those who wish to learn this information, and analyze and share baseline data. For Aim 2, we will work with our Novartis and academic colleagues to analyze data from the Generation Program as soon after datalock as possible and data is transfered to Banner. For Aim 3, we will work with our Novartis colleauges to implement a data and sample sharing program, following the "Collaboration for Alzheimer's Prevention" (CAP) data and sample sharing principles. To accomplish Aim 4, we will continue to work with our A4 and Roche colleauges to develop plans for a prevention trial with gantenerumab, aiming to begin enrollment in 2021. In addition, API leadership will continue conversations with other pharma companies regarding other potential prevention trials (e.g., amyloid negative *APOE4* HMs). To accomplish Aim 5, we will continue to expand the API Colombia Registry, for PSEN1 E280A kindred members, the web-based Alzheimer's Prevention Registry, and its GeneMatch program.

Proposed One-Year and Long-Term Outcomes:

For Aim 1, we will continue to work with our colleagues at Roche to expand the baseline data sharing program to include additional variables. For Aim 2, soon after database lock, Novartis and Amgen will transfer trial data to Banner for analyses. We expect this to occur in Q3 or Q4 2020. Banner will work with key collaborators to analyze fluid biomarker and DNA samples. For Aim 3, Banner will work with data and sample sharing programs such as LONI and NCRAD to share all trial data with the scientific community following CAP principles. For Aim 4, we will work with our colleagues from A4 and TBN industry partner to finalize the trial protocol and operational details to meet our goal of beginning trial enrollment in 2021. The API will continue to seek additional external, non-state funding from NIH, industry and philanthropic organizations to support our efforts to conduct trials in at-risk populations.

Year End Progress Summary:

1. API ADAD Trial. With primary support from initial and competitive NIA renewal grants, philanthropy, Genentech and its parent organization Roche, the API ADAD Colombia Trial continued to meet its stated goals. 365 participants were screened, 252 participants (including 162 PSEN1 E280A mutation carriers) were enrolled, with the last participant enrolled in early 2017 (4;11;12). Retention has been extremely high, and the placebo-controlled trial is intended to continue until early 2022, when the last person enrolled has been treated for 60 months. In addition to other clinical, cognitive and biomarker assessments, we began to acquire mid-treatment tau PET scans during this funding year (follow-up tau PET scans will be acquired at the end of the study). In accordance with Collaboration for Alzheimer's Prevention (CAP) principles we and industry partners have developed mechanisms to share baseline trial data and analyses with the field in ways that protect research participant anonymity, confidentiality and genetic risk disclosure and clinical trial integrity, and we have an agreement to provide a public resource of trial data and biological samples after the trial is over. Approximately 50% of the enrolled carriers had a negative Aβ PET scan at the time of their enrollment, suggesting that trial participants may provide a particularly good test of the amyloid hypothesis, and we continue to analyze these and other cognitive, brain imaging and biomarker data from members of this kindred. We have described the participants' baseline characteristics(13) and provided PET evidence of cerebellar amyloid-β (Aβ) plaque deposition prior to the onset of cognitive decline in ADAD mutation carriers

(Ghisays et al, AAIC Abstr 2020; submitted manuscript).This trial has also advanced the development of emerging blood-based biomarkers (BBBs) for AD and AD related dementias (ADRD). We and our colleagues have used this resource to demonstrate the promise of plasma neurofilament light (NfL) measurements in the early detection and tracking of neuronal injury and/or neurodegeneration(14), detecting the onset of cross-sectional and longitudinal NfL increases ~22 years before the carriers' estimated age at MCI onset and demonstrating more modest age-related increases in the non-carrier group. In a landmark article, we and our colleagues demonstrated the promise of plasma p-tau217 in the diagnosis and unusually early detection of AD, including the onset of measurements p-tau217 elevations about two decades before the ADAD mutation carriers' estimated age at MCI onset(15). We are preparing for the future use of these and other BBBs to detect and track AD and evaluation crenezumab's AD biomarker effects before the API ADAD trial is completed.

2. API Generation Study 1 and Generation Study 2. The Alzheimer Prevention Initiative (API) Generation Program evaluated the effectiveness of the BACE1 inhibitor, umibecestat, and the active immunotherapy, CAD106, in delaying the onset of AD symptoms in APOE4 carriers(16). The Generation Program included two studies implemented in 23 countries at 207 sites. Recruitment in the program and treatment with umibecestat was terminated in July 2019 after detecting an early signal of mild worsening in some measures of cognitive function with umibecestat. At the time of discontinuation, 9623 participants had been recruited, more than 2700 completed the 12-week screening phase with amyloid (PET or CSF) testing; approximately 27% were APOE4 homozygotes (HM). About 60% of HMs and 35% of heterozygotes (HTs) had elevated brain amyloid. A total of 1623 participants were randomized: 478 to Generation Study 1 (all HMs) and 1145 to Generation Study 2 (20% HMs and 80% HTs with elevated amyloid). The last participant last visit occurred in Q2 2020 after which database lock occurred. Data and samples will be analyzed and shared with the scientific community in 2021 to help inform the design of future trials.

3. API A4 Alzheimer's Prevention Trial. In 2018, API and A4 leaders received a $33M NIA grant to help support a proposed prevention trial of an Aβ-plaque antibody in cognitively unimpaired Aβ+ adults. Although we originally intended to partner with Biogen and use aducanumab, in March 2019, Biogen announced the discontinuation of their two Phase 3 trials (ENGAGE and EMERGE) of aducanumab in patients with MCI due to AD and mild AD dementia. The decision to stop the trials was based on results of a futility analysis indicating the trials were unlikely to meet their primary endpoint upon completion. Soon thereafter Biogen decided to pause any further decisions on a preclinical/prevention trial of aducanumab. As a result, the API and A4 leaders entered discussions with another industry partner and are planning for a prevention trial of a different Aβ-plaque antibody in cognitively unimpaired Aβ+ adults.

4. Participant Recruitment Registries. We continue to expand the Alzheimer's Prevention Registry (APR), a web-based registry focused on encouraging enrollment into prevention studies. The Registry has >350,000 enrollees and is actively recruiting for studies locally and nationally(17). In November 2015, the Registry launched its GeneMatch program which collects genetic samples from participants for APOE genotyping and uses the genetic results in part to help match people to research studies(18). More than 90,000 have joined GeneMatch to date. In Q1 2021 the age eligibility was expanded from 55-75 to 50-90 to aid with recruitment for the new Arizona APOE Cohort study. lab. GeneMatch is also helping with recruitment for several studies. We exceeded our ambitious goals for the Colombian API Registry, to date having enrolled nearly 6,000 members of the Colombian PSEN E280A kindred, including nearly 1,200 mutation carriers (19), and we continue to advance the study of AD in members of this extraordinary kindred. We submitted a revision of our R33 grant in November 2020 entitled "*Optimizing Research Infrastructure of Registries to Accelerate Participant Recruitment into Alzheimer's Focused Studies."* This grant received a favorable funding score and would complement our awarded R01 (R01AG063954).

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Alzheimer's Prevention Registry. Jessica B. Langbaum, PhD, Eric M. Reiman, MD, Pierre N. Tariot, MD. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. To increase enrollment into the Alzheimer's Prevention Registry, particularly within Arizona.
2. To increase the number of study opportunities available to Alzheimer's Prevention Registry members, particularly within Arizona.
3. To provide initial metrics of success at connecting Alzheimer's Prevention Registry members with study opportunities, particularly within Arizona.

Background and Significance:

Enrollment and retention of participants are 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, with 30% under-enrolling and only 7% of sites enrolling the projected number of participants in their originally stated timelines. Delayed or inefficient recruitment has scientific, financial, and ethical consequences. The web-based Alzheimer's Prevention Registry (www.endALZnow.org) ("APR") was created in 2012 to help studies meet their enrollment goals in an efficient and timely manner(1). At enrollment, individuals are asked to provide their email address and basic demographic information. Members receive regular email communication to keep them apprised of the latest news in Alzheimer's prevention research. In addition, members receive email notifications when study opportunities become available in their communities, with information on whom to contact to explore the possibility of their participation. In November 2015, the APR launched its GeneMatch program, an IRB approved research program open to adults age 55-75 in the United States who do not have a diagnosis of cognitive impairment(2). Upon enrollment into GeneMatch, participants are provided a cheek swab kit to provide a DNA sample for APOE genotyping, the results from which are used in part to help match to studies. As we continue to promote awareness of the APR and increase enrollment, it is imperative that we increase the number of and types of study opportunities available to members and provide initial metrics of success for connecting APR members to study opportunities, particularly within Arizona.

Preliminary Data:

As of March 2021, more than 353,000 individuals have joined the Registry. Most members have provided some additional demographic information, but the actual number varies from question to question. Based on those who provided additional demographic information, members are predominantly women (75%), report a family history of dementia (50%) (12% are unsure and 18% prefer not to answer) and self-report not having a diagnosis of cognitive impairment (94%).

As of March 2021, the Registry has helped recruit for 131 studies and is currently assisting with recruitment for 46, including 19 Arizona-based studies. We are in the process of onboarding several new studies, including studies taking place in Arizona. The Registry email newsletters are well-received, with an average open rate of 38.7%, and unique click rate of 12.2% in the past 12 months, compared to the industry standard of 16% and 1.6%, respectively. Over the past 12 months, study opportunity emails had an average open rate of 38.1% and unique click rate of 12.6%. We recently received an R01 grant from the NIA (R01AG063954; "Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and

accelerating enrollment into trials"), 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, and an 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. We recently submitted a revision to our R33 application to the NIA, entitled "Optimizing research infrastructure of registries to accelerate participant recruitment into Alzheimer's-focused studies" which received a favorable score and will be reviewed by Council in May 2021.

Experimental Designs and Methods:

To achieve Aim 1, we will work to expand Registry enrollment in Arizona through community outreach efforts and promotion on social media, tracking the success of each strategy and tactic. Concerted efforts will be made to increase the enrollment of individuals from underrepresented populations, particularly of individuals who identify as Hispanic/Latino and African American.

To achieve Aim 2, we will work with researchers across the country to request permission to add their studies to the Registry website, with a particular focus on studies led by Arizona Alzheimer's Consortium researchers. We will monitor clinicaltrials.gov for new study listings while also communicating with researchers on a regular basis to inquire about new studies.

To achieve Aim 3, we will provide initial metrics of success at connecting Registry members with study opportunities, particularly within Arizona. We will track referral and enrollment numbers and time to fill sites' enrollment goals to assess the ability of the Registry to accelerate enrollment.

Proposed One-Year and Long-Term Outcomes:

Results from the Registry will be submitted for publication in peer-reviewed journals and presented at scientific meetings. In addition, data and findings will be used to inform future goals of the Registry. We will continue to seek additional external, non-state funding from NIH, industry and philanthropic organizations to support our efforts to expand the Registry and study the "science of recruitment" leveraging the Registry.

Year End Progress Summary:

The Alzheimer's Prevention Registry is an online community of individuals age 18 and older who agree to receive emails with information about Alzheimer's prevention related research updates as well as notifications about study opportunities within their communities. As of March 2021, the Registry had over 353,000 members and GeneMatch enrolled over 90,000. Enrollment in GeneMatch was paused in April 2019 and reopened in September 2020 following onboarding of our new genetic testing lab. A manuscript describing the design, rationale, and initial results from the APR was published summer 2020(1). A manuscript describing the effectiveness of GeneMatch compared to traditional study site outreach efforts for recruiting participants to AD prevention trials was published in late 2020(3). In September 2020 we were awarded a competitive supplement to our R01 (R01AG063954) to 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. Data collection for this supplement is underway. In November 2020 we submitted a revision to our R33 application to the NIA, entitled "Optimizing research infrastructure of registries to accelerate participant recruitment into Alzheimer's-focused studies" which received a favorable score and will be reviewed by Council in May 2021. In late 2020 we received IRB approval to expand the age eligibility for GeneMatch to ages 50-90 to support enrollment into the recently awarded NIA grant (R01AG069453) "APOE in the

Predisposition to, Protection from and Prevention of Alzheimer's Disease). In Q2 2021 we will begin efforts to enroll >20,000 new participants into GeneMatch, focusing efforts on enrolling new members who live in Arizona.

Aim 1). During the funding period, considerable effort was undertaken to increase enrollment into the Alzheimer's Prevention Registry (APR) and maintain engagement of existing members. Due to COVID-19, we had to pause traditional community outreach efforts (e.g., community talks). As of March 2021, 22,138 APR members indicate they live in Arizona. As part of our engagement strategy, APR members opt in to receive our monthly e-newsletter with the latest news and information in AD research. Of the >353,000 members, 76,166 are considered "actively engaged." In 2020, 12 monthly e-newsletters were sent to APR members. The average e-newsletter open rate was 38.7% (compared to nonprofit healthcare industry average of 16%); the average e-newsletter click rate (percentage of APR members who clicked on the email in relation to those who opened/viewed the email) was 12.2% (compared to the industry average of 1.6%). To date, approximately 68,580 members have been added to the re-engagement campaign, and nearly 16,630 (24.2%) have been successfully re-engaged. We received an R01 grant from the NIA in September 2019 entitled "Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials", data from which will help increase enrollment of men and individuals from underrepresented populations into the APR (and other AD-focused recruitment registries).

Aim 2). The APR has helped recruit for more than 82 AD-focused studies since its inception. Currently, we are assisting with 15 studies in Arizona (including online studies led by Arizona-based researchers), with 3 more in the startup process.

Aim 3). During the funding period (July 2020 to current) we actively promoted 43 studies, including 24 studies taking place in Arizona or open to Arizona residents and taking place online. In June 2019, the "Find a Study" section was updated to include a "contact form" for studies. Under the contact form model, individuals visiting the APR website and who are interested in a study are asked to fill out the form with their name, email address and phone number, review and acknowledge the study's eligibility criteria and authorization for APR to share their contact information with the enrolling study team. Individuals do not need to have joined the APR to search for studies on the website or to complete the contact form. We provide each enrolling study with a dashboard to track their referrals (i.e., inquiries from people who submitted their information via the contact form). Under this contact form model, studies and/or sponsors are required to execute a Data Use Agreement (DUA) due to the transfer of Personally Identifiable information (PII). Implementation of this contact form model allows us to collect the data necessary to compare the success rates of various approaches to promote study opportunities to APR members, tracking members' interest in each study opportunity. During the funding period, 15 studies were using the contact form model, including 6 Arizona-based studies. To date during the funding period we sent 123 referrals to these studies. As mentioned previously, not all studies being promoted on the APR use the contact form, making it difficult to determine how many referrals were sent to these studies. Efforts are underway to transition all studies to the "contact form model" by end of 2021 to allow for better tracking and reporting of referral metrics.

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ARIZONA ALZHEIMER'S CONSORTIUM
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Enhancements to a Centralized Data Management System for the Arizona Alzheimer's Disease Core Center (ADCC), Brain and Body Donation Program (BBDP), and Apolipoprotein E4 (APOE4) Gene Dose Program. Don Saner, MS, Ricardo Amador, MS, Matthew Huentelman, PhD, Bruce Petersen, BS, Thomas Beach, MD, Richard J. Caselli MD, Eric M. Reiman, MD, David Coon PhD, Dave Parizek, BS and colleagues from each of the participating sites. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Mayo Clinic Arizona; Banner Sun Health Research Institute; Translational Genomics Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims

1. Incoporate our online tools into a single portal / code base, so end users do not need to go to multiple URLs. This will make maintenance of the code much easier and more portable.
2. Link data from the APOE Gene Dosing progam, when live on GAAIN, to our Data Discovery Tool to enable investigators to easily request data from the APOE program.
3. Expand on the number of Tableau and Online Reports that are designed to measure enrollment and track over all project health for ADCC, BIFB and APOE cohorts.
4. Expand data, sample and image sharing to the ADCC Brain Imaging and Fluid Biomarkers (BIFB) Core to enable correlations from biomarker data, CSF and imaging to help facilitate less expensive and invasive diagnositics.

Background and Significance

The Arizona Alzheimer's Consortium has three longitudinal research programs which are internationally recognized for their productivity, impact, and value to researchers inside and outside of Arizona in the scientific fight against AD, PD, and related disorders, and the study of normal brain aging. These programs include common data elements, are administered through separate data management programs, and could provide even greater value under a common data management program that is optimized to fulfill the programs' common and complementary research goals. In this project, we propose to enhance the work done in the previous year on a centralized robust data management platform to include more real time reporting, include more data sources, optimize the code that extracts data for NACC submissions to include data consistency checks and create a data sharing platform.

Preliminary Data

Over the past year, with the support of AARC funding, we have continued to build new reports and tools over our centralized database to assist in operations and program optimization including a) incorporating ADCC and APOE data into an ad-hoc query tool; b) the addition of new online reports focused on optimizing day to day operations; c) creation of interactive Tableau reports; d) working with participating sites to optimize workflows; e) changing of our issue tracker tool to be packet based versus single issue; f) executing a three party agreement between USC, Mayo and Banner to enable us to deposit data on GAAIN.

During the current funding period, we completed the first version of a custom application called the Data Discovery tool which will permit internal and external investigators to form ad-hoc queries of the data from our Clinical Core as well as our ancillary APOE Gene Dosing core which collects bi-annual UDS data, biospecimens and imaging.

Experimental Designs and Methods

In the coming year, we will begin the roll out of our Data Discorvery Tool; collecting feedback from internal investigators and making appropriate changes to satisfy internal needs before making it available to external investigators in order to take in reqests for data from our APOE gene dosing program. We have made an initial release of the tool to coordinators who work in the ADCC and APOE programs and are actively soliciting their feedback.

We have executed a three party agreement between GAAIN (USC), Mayo Clinic and Banner Health which will enable us to deposit data on the GAAIN platform enabling investigators to run statistics over the de-identified data set to determine it's utility. We have shared our data dictionary and sample data with GAAIN and will be live soon. Once live we will have a link to the Data Discovery Tool, which permits investigators to submit a request for a data set.

As part of our Data, Biospecimen and Image sharing intiative we have completed the uploading and de-identifying and cataloging of images obtained over 25 years to our Image Analytics Platform, XNAT. All new images aqcuired at BAI under the BIFB and APOE programs are now automatically de-identified and transferred to XNAT through relay boxes.

Proposed One-Year and Long-Term Outcomes

We anticipate that by focusing on building infrastructure to share Data, Images, Biomarker Data and Samples from our affiliated cores we will enable further research into Alzheimer's Disease. More specifically, by sharing data from our BIFB we have the potential to correlate imaging with biomarker data resulting in less expensive and invasive diagnostic tools.

Year End Progress Summary

We have continued to leverage the IT infrastructure built with the assistance of AARC funding to support new programs such as the Bioimaging and Fluid Biomarker (BIFB) core and the new APOE gene dosing (APOE2) grant which was recently awarded as well as expanding our support for existing research programs such as ADCC/ADRC. We are pleased to report that after executing a three way agreement between GAAIN, Banner and Mayo in the previous funding period, we have successfully uploaded data from our APOE Gene Dosing grant to GAAIN and have linked the site to our Data Discovery tool which enables researchers to further explore our data by leveraging an intuitive web based query builder and to submit and process requests for the data and samples.

During the current funding period we have integrated our tools including Redcap2Relational, Issue Tracker, Online Reports, Data Discovery Tool and PDF Generator into a single code base built around the ASP.NET Zero framework. We made significant changes to the Issue Tracker by implementing code to parse the raw output from NACC error reports into discrete issues and assigning them to the appropriate site which significantly reduced the time to get errors and alerts into the Issue Tracker. The code was additionally refactored to remove dependencies on SQL Server Integration Services which made troubleshooting any errors significantly easier. We also extended the Data Discovery tool to permit consortium users to directly download data from the tool, providing a self-service option. We have enhanced our NACC extract tool to allow the extraction of a single participant's data to add more flexibility in the upload process. Online documentation has also been updated to reflect all these changes.

Our library of Online Reports and custom Tableau reports has continued to grow throughout the reporting period. We have enabled PDF versions of Tableau reports to be uploaded alongside our catalog of Online Reports. New reports this year include but are not limited to: Under-Represented Group details and participants likely lost to follow-up. With respect to the Online

Reports we have added the ability to subscribe to have them delivered monthly by email. Towards the end of this reporting period Banner has shifted from Tableau to Microsoft PowerBI which will have greater flexibility in terms of being able to share reports outside of our institution due to the integration with Microsoft Azure. We have begun the process of re-writing our Tableau reports in PowerBI and have so far found it to be a more powerful and flexible tool.

During the past year we have continued to share data and samples with Academic and Corporate partners including: Stanford(SAGA – plasma/serum), USC(PPG – plasma/serum), University of Gothenburg(CSF/Plasma for Blood Based Biomarkers(BBB)) and University of Porto (Serum). We have received 1282 results for NfL BBB are in the process of incorporating these into our Centralized Database while we await amyloid and tau results. We have cataloged 223 imaging sessions in our imaging analytics platform, XNAT during the reporting period which we will be a resource to draw correlations between Blood Based Biomarkers and Imaging.

Project	AV-1451	Florbetapir	PiB	MR	Total
APOE	15		12	12	**39**
BIFB	62	15	50	57	**184**
Grand Total	**77**	**15**	**62**	**69**	**223**

Figure 1: Summary of imaging sessions performed during reporting period

We have continued to send samples to NCRAD from our Alzheimer's Disease Center (ADC) and Bioimaging and Fluid Biomarker which are summarized below.

Samples Sent to NCRAD since 7/1/2020-4/1/2021

	ADCFB	ADCFB/BBBSR	ADCFB/BBBSR/BIFB	ADCFB/BIFB	BIFB	Total
CSF				12	4	16
BUFFY COAT	99	14	17	41	1	172
PLASMA	99	14	17	41	1	172
PBMC	44			31	3	78
RNA	54			38	1	93
SERUM	54			41	1	96

Figure 2: Summary of samples sent to NCRAD. ADCFB: Samples from ADC, BBBSR: Blood Based Biomarker Shared Resource, BIFB: BioImaging and Fluid Biomarker

In addition to the above samples we also have retained plasma and serum samples for our local biorepository as well as CSF from 26 participants in the APOE and BIFB programs. We are very appreciative of the AARC funding which has enabled much of the progress we made this year and in previous years.

Advanced Image and Statistical Data Analysis Techniques for Detection and Monitoring of Alzheimer's and Related Disease. Yi Su, PhD, Dhruman Goradia, PhD, Hillary Protas, PhD, Michael Malek-Ahmadi, PhD, Yinghua Chen, MS, Wendy Lee, MS, Teresa Wu, PhD, Jing Li, PhD, Yalin Wang, PhD, Kewei Chen, PhD, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims

1) To continue maintain and refine automated image processing and analysis pipelines for optimal sensitivity and robustness.
2) To develop and validate machine/deep learning-based techniques that can improve image quantification, facilitate biomarker harmonization, and allow prediction of longitudinal changes.
3) To further develop and validate tau and amyloid PET analysis approaches using network and graph theory.

Background and Significance

Although the disease mechanisms are still not fully understood, AD is characterized neuropathologically by extracellular amyloid accumulations and intracellular tangles of hyperphosphorylated tau protein, both of which can now be measured in vivo using positron emission tomography (PET) imaging. In addition, other AD related changes of the brain such as reduction in glucose metabolism, inflammatory microglia activation, synaptic density changes, and global and regional brain structural changes can be measured and monitored in vivo using either PET or magnetic resonance imaging (MRI). Reliable quantifications of these pathological events using imaging data are critical to the better understanding of AD and the development of successful management strategies. However, several technical hurdles are hampering the derivation of reliable and accurate imaging biomarkers from the raw data. 1) PET has inherently low spatial resolutions due to limitations of imaging physics, and hence, measurements derived from PET data are inaccurate due to artifacts caused by the low resolution. 2) Heterogeneity in quantification methodology for PET and MRI and the imaging PET tracers lead to inconsistent quantitative measurements. 3) The high dimensionality of imaging data calls for advanced statistical methods. We aim to address these challenges in this year's methodological development efforts and making tools available to the local and external research communities.

Experimental Designs and Methods

Aim 1. We will continue to maintain and refine automated image processing and analysis pipelines for optimal sensitivity and robustness. This includes our PET unified pipeline (PUP), the sROI, HCI (both cross-sectional and longitudinal), IPCA, and our SPM based amyloid PET quantification pipelines. We will further streamline our PET processing procedure and integrate the FreeSurfer based ROI analysis with SPM based voxel-wise analysis procedures in a unified pipeline.

Aim 2. We will continue to explore the application of advanced machine learning and deep learning techniques that allow improved image quantification, harmonized image derived biomarkers from multi-center data, and differential diagnosis and prognosis using multi-modal data.

Aim 3. We will further develop and validate the graph theory-based methods using Tau PET data from ADNI and Arizona APOE cohort. We will correlate the novel Tau measurements with

conventional region-based uptake measure, and examine the ability of this approach to differentiate participants at different preclinical and clinical stages of AD. We will also examine the ability of this measurement to track longitudinal changes of Tau burden.

Proposed One-Year and Long-Term Outcomes

In the upcoming year, we anticipate to generate results that further demonstrate feasibility of the proposed techniques in Aim 1-3 and build the foundation for future development and optimization of these techniques. We aim to publish these results in high-impact journals. In long term, we aim to strengthen our imaging and statistical expertise and build a cluster of advanced tools that facilitate the investigation of AD and related disease and the successful development of disease modifying treatments. We also intend to pursue extramural fundings to allow expansion of our methodology development efforts.

Year End Progress Summary

In the past year, the computational image analysis team has continue to maintain and improve its automated image processing and analysis pipelines, develop and validate machine learning and deep learning-based techniques for neuroimaging applications, and continue to investigate graph theory-based methods for tau PET data analysis. It has also used our developing pipelines and algorithms to generate findings in support of new grant applications, abstracts and publications, and support the Consortium's scientific goals.

We further integrated our PET unified pipeline (PUP) using FreeSurfer defined regions-of-interest (ROIs) in the native space with the SPM-based template space PET analysis workflows and created automated procedures to generate hybrid versions of imaging-derived measurements that take advantage of both subject specific information derived from native space analysis, and the stability and consistency provided by a template space approach. We have been using this approach to analyze brain imaging data from our Arizona AD Center, Arizona APOE cohort study, and ADNI, provided new information about the impact of different cerebral and reference ROI's on the power to detect and track AD and evaluate AD-modifying and prevention therapies using amyloid and tau PET images generated using different radiotracers, and we have used this information to inform tracer selection, size and design in upcoming AD prevention trials. Using this hybrid PET quantification workflow, we are currently investigating the optimal imaging measurements for tracking longitudinal tau changes in preclinical and early symptomatic phases of AD using flortaucipir (FTP) data from ADNI and MK6240 data in collaboration with Cerveau. Initial result suggests entorhinal tau SUVR as the most sensitive tau indices in tracking longitudinal tau accumulation in amyloid positive cognitively unimpaired individuals using FTP. A white matter reference region previously optimized for tracking FBP measured amyloid burden may provide some improvement to the statistical power although further investigation is needed. Part of these results is currently included in a manuscript investigating sample size needed for brain imaging endpoints in AD prevention trials. The analysis of MK6240 data also suggest the entorhinal SUVR as an optimal measure to track tau changes in preclinical AD, while Braak stage III regions and temporal meta-ROI regions may be a better choice after symptomatic onset.

We also continue to expand our efforts in using mechine learning/deep learning techniques in AD and neuroimaging research in the past year. In collaboration with Dr. Teresa Wu's team at ASU, we continued our examination of deep learning models to estimate the biological age from T1-weighted MRI data and then use the difference between the estimated biological age and the participant's cronological age to facilitate the prediction of the conversion from MCI to AD. In the previous funding cycle, we developed a deep learning model (AD-NET) for the estimation of an MCI participant's risk of converting to AD within 3 years and achieved an overall accuracy of 76%, a sensitivity of 77% and specificity of 76%, and outperformed all competeing models in terms of the area under the ROC curve. This finding was reported towards the end of the previous funding cycle (Gao et al. NeuroImage: Clinical 2020) and we continued to improve this model and explore

the similar application of this approach in predicting relevant biomarkers and cognitive measuement.

In the past year, we also initiated a major effort to develop and investigate the feasibility of using deep learning/machine learning technques to improve PET image harmonization across different tracers. Currently, the Centiloid scale was proposed to define a standard scale for global amyloid burden measures derived from different acquisition protocols, quantitative pipelines, and imaging tracers. While this is an important step towards standardization, global amyloid measurements obtained from different tracers remains to be statistically different even after transformation into the Centiloid scale. In addition, currently there is a lack of strageies to harmonize across tracer measurements at regional and voxel level. To address this challenge, we developed two different approaches using machine learning and deep learning techniques. We identified two independent datasets, one from the Open Access Series of Imaging Studies (OASIS) with 92 subjects who underwent PIB and florbetapir (FBP) PET within 3 months, and another from the Centiloid Project FBP calibration dataset hosted at the Global Alzheimer's Association Interactive Network (GAAIN) with 46 participants. In the first approach, a Residual Inception Encoder Decoder network (RIED-Net) deep learning model was trained and validated under a cross-validation framework using OASIS dataset and further tested using the independent GAAIN dataset. We demonstrated that the RIED-Net model was able to improve the agreement of global amyloid burden indices from the two tracer from a Pearson's correlation r=0.90 prior to harmonization to r=0.95 after (p=0.0006) in the OASIS dataset and a similar improvement (r=0.97 vs. r=0.93, p=0.0001) was observed in the independent testing dataset. In addition, visual improvements can also be observed in comparing the harmonized FBP image with PIB, and voxel-wise correlation also improved from r=0.89 to r=0.95 for the OASIS data (p<0.0001) and from r=0.90 to r=0.95 for the GAAIN data (p<0.0001). In our second approach, machine learning techniques including ensemble regression, partial least square regression (PLSR), and artificial neural network (ANN) were trained using the OASIS dataset to estimate a virture PIB mean cortical SUVR from regional SUVRs from FBP imaging data, and then the models were tested on the independent GAAIN datset. In the training set, the Centiloid based PiB-FBP correlation was r=0.904. An ANN with 7/6 neurons in the 1st/2nd hidden layers improved it to 0.987 (p<0.0001) and PLRS to 0.973 (p<0.0001). In the independent test set, ANN improved r to 0.981 from 0.927 (p<0.0001) and PLSR to 0.964 (p=0.011). Ensemble regression did not improve r. While we only tested this approach in harmonizing the global amyloid indices, it could be generalized to harmonize regional measurements and will be further investigated. Partial results of this research have been submitted to AAIC 2021 as two abstracts, and two manuscripts are under preparation to report our findings. Building on this research, we also submitted an R01 application (R01AG073424) in October 2020 and received a 36% percentile ranking and positive comments. If the grant is not funded, we will submit a revised application shortely thereafter.

We also continued to develop and examine network analysis approaches to assess tau PET imaging data at individual level. We introduced a novel approach constructing individualized tau network structure and deriving its graph theory-based measures. Using data from the Alzheimer's Disease Neuroimaging Initiative, we demonstrated that the derived network measures were able to differentiate three clinical stages of AD, cognitively unimpaired, MCI and AD. We also demonstrated that these network measures were strongly correlated with regional tau burden measures and memory performance overall. Unlike regional tau measurements, the tau network measures were significantly associated with AVLT-LTM scores even in cognitively unimpaired individuals, supporting its promise in the unusualy early detection of tau tangle deposition. Preliminary results were presented at AAIC 2020; a revised manuscript is in preparation.

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Harmonized Imaging and Biomarker Datasets and Statistical Services for the Arizona Alzheimer's Consortium. Yi Su, PhD, Dhruman Goradia, PhD, Hillary Protas, PhD, Michael Malek-Ahmadi, PhD, Yinghua Chen, MS, Wendy Lee, MS, Gene Alexander, PhD, Rui Chang, PhD, Katrina Devick, PhD, Ben Readhead, PhD, Don Saner, MS, Kewei Chen, PhD, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Mayo Clinic Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims

1) To continue to generate and share brain imaging measurements using state-of-the-art methodologies for multiple large datasets including Arizona APOE study, the Arizona ADCC, and ADNI.
2) To provide extensive statistical research tools, mentorship and/or support for researchers, trainees, and collaborators inside and outside the AAC.

Background and Significance

AD is a disorder with complex etiology and multiple pathogenesis pathways, and currently, there are no disease-modifying therapies for AD, although a variety of treatment strategies are being explored. 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, which in turn result in cognitive decline and dementia. Such efforts are greatly enhanced by the availability of comprehensive dataset such as ADNI, with imaging, fluid biomarkers, cognitive, and clinical measurements. A major local effort within the Consortium is the long running Arizona APOE study which has collected neuroimaging data on over 400 participants with more than 1500 magnetic resonance imaging (MRI) scans and over 2,100 positron emission tomography (PET) scans that characterize the structural, metabolic, and pathological changes of the brain. Another local effort is led by Bioimaging and Fluid Biomarker (BI-FB) core of Alzheimer's Disease Core Center (ADCC) and ancillary programs which aims to acquire imaging data from in both cognitively impaired participants and those who are enrolled in the Brain and Body Donation Program. To leverage the utility of these local and public datasets and allow combined analysis with larger sample size and improved statistical power, we will investigate strategies to generate harmonized imaging and cognitive measurements for these datasets. Our team also has a long history of supporting consortium investigators and provide statistical expertise, we will continue doing so in this year.

Experimental Designs and Methods

Aim 1. We will continue our efforts to provide high quality imaging analysis results from the Arizona APOE cohort, ADCC BI-FB Core, ADNI and OASIS-3 to Consortium investigators. We will develop and validate novel approaches to allow harmonization of imaging and cognitive measurements obtained from different cohorts using different techniques. This includes the continued examination and expansion of the Centiloid approach for harmonizing PET derived amyloid burden measurements and advanced statistical approaches for harmonizing cognitive measurements from different cohorts.

Aim 2. We will continue our effort to facilitate AD research by providing data access and statistical expertise. In this year, we provided support for numerous researchers. Here are a few examples:

a. Dr. Sydney Schaefer (ASU), providing statistical support for her development of novel motor tasks in the application of AD related research and her R01 grant application

b. Dr. Roberta Brinton (UA), providing statistical support for her clinical trial design and potential data analysis
c. Dr. Jiah Yoo (UA), providing statistical support for sample size estimation of her NIH grant application
d. Drs. Thomas Beach and Alireza Atri (BSHRI), providing statistical support to his research.

Proposed One-Year and Long-Term Outcomes

In the upcoming year, we will generate and curate a standardized imaging dataset based on the Arizona APOE cohort and make it available to collaborators. 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 service and assistance.

Year End Progress Summary

In the past year, the Computational Image Analysis Laboratory (CIAL) continued to serve as a core resource for the consortium and local, national, and international investigators to facilitate sharing of data and expertise in imaging and statistical methodology. We extended our efforts to generate and curate imaging derived measurements using standardized pipelines developed in the lab and commonly used imaging analysis tools by the broad AD research community. For the Arizona APOE cohort, in addition to what has been collected in the previous year, 139 FreeSurfer sessions, 148 FDG PUP sessions, 45 FTP PUP sessions, 25 PIB PUP sessions were obtained. For the ADNI cohort, 576 FreeSurfer sessions, 197 FBP PUP sessions, 117 FTP PUP sessions, SPM analysis of 118 FBP scans and 545 FDG scans were curated in the past year. We also collected 128 FreeSurfer sessions, 39 FBP PUP sessions, 85 PIB PUP sessions, and 119 FTP PUP sesssions from the BIFB cohort. Combined with previously processed and curated datasets, across Arizona APOE, BIFB, ADNI, and OASIS, we currently have a database of 4312 T1w-MRI, 1309 PIB, 3393 FBP, 924 FTP, and 5453 FDG scans with quantitative measurements obtained using established pipelines. A summary datasheet for 834 historical and active Arizona APOE participants from 3569 visits were also compiled with 57 variables including basic demographic information, cognitive and clinical assessments, imaging biomarkers, CSF and plasma biomarkers. This data has been shared with several AAC investigators and is available to the broad research community upon request.

The team also continued to working on harmonization of amyloid PET measurements from different tracers and processing pipelines. Using Centiloid calibration datasets deposited at the Global Alzheimer's Association Interactive Network (GAAIN) website, we followed the recommended procedures to establish the Centiloid conversion equations for our SPM and PUP based PIB PET global index measures for 50-70 minutes post-injection time window. We also examined the Centiloid FBP calibration dataset from the same website and established the corresponding Centiloid threshold for any amyloid, moderate amyloid, and frequent amyloid according to previously published studies and Centiloid conversion equations. We are also currently examining the flutemetamol (FTE), florbetaben (FBB), and flutafuranol (NAV4694) centiloid calibration dataset to establish conversion equations for our quantification pipelines.

With state funding support through the Arizona Alzheimer's Consortium, our lab continued to help collaborating investigators performing statistical analysis and experimental design using state-of-the-art methodologies developed by our lab and elsewhere. The lab has also helped collaborating investigators with preliminary data analysis, study design and statistical power analysis to facilitate their grant applications in the planning phases and participate as part of their research team if funded. We also continue to work with Dr. Schaefer (ASU) on sample size/power estimates for her R01 application in addition to her pilot study investigating the utility of a novel motor function assessment in the context of memory and aging. Dr. Malek-Ahmadi co-authored

a recent paper with Dr. Schaefer which was published in the International Journal of Geriatric Psychiatry. We also continue to work with our long term collaborators Drs. Beach and Atri (BSHRI) by providing statistical support for secondary data analyses. Dr. Malek-Ahmadi recently co-authored a manuscript with Dr. Beach that characterized AD pathology burden in adults age 60 and younger. With this support, we also provided initial statistical and trial design service to Dr. Brinton and her team (UA). We also supported Dr. Yoo (UA) for her R21 original and re-submitted applications.

This state funded Statistics and Neuroimaging core resources also continued to work with the Data Management and Statistics Core (DMSC) of the NIH funded Alzheimer's Core Center (P30AG019610) to collaborate with core investigators and serve research communities inside and outside Arizona, organizing monthly meetings, reaching out to consortium-wide investigators for their statistical and machine learning needs, organizing statistical seminars and conferences, and providing mentoring and support to students and junior investigators. Drs. Malek-Ahmadi and Chen have been mentoring a UA-Phoenix medical students to analyze KIBRA and APOE interactions on cognition and neuroimaging markers and the relationship between cerebral hypometabolism and amyloid beta burden separately. Dr. Malek-Ahmadi also mentored a Midwestern medical student who examined the relationship between vascular lesions and tangle burden (published in the Journal of Neuropathology and Experimental Neurology). In May 2021 the DSMC will be presenting a webinar through the National Alzheimer's Coordinating Center where several members will detail methods and approaches used in their genomic and neuroimaging analyses.

Resource to Support Computational Data Analysis and Collaborative Research. Yi Su, PhD, Dhruman Goradia, PhD, Hillary Protas, PhD, Valentina Ghisays, PhD, Michael Malek-Ahmadi, PhD, Yinghua Chen, MS, Ji Luo, MS, Wendy Lee, MS, Rui Chang, PhD, Qi Wang, PhD, Ben Readhead, PhD, Richard J. Caselli, MD, B. Blair Braden, PhD, Astrid M. Suchy-Dicey, PhD, Willemijn Jansen, PhD, Thomas G. Beach, PhD, Geidy E. Serrano, PhD, Don Saner, MS, Kewei Chen, PhD, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Mayo Clinic Arizona; Washington State University; Maastricht University Medical Center; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims

The goal of this project is for the Computational Image Analysis Laboratory (CIAL) at the Banner Alzheimer's Institute to serve as a resource for investigators within and outside of the AAC and provide comprehensive statistical and image analysis services to enable underfunded research efforts that are important to the advancement of Consortium goals and AD research in general.

Background and Significance

Over the years, the CIAL team has continued to serve as a core resource of imaging and statistical expertise to facilitate AD and neuroimaging research by collaborating with local, national, and international investigators. With state funding support through the Arizona Alzheimer's Consortium, our lab has helped collaborating investigators perform imaging and statistical analysis using state-of-the-art methodologies developed by our lab and elsewhere. The important research and analysis performed through this grant has the potential for publication and lasting impact on the general research field that would otherwise lack funding support. The lab has also helped collaborating investigators with preliminary data analysis, neuroimaging study design and statistical power analysis to facilitate their grant applications in the planning phases and participate as part of their research team if funded. We would like to continue this effort to enhance collaborations in important areas of AD research.

Experimental Designs and Methods

We will continue our effort to facilitate AD research by providing data access in addition to imaging and statistical expertise. Originally identified projects include:

a. Dr. Caselli (Mayo), continuing the analysis of longitudinal Arizona APOE cohort to identify early predicators of cognitive decline.
b. Dr. Braden (ASU), supporting her K01 training award and developing her expertise in imaging and statistical methodologies.
c. Dr. Chang (UA) and Drs. Readhead and Wang (ASU), continuing ongoing collaborative research in the investigation of aging and AD related change in metabolic profiles and approaches to leverage Big Data techniques.
d. Dr. Suchy-Dicey (Washington State University), continuing the collaboration on the investigation of the native American cohort in aging and AD using structural MR techniques.

Additional projects during the past year partially supported by this grant:

e. Dr. Yalin Wang (ASU), supporting his R21 research and AD related research efforts
f. Dr. Gwenn Smith (John Hopkins), supporting her depression and dementia research
g. Dr. Yakeel Quiroz (MGH), supporting her R01 research
h. Dr. Longo (Stanford), FDG data analysis for early phase intervention in paitents with AD

i. Investigation of blood-based biomarkers

Proposed One-Year and Long-Term Outcomes

In the upcoming year, we anticipate an abstract/manuscript on the early imaging markers that are predictive of cognitive decline and progression to MCI based on the collaboration with Dr. Caselli. We also anticipate at least one manuscript on the validation of novel blood-based biomarkers. We will continue to work with Dr. Chang and Readhead to develop studies aiming at leveraging Big Data resources and approaches in the investigation of AD. We will also support other investigators as needed inside and outside AAC to advance AD research.

Year End Progress Summary

The past year has been challenging due to the COVID19 pandemic, for which one of the consequences was the reduced overall funding to AD research from the State of Arizona. To maintain the level of support that our analysis team provides to ADRD researchers in and out of Arizona, this resource grant was set up to supplement our long running Statistcs and Neuroimaging Core Resources grant and help collaborating investigators perform imaging and statistical analysis using state-of-the-art methodologies developed by our lab and elsewhere. The important research and analysis performed through this grant has the potential for publication and lasting impact on the general research field that would otherwise lack funding support. The lab also helped collaborating investigators with imaging and data analysis to facilitate their grant applications. Here we summarize the research fully or in part supported by this award.

We continued to work with Dr. Caselli (Mayo), sharing imaging derived measurements on the Arizona APOE cohort, and investigating the relationships of biomarker changes in this cohort. Based on this research, Dr. Malek-Ahmadi has completed an analysis involving the correlation of plasma NfL with neuroimaging measures and will be submitting the abstract to Society for Neuroscience 2021. In the continued collaboration with Dr. Braden (ASU), we provided data and image analysis for her K-ward on the study of autism and we are in the process of assisting her subsequent R01 application. We continue to work with Dr. Chang (UA) to follow up with our earlier joint R01 application for the Predictive Network Study of Blood-based Aging-related Metabolic Biomarker and Therapeutics for Preclinical Stage of Alzheimer's Disease. Working with Drs. Qi Wang and Benjamin Readhead at ASU, we continue our effort to leverage multi-omics data for AD research. With leading efforts from Dr. Qi Wang, we facilitated the examination of whole-genome DNA methylation data from peripheral blood collected by the ADNI study and confirmed a previously identified quantitative trait locus for AD from brain tissue studies and implicated its dynamic role in the disease progression. This research was presented in AAIC 2020 and subsequently published in Clinical Epigenetics. More recently, we worked with the same ASU team to facilitate the analysis of transcriptomics data from the AMP-AD consortium to identify and characterise the transcriptomic signature of AD and its progression trajectory. Based on this trajectory, a AD severity index was derived and its relationship to the accumulation of amyloid and tau burden in addition to the degradation of cognitive and clinical symtoms were characterized. This research is currently under consideration for presentation at AAIC 2021 and we are also working with Drs. Wang and Readhead on a manuscript. In the continued collaboration with Dr. Suchy-Dicey at Washington State University, our analysis team completed the initial analysis of structural MR data from the Native American Strong Heart Study cohort and is working on summarizing quantitative measurements. Dr. Suchy-Dicey also presented at AAIC 2020 on the relationship between APOE genotype, brain imaging measures, and neuropsychological measures in this cohort.

In addition to the research and collaboration originally planned, we also worked on several other projects with partial support from this resource award. We are corrently working with Dr. Yalin Wang (ASU) to support his R21 projects aimed at developing univeriate neurodegeneration imaging markers. We also worked closely with him on two grant applications in the past year

providing our strong imaging and statistical supports. This collaboration resulted in two journal articles and a peer reviewed conference paper (Stonnington et al. JAD 2021; Wang et al. MIA 2021; Wu et al. ISMIPA 2020). Last year we also initiated with our statistical and imaging analysis assistance to Dr. Gwenn Smith (JHU) in her study on depression, a risk factor for dementia. Using our multi-modal partial least square (MMPLS) methods, we characterized the covarying patter between serotonin transporter and beta amyloid deposition in people with late-life depression compared to healthy controls. We found the covarying patterns are significantly associated with the severity of the depression. A manuscript was submitted recently. We also subsequently joined her team for an R01 grant application earlier this year. Using the same MMPLS algorithm and collaborating with Dr. Yakeel Quiroz (MGH) for co-analyzing her PiB amyloid PET and task functional MRI data to unearth the association between the degree of brain activation and the beta-amyloid burden. We also used our statistical region of interest (sROI) method to help Dr. Longo (Stanford) for his AD intervention effect on cerebral glucose metabolism with interesting and positive findings.

Blood-based biomarkers (BBB) has become an emerging area of active research in AD, and our team has also contributed to the effort of validating and examine BBB in their ability to detect early pathological changes and tracking disease progression. Based on work initiated in previous funding cycles, two papers were published at the beginning of this funding period, one validating plasma ptau217 for discriminating AD from other neurodegenerative disorders (Palmqvist et al. JAMA 2020, Janelidze AAIC 2020), the other investigating serum neurofilament light chain levels in relation to white matter integrity in the DIAN cohort (Schultz et al. Neurobiology of Disease, 2020). We also continue our effort to examine BBB data from our Arizona APOE cohort and ADNI.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Native American Outreach, Recruitment, and Retention Program. David Weidman, MD, Lori Nisson, LCSW, Richard Caselli, MD, Alireza Atri, MD, PhD, Eric M. Reiman, MD, Pierre N. Tariot, MD, Jennifer Craig-Muller, and David Coon, PhD. Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims

1. To forge close working relationships with members of our Native American Community in the awareness, care, and scientific understanding of Alzheimer's disease (AD) through educational and service-related outreach activities.
2. To support the participation of interested Native Americans in the ADCC clinical core and research studies of interest.
3. To work with partners that specialize in Native American recruitment to increase Native American enrollment to advance AD research from this understudied, underserved population.

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 participate in research studies. We have continued to attract a number of interested participants from the Urban Native American community to participate in the Arizona Alzheimer's Disease Core Center (ADCC) Clinical Core. In addition, we recently partnered with Medstar who operate the Strong Heart Study in Phoenix and have strong relationships with the urban Native American Population. Through the partnership, Medstar educates their community about research and facilitates enrollment (scheduling and transportation) for those who are interested.

Preliminary Data

A cumulative 94 Native Americans have been enrolled across the consortium as of February 2021. Of those 94, 63 are currently included in the NACC database. Overall, there are 50 active ADCC participants, 42 discontinued participants, and 2 deceased participants.

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 seniors and caregivers. Many tribes have been working to sustain their communities with the basic needs of food, water, medical supplies and other essentials. In addition, limited staffing, limited internet access and a high rate of disease spread created serious challenges for these communities. Therefore, the outreach team pivoted and restructured efforts in collaboration with departments that serve the elder population to balance tribal community priorities. Due to safety concerns, the 16th Annual Conference on Native Americans and Alzheimer's disease was canceled. Despite these challenges, the Native American outreach team reached 225 professional care providers during this time in virtual programs including a train-the-trainer Workshop on Intellectual Disabilities and Native Peoples: Dementia Capable Care of Adults, which reached 40 allied health professionals.

The program launched a new Native American BAI Beacon e-Newsletter offering caregiver topics, brain health and opportunities for care reaching 500 family caregivers and community members per month. Due to limited face-to-face contact, Beacon Spotlight handouts were developed featuring culturally sensitive Alzheimer's disease information to support caregiving during this challenging providing education, care strategies and available resources. During the second half of 2020, more than 2,000 Native American Beacon Spotlights were developed, printed and distributed to eight tribal community programs: Zuni Senior Center, Mo-Chem-Ho-Na Senior Center / Colorado River Indian Tribe, Quechan Senior Center, Ak-Chin Indian Community, Tohono O'odham Department of Health and Human Services, Pascua Yaqui Tribe Health Department / Tucson, Pascua Yaqui Tribe / Guadalupe, and Liogue Senior Center at Pascua Yaqui Tucson. In 2021, more than 750 Native American Beacon Spotlights have been developed, printed and distributed to Yavapai Apache Nation Senior Program, San Carlos & Bylas Apache Older Adult Center and Fort McDowell Yavapai Apache Nation. In August 2020, our team launched an original, monthly Native American Circle Group phone discussion group with a focus on living well during COVID times, offering care strategy topics, support and resources for family caregivers of persons with dementia reaching more than 25 family caregivers located in Arizona, New Mexico and Oregon.

In 2020-2021, despite the continued challenges from the pandemic, we were able to reschedule 22 of the remaining 29 referrals from the SHSS, which has resulted in 12 initial visits and 10 more enrollments to date, for a total of 14 enrollments. As a comparison (mostly pre-pandemic), in the prior budget year, 2019-2020, we initiated interactions with the Strong Heart Stroke Study (SHSS) which resulted in 33 referrals, 20 scheduled visits and 4 enrollments within the first 2 months of the partnership. Unfortunately, the remaining visits were cancelled because of the COVID-19 pandemic.

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. Adapt recruitment and enrollment techniques to remove the common barriers that prevent Native American referrals from enrolling into the ADCC
    a. Full IRB approval of remote visits
    b. Modify cognitive battery to shorten overall visit length
    c. Coordinate participant visits who are traveling far distances to ease the burden of locating transportation
3. Help to recruit and retain Native Americans into the ADCC Core, such that we are following >75 actively enrolled NAs at BAI, and >100 NAs at all of our clinical core sites by July 2022, capitalizing in part on emerging relationship with our colleagues from the SHSS
    a. Target 2 enrollments per month from Native American outreach; goal of 24 new enrollments per year
    b. Expand contract with SHSS to maintain referral stream and supplement enrollments from outreach efforts; goal of 40 enrollment per year
4. Refine methods to reach more Native Americans from youth to elders to educate using the Native American Brain Health and Dementia Friends programs.
5. Increase national engagement, knowledge, and collaboration amongst clinicians and researchers treating Native Americans using data gathered through the study. Leverage available data for educational purposes at the Annual Conference on Alzheimer's disease in Native Americans.

Year End Progress Summary

Aim 1: During the past year, our education and outreach programs reached 225 professionals and approximately 500 family caregiver and community participants from the Native American tribal communities across Arizona. Many topics focused on Brain Health and caregiver wellness, Alzheimer's disease education and encouraging tribal communities to help raise awareness and lower stigma. Due to limited face-to-face contact Beacon Spotlight handouts were developed featuring culturally sensitive Alzheimer's disease information to support caregiving during this challenging providing education, care strategies and available resources.

Aim 2: During the 2020 calendar year for the Native American cohort, across the consortium, we enrolled 15 new participants, 22 initial and follow-up assessments were conducted, 17 participants were withdrawn, and 1 participant died. As of second quarter 2021, we enrolled an additional Native American participant and anticipate enrolling two more. We will continue to work with the ADCC Education Core to find ways to optimize retention in our longitudinal research program. With our SHSS partnership, and resumption of in-office participant visits, we anticipate recruiting and retaining interested Native American participants at a greater frequency the remainder of 2021 through 2022. We have continued to reach participants through community outreach, anticipate community events to resume should pandemic restrictions lift, and we have begun to explore new relationships with partnering organizations to help in the recruitment, retention, and productive study of Native American research participants.

Aim 3: BAI Native American Program has received funding from the Mary and Stanley Smith Charitable Trust for NA Outreach, to support development and advancement of culturally sensitive Native American education and support programs. In addition, we recently partnered with Medstar who operate the Strong Heart Study in Phoenix and have strong relationships with the urban Native American Population. Medstar maintains an active database of Native Americans that are interested in participating in research and provides regular communication to those in the database. Medstar also pairs each referral with an outreach coordinator who supports the participant throughout the enrollment process. This model provides the participant a trusted, well-known resource which contributes to the higher conversion rate compared to general outreach. According to Medstar's director, Cyd West, the overall willingness to participate in research has increased in the Native American community during the COVID-19 pandemic and they have seen an increase of people joining their referral database. We have extended our partnership with Medstar and will continue to utilize their expertise to increase enrollment into the ADRC.

In Fall of 2020, in conjunction with colleagues at Washington State University, we generated an original public health report, which used Banner Health system EHR data to estimate age-adjusted prevalence of AD and related disorders (ADRD), and assess the medical risk factors associated with an increased risk of an ADRD in American Indians.[1] We plan to continue this collaboration and maintain a dialogue on what strategies they have implemented to successfully recruit and retain Native American participants into various research studies.

References

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Project Progress Reports
Barrow Neurological Institute
at St. Joseph's Hospital and Medical Center

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Comparative transcriptomics of the blood-CSF barrier in frontotemporal dementia (FTD), Alzheimer's disease and Amyotrophic lateral sclerosis (ALS)-FTD. Nadine Bakkar, PhD.
Barrow Neurological Institute and St Joseph's Hospital and Medical Center; Arizona Alzheimer's Consortium.

Specific Aims:

We hypothesize that FTD, AD and ALS-FTD have distinct BCSF barrier molecular signatures contributing to pathogenesis and aim to find disease commonalities as well as unique profiles.

1) **Specific Aim 1**: Comparative transcriptomic analysis of post-mortem CP from AD vs FTD vs ALS-FTD
2) **Specific Aim 2**: To develop and characterize in vitro CP models from patient-derived iPSC cultures for target validation

Background and Significance:

The choroid plexus (CP) is a single polarized epithelial cell layer that forms the BCSF barrier and constitutes a highly selective gate into the CNS. It functions in the regulation of the neuroimmune response under inflammatory conditions, the secretion of growth factors to support neural stem cells, as well as the transport of nutrients into and out of the CSF. To date, there have been some indirect implications of impaired or leaky BCSF barrier, but there are no studies that focus and investigate in depth the BCSF barrier and CP alterations in FTD, AD and ALS-FTD patients. As such, the CP is a novel unexplored area and as such warrants further investigation. Moreover, there have not been any attempts in the literature so far to compare and contrast these diseases that cause superficially similar neuronal loss in the frontal cortex, yet have very distinct phenotypes in other regions of the brain. Developing and characterizing *in vitro* models of CP from human samples has not been previously attempted and will prove to be of utmost importance for the fields of neurobiology as well as drug delivery.

Proposed One-Year and Long-Term Outcomes:

Data generated from this project will shed the light onto potential inherent commonalities and differences in the CP of AD, FTD and ALS-FTD compared to controls, and establish novel *in vitro* patient-cell derived models to study the BCSF barrier. Given the unique role of the CP as a gate into the CNS, this will in turn help with development of better drug delivery routes for neurodegenerative diseases. As a junior investigator, this grant will help generate preliminary data to apply for larger national multi-year grants to further my scientific career.

Progress Summary:

With the obtained funding we have been focusing on establishing models of BCSF barriers based on induced pluripotent stem cells (iPSC), as well as characterizing them. We have been growing these cells and optimizing a differentiation protocol into choroid plexus epithelial cells. This is a very delicate process that requires a balance of growth factors (BMP4), a specific cellular density and a cellular matrix. After multiple failed rounds, we now have a batch of control iPSC successfully differentiated into choroid plexus cells and are characterizing all the cellular markers expressed by these cells to assess their full phenotype. We have also meanwhile started the differentiation of FTD iPSCs.

In addition, we have postmortem CP explants growing. We have collected CP from 3 autopsies, and are growing some explants in cellular media. These explants have been successfully kept in culture for one month now and we are getting ready to treat them with patient-CSF to assess whether exposure to CSF can activate these cells. This model of CP explants will prove highly useful for in-vitro studies as it contains stromal cells in addition to CP epithelial cells.

Third, and in regard to Aim 1, we have compiled a first set of fresh frozen postmortem CP samples, with 6 AD, and 6 FTD for use in the comparative transcriptomic analysis using Nanostring. RNA was extracted and the samples should be loaded onto the plates by end of the month. We have also collected paraffin slides of AD, FTD and ALS-FTD that we are planning to use laser-capture microscopy to separate CP cells and stroma and perform a similar transcriptomic analysis. This latter analysis will be more specific as it will focus on signals originating exclusively from the CP.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Synapse loss in frontotemporal dementia (FTD): Validation by immunohistochemistry in FTD/ALS patient post-mortem tissues and PET imaging in a FTD mouse model. Rita Sattler, PhD; Chad Quarles, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

In almost all neurodegenerative disease with a cognitive component, synapse damage or loss is the major driver of cognitive decline, even more than the amount of neurotoxic plaque, tangles. proteinopathies and neuronal loss. Based on genetic, pathologic and symptomatic overlap, ALS, a motor neuron disease, is now recognized as a spectrum disorder with FTD. Up to 50% of ALS patients exhibit some degree of FTD-like cognitive impairments, while a large degree of FTD patients exhibit motor neuron dysfunction. Therefore, it is not surprising to see increased synapse loss in prefrontal cortical regions of ALS patients with cognitive impairment compared to cognitively normal ALS patients. Identifying these deficits early in the disease progression of a patient will not only improve patient care, but also allow patient stratification towards clinical trials targeted specifically at this patient subgroup. Recent early developments of novel positron emission tomography (PET) ligands targeting synapse directly, such as synaptic vesicle glycoprotein 2A (SV2A), are hypothesized to allow for the early detection of synapse loss in patients characterized by synaptopathies [1-6]. Until these ligands are fully characterized and can be synthesized more readily, measurements of glucose metabolism rates using fluorine-18 fluorodeoxy-glucose (^{18}[F]-FDG) PET provides an indirect measurement of synaptic density. Synaptic transmission, which includes neurotransmitter synthesis, release and recycling, heavily depends on ATP, which is why a disruption in glucose metabolism is hypothesized to be a direct measure of synaptic dysfunction [7-10].

Here, we will examine postmortem autopsy brain tissues of FTD/ALS patients for synapse loss via immunohistochemistry. At the same time, we will validate ^{18}[F]-FDG PET tracer as a marker for synapse damage or loss in a progranulin knock out mouse (*Grn*$^{-/-}$), a well characterized model of FTD and which has been shown to exhibit cortical synapse loss and other pathologies seen in FTD/ALS patients, including cytoplasmic inclusions of TAR DNA-binding protein 43 (TDP-43).

Specific Aim 1: Immunohistochemistry of SV2 and other synaptic marker proteins in FTD/ALS postmortem tissue sections

Specific Aim 2a: Visualization of glucose metabolism as a surrogate for synaptic function in *Grn*$^{-/-}$ mice using ^{18}[F]-FDG PET ligand.

Specific Aim 2b: Validation of PET imaging data using Golgi stain for spine densities and immunohistochemical analyses for SV2 in *Grn*$^{-/-}$ mice

Background and Significance:

Cognitive dysfunction observed during normal ageing is known to parallel selective loss of synapses and changes in spine density and morphology [38]. These changes are also observed in numerous neurodegenerative dementias (e.g. Alzheimer's disease (AD) [39-41] and FTD [42, 43], and other neurodegenerative diseases (e.g. Huntington's disease, Parkinson's disease) [44-47]). The degree of synapse loss in AD strongly correlates with cognitive decline, even more than the amount of plaque, tangles or neuronal loss [40, 48-51]. Most interestingly, a recent study of ALS postmortem tissues confirmed increased synapse loss in the prefrontal cortex of patients with reported cognitive impairments compared to ALS patients without cognitive deficits, suggesting that dementia-associated synapse loss is not unique to AD [52]. Furthermore,

neuronal dysfunction in FTD is often associated with changes in dendritic branching and/or spine density [43], known to contribute to cognitive impairment and learning deficits [41, 53, 54].

The progranulin knock out mouse, *Grn*$^{-/-}$, is one of the most well characterized FTD mouse models available and was chosen for the proposed studies based on its prior characterization of significant synapse loss and the generation of TDP-43 cytoplasmic accumulations [43, 55-57], the latter being a hallmark of ALS disease pathogenesis as well.

Preliminary Data, Experimental Design and Methods:

Aim 1: Immunohistochemistry of SV2 and other synaptic marker proteins in FTD/ALS postmortem tissue sections

Immunohistochemistry. To measure synapse loss in FTD/ALS patient postmortem tissues, we will obtain tissues from 15 individuals per group (FTD/ALS, healthy controls) through the Target ALS Multicenter Postmortem Tissue Core, which the Sattler lab has been using for over 5 years. Tissues will be immunostained for synaptic marker proteins including SV2, synaptophysin, PSD-95 and Homer. Images will be taken on a Zeiss 800 confocal microscope, followed by Imaris image analysis. If necessary, structure illumination microscopy (SIM) will be applied through the microscope facility at ASU.

Aim 2a: Visualization of glucose metabolism as a surrogate for synaptic function in Grn$^{-/-}$ and wildtype mice using ^{18}[F]-FDG PET ligand.

Breeding. B6(CG)-Grn$^{tm1.1Aidi}$IJ mice (2 male, 6 female) will be obtained from Jackson Laboratories and used for breeding using standard protocols for homozygote x homozygote mating. We will breed 12 *Grn*$^{-/-}$ mice (6 male, 6 female) for the proposed PET tracer analysis. 12 wild type mice (6 male, 6 female) of the same background and age will be bred at the same time. Mice will be used for PET analysis at 9 months of age based on the published phenotypes of these mice.

PET/MRI imaging. Mice will undergo PET scans with an 3 ring ALBIRA SI preclinical PET scanner (Bruker, Billerica MA). Mice (fasted overnight) will be anesthetized with 2% isoflurane and injected with ~8MBq of PET tracer via intraperitoneal injection, then returned to their cages. After 60 minutes, mice will be anesthetized again with 2% isoflurane and placed on a Bruker multi-modality mouse bed for PET scanning. A 20 minute PET scan will then be initiated while the animal is anesthetized with 2% isoflurane.

After finishing the PET scan, the mice will be moved to the preclinical MRI (Bruker, Billerica MA) for scanning. The mice will be kept anesthetized when moved between scanners and will be kept in the same Bruker multi-modality bed for both PET and MRI scanning. A tube filled with water and PET tracer will be placed in the bottom of the multi-modality bed and will act as a fiducial for registering the PET and MRI images.

Data analysis. The raw list mode PET data will be reconstructed using Bruker's 3D iterative ordered subsets expectation maximization algorithm with a grid size of 150 x 150 x 550 (voxel dimensions 0.5 x 0.5 x 0.5 mm^3).

Aim 2b: Validation of PET imaging data using Golgi stain for spine densities and immunohistochemical analyses for SV2 in *Grn*$^{-/-}$ mice

Golgi staining. Freshly dissected mouse brains (50% of imaged animals) will undergo standard Golgi staining procedures [64], as shown in our preliminary data. After complete incubation steps, frontal cortex and hippocampus will be cut using a Leica CM3050S cryostat and mounted on gelatin-coated slides. Staining procedures will be followed as described. Slides will be dehydrated with ethanol and mounted with Permount (Fisher Scientific) for microscopy. Dendritic branching, length and synapse density will be quantified using Image J and Zen imaging software.

SV2 and other synaptic maker protein immunolabeling. The remaining animals will be used for standard immunostaining for SV2 and other synaptic marker proteins (synaptophysin, PSD-95, Homer) of PFA fixed 20µm thin brain sections. After the quantification of protein labeling using

Imaris software, the data will be directly compared to the uptake of PET tracer between the two study groups.

Proposed One-Year and Long-Term Outcomes:

By the end of this proposal we expect to show reduced SV2 labeling in FTD/ALS patient postmortem tissue to justify a biomarker trial with a small cohort of FTD/ALS patients. We further expect a validation of the use of [^{18}F]-FDG PET tracer as a measure for loss of synaptic activity. The direct comparison between PET images and immunolabeling, together with Golgi analyses, will provide further justification for the use of this PET tracer to quantify synapse loss. The data will be integrated into a larger NIH proposal to support the proposed patient biomarker study.

Year End Progress Summary:

Aim 1:

We have just received postmortem tissue samples from ALS/FTD and healthy control samples, which we will process for immunohistochemistry.

Aim 2a/2b:

The Grn-/- mice are aging in the BNI animal facility and will reach the 9 months time point at the end of May 2021. At that time, we will proceed with the proposed experimental plan outlined above.

The team is scheduled to meet March 25th, 2021 to go over the exact experimental protocol and procedures for the mouse PET scans and the follow up brain tissue analysis.

Diagnostic and Potential Prognostic Value of Finger Tapping Abnormalities in Assessing Older Adults with Memory Complaints. George P. Prigatano, PhD, Ashley M. Stokes, PhD, Anna Burke, MD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Demonstrate that abnormally slow speeds of finger tapping, larger variability in finger tapping speeds, and the presence of "invalid" tapping movements can reliably separate older patients with Subjective Memory Complaints (SMC) with normal neuropsychological status from older patients who meet clinical criteria of Mild Cognitive Impairment of the Amnestic Type (MCI-A) and the early stage of probable Alzheimer's Disease (AD).

Aim 2: Investigate neuroimaging correlates of finger-tapping abnormalities that may shed insight into neurodegenerative processes in regions structurally and functionally connected to finger-tapping task activity. We hypothesize that correlations between neuroimaging-based connectivity will be observed in the frontoparietal region (with less structural connectivity in the AD and MCI groups compared to the SMC and HC groups); moreover, we hypothesize that reduced activation will be observed in the contralateral sensorimotor cortex and ipsilateral cerebellum, while ipsilateral deactivation will be inhibited in the motor cortex in the affected (MCI and AD) groups, relative to SMC and HC groups.

Background and Significance:

Cognitive decline is a common concern in aging populations. A proportion of older individuals exhibit a mild but objective decline in their memory (MCI), and these patients have a higher risk of progressing to AD. In addition, individuals who complain of memory impairment but demonstrate normal performance on tests of memory may be classified with SMC. Identifying individuals with SMC and MCI on either trajectory (to develop or not develop AD) is important for reducing emotional distress and helping them and their families make decisions concerning their future care. Recent evidence has suggested that finger tapping measures (speed, inter-tap intervals, and variability) could separate healthy older individuals from those with AD and MCI. Finger tapping abnormalities may have diagnostic value for separating SMC patients from AD and MCI and for identifying which MCI patients will progress to AD. Combining these metrics with an advanced MRI protocol will provide insight into the underlying early neuropathological changes associated with altered finger-tapping performance.

Preliminary Data:

We previously performing a modified version of the Halstead Finger Tapping Test (HFTT) in 107 normal functioning individuals. Tapping performance was classified in terms of speed and inter-tapping variability, as well as the presence of "invalid" tapping movements that occurred during the tapping task. Older individuals (60-80y.o.) were expectedly slower in tapping speed and had more invalid tap movements compared to younger individuals. In addition to age differences in speed and invalid tapping movements, we have also observed differences in older adults with varying cognitive complaints, where AD and MCI patients tapped significantly slower than the normal functioning individuals. We also previously studied neuroimaging correlates of HFTT and have developed an advanced MRI protocol specifically for use in aging and AD, which includes structural, microstructural, and functional biomarkers. This study will assess neuropsychological (including finger-tapping) and neuroimaging biomarkers in healthy aging and patients with SMC, MCI, and AD.

Experimental Designs and Methods:
This study is a cross sectional group design without repeated measures. Four groups of participants will be studied (n = 20 in each group), including normally functioning older adults, SMC, MCI, and probable early AD. A standard clinical neuropsychological examination will be conducted for all patient groups. This clinical evaluation will include a clinical interview, the BNI Screen for Higher Cerebral Functions (BNIS), Wechsler Adult Intelligence Scale-IV, Rey Auditory Verbal Learning Test, Brief Visual Memory Test-R, Trail Making Test A and B, and the modified version of the Halstead Finger Tapping Test. Following neuropsychological assessment, subjects may undergo an optional MRI sub-study. MRI will be performed at 3T (Philips) using an advanced protocol developed by Dr. Stokes. The MRI protocol will include standard structural imaging (to assess regional atrophy patterns), microstructural imaging (using diffusion MRI to assess WM structural connectivity), perfusion MRI (to assess blood flow), and functional MRI with both resting-state and task-based paradigms (to assess connectivity and neuronal activation patterns). We will assess finger tapping measures across groups, as well as neuroimaging correlates of these finger tapping measures.

Proposed One-Year and Long-Term Outcomes:
The first goal of this study is to test the general hypothesis that abnormalities of finger movements (including invalid tapping movements) when performing the modified HFTT can reliably separate patients with SMC, MCI and early AD. The second goal of this study is to establish neuroimaging correlates related to finger tapping abnormalities, which may shed light into structurally and functionally connected regions implicated in this early signature of incipient cognitive decline. Finally, this study will establish a database which would allow for future monitoring of finger tapping movements over time in each of these three groups. We plan to use these results as preliminary data to support further funding from the National Institute of Aging (NIH/NIA).

Year End Progress Summary:
Four subject groups are being recruited for this study (current recruitment indicated): cognitively normal (CN) (n = 6), SMC (n = 5), MCI (n = 7), and AD (n = 2). Of these 20 subjects (age (mean ± standard deviation (S.D.)) = 73 ± 5 years, 8 male), 9 have completed MRI and another 5 are scheduled for MRI. We have 6 additional subjects in screening. All subjects were right-handed.

The patient cohorts (SMC, MCI, and AD) underwent cognitive testing using the standard neuropsychological battery, as described above, as part of their standard of care. Following their clinical visit, all subjects were electronically consented for this study. Their neuropsychological data was then entered into the REDCap database for each assessment. For the healthy controls, participants consented prior to completing an abbreviated battery (BNIS and HFTT). In a subset of subjects, MRI data were acquired at 3T (Ingenia, Philips) at the Barrow Neurological Institute. Structural MRI data are obtained using ADNI (Alzheimer's Disease Neuroimaging Initiative) protocols. Diffusion MRI data are acquired to assess microstructural integrity. An advanced multi-echo, multi-contrast MRI method is used to measure functional activation (via the fMRI blood oxygen level dependent (BOLD) response) with distinct, complementary global and microvascular sensitivities. Tasks include vision, self-reflection, and motor tasks (right and left finger-tapping), as well as resting-state fMRI.

Preliminary analysis shows a trend for the BNIS across cohorts, where the CN, SMC, MCI, and AD groups show age-corrected total t-scores of 58 (SD 0), 55.4 (SD 8.3), 29.3 (SD 12.8), and 16.5 (SD 2.1), respectively. Domain-specific trends in the BNIS were observed for memory and visuospatial sub-scores, with more subtle trends in awareness, orientation, and language. For the HFTT scores, we observed mean finger-tapping scores of 47, 42, 41, and 40 (right hand) and 40, 38, 36, and 32 across the CN, SMC, MCI, and AD groups, respectively. The corresponding t-scores were 46.0, 46.8, 45.9, and 43.0 (right hand) and 44.0, 46.8, 43.0, and 38.0 (left hand) across the CN, SMC, MCI, and AD groups, respectively. Finally, the range of scores for the right

hand was 7, 11, 16, and 21 across the groups. Further analysis of scores for the remaining cognitive assessments is currently underway across groups.

For the MRI data, segmentation and parcellation is performed on the structural T_1-weighted images using standard FreeSurfer (http://www.freesurfer.net) pipelines. Diffusion MRI data undergo our standard pipeline, including denoising, motion and eddy current correction, bias field correction, brain extraction, and creation of a group-wise template. Diffusion tensor imaging parameters are obtained using FSL (https://fsl.fmrib.ox.ac.uk/fsl/), and anatomically-constrained tractography is performed to assess structural connectivity. Functional MRI analysis steps include motion alignment, distortion correction, de-spiking, and temporal alignment. Subsequently, dynamic maps of quantitative relaxation times are generated to assess global and microvascular activation. All images are then normalized to standard space and group-wise statistical analysis of task response is performed for each task. For resting-state fMRI, independent component analysis (ICA) is performed to assess functional connectivity. Correlations between neuropsychological assessments and neuroimaging data will be performed using Spearman's correlations. Data analysis for MRI is ongoing.

Based on our preliminary data, we submitted a new R01 application (Stokes – PI, Prigatano and Burke – Co-I) entitled *Development of multi-contrast functional MRI biomarkers of aging and Alzheimer's disease* to NIH-NIA in October 2020.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Collection of biofluids and generation of cell lines from AD and FTD patients. Meredith Wicklund, MD, Anna Burke, MD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) Collect longitudinal clinical information, blood, CSF and urine samples from AD and FTD patients.
2) Process samples and store serum, plasma, CSF and urine samples in the Biobank at Dignity Health to make these samples available to the research community.
3) Isolate patient PBMCs for the generation of pluripotent stem cells.

Background and Significance:

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are neurodegenerative disorders that cause progressive cognitive decline in older adults. While a number of model systems and hypotheses regarding mechanisms regulating neurodegeneration during AD and FTD have been generated, a critical issue is the demonstration that these same mechanisms occur in the patient population. There remains an urgent need to collect biofluids (blood, CSF, urine) from AD and FTD patients for use in research studies. In addition, the generation of pluripotent stem cells from these patients will greatly facilitate research using patient derived cells. Such pluripotent stem cells can be generated using isolated PBMCs from patient blood samples.

Preliminary Data:

We have significant experience within the BNI and Dignity Health to collect patient derived biofluids linked to clinical information, process and store biofluid samples for research purposes and the generation of adult stem cell lines. These activities are common in the neuromuscular disease clinic and the Biobank is currently processing and storing samples linked to clinical information for many projects, clinical research studies and trials throughout the hospital. We have recently initiated a web portal for investigators to search for samples within our Biobank that can be requested for research purposes. Therefore, the infrastructure is already in place to successfully complete the proposed study.

Experimental Designs and Methods:

1) Collect longitudinal clinical information, blood, CSF and urine samples from AD and FTD patients.
2) Process samples and store serum, plasma, CSF and urine samples in the Biobank at Dignity Health to make these samples available to the research community.
3) Isolation of patient derived PBMCs.

Proposed One-Year and Long-Term Outcomes:

We will initiate our biobanking efforts and collect biofluids and data from at least 25 subjects. Samples will be made available to investigators for research purposes using the Dignity Health Biobank web portal. We will seek external support to continue our biobanking efforts for AD and FTD. We also hope to enroll participants in post-mortem tissue banks so that we will ultimately have longitudinal biofluids and clinical information, patient derived stem cells, and post-mortem tissue samples. This provides an extremely valuable resource to the research community.

Year End Progress Summary:

1) We recruited 2 individuals who provided biofluids for banking. Recruitment was far less than expected due to limitations imposed by the COVID-19 pandemic. During much of the time

over the last year, per our institutional guidelines, we were unable to conduct non-therapeutic research visits or visits that could not be completed via telehealth mechanisms.

2) We identified that participant interest was low in a biobanking study that did not have pre-determined use in particular research studies.
3) Due to low recruitment and low interest by potential participants, this study was terminated in early 2021. This allows for good stewardship of research funds to be diverted to studies with higher likelihood of success.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

***H*ispanic *E*nrollment in *A*lzheimer's *R*esearch *T*rials (the HEART Program at BNI).** Meredith Wicklund, MD, Anna D. Burke, MD. Barrow Neurological Institute; St. Joseph's Hospital and Medical Center; St. Joseph's Westgate Medical Center; Chandler Regional Medical Center; Mercy Gilbert Medical Center; Arizona Alzheimer's Consortium.

Specific Aims:

1) Implementation of the HEART Program includes a formal development plan outlining internal and external outreach strategies to increase recruitment and the establishment of organizational infrastructure, resources, and written translational materials to promote trial retention while recognizing unmet needs of a large Spanish-speaking community seeking care within Maricopa County.
2) To forge a close working relationship with members of our Hispanic community to formalize the HEART outreach program to increase Alzheimer's disease awareness while addressing clinical research opportunities and family/caregiver support needs to increase trial retention through novel service-related solutions.
3) To 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.

Proposed One-Year and Long-Term Outcomes:

The HEART Program's outreach objective is designed around an internal (within BNI and Dignity Health opportunities) and an external outreach plan (community) for recruitment, with an established recruiter training program, metrics, and goals to maximize engagement among the Hispanic community. Our retention plan includes focused translational tools (such as Spanish translated rating scales) and expanded training among research team personnel offered by Promotores and Hispanic Community Stakeholders to address unique cultural needs. The HEART Program plans to recruit participants from the community through education, outreach, and various events such as memory screens. To support the core in recruiting, enrolling, and retaining 100 Hispanic participants, we will attend community events celebrating Hispanic culture, develop written materials, including a caregiver dementia handbook, in both English and Spanish to expand our reach, and partner with various agencies serving both English and Spanish-speaking Latino seniors. The enrollment goal for BNI will be to have 40-50 actively enrolled Hispanic participants by 2020.

Year End Progress Summary:

1) We have partnered with the Promotores program to provide education to our research team on development of culturally sensitive education and outreach materials as well as foster collaboration in recruitment of Hispanic individuals.
2) Conversely, we have developed a reciprocal collaboration with the Promotores program to provide education to the Promotores on dementia and available resources for the Hispanic community.

3) We have developed a dementia caregiving guide with Spanish translation and materials sensitive to the Hispanic culture. The guide is currently in production via print on online materials, and is in use.
4) We additionally have developed dementia tip cards (eg bathing, driving) with Spanish translation and materials sensitive to the Hispanic culture. The tip cards are currently being sent for print and online use.
5) We have developed a monthly Spanish speaking “Memory Café” for individuals with AD and their caregivers to find support, education and resources on AD. This is the first and only of its kind solely for Spanish speaking individuals in the Phoenix metro area.
6) We have partnered with the Center for Senior Living and other area senior organizations to provide free memory screenings, which has resulted in recruitment of several new participants.
7) We have partnered with area Hispanic media organizations to provide targeted education and outreach on Alzheimer’s disease the local Hispanic community.
8) We have recruited Spanish speaking Health Care Advisor and a Spanish speaking Social Worker to develop additional educational and outreach to the Hispanic community. They provide one on one counseling in the clinic for education, resources, behavioral management and other needs in caring for Hispanic individuals with dementia.
9) Through the above efforts, we have been able to recruit 8 new Hispanic participants since January 2020, with overall 25 active Hispanic participants, including 8 participants that are Spanish speaking only. We have identified that financial barriers for caregivers to take time for work, provide transportation and support Hispanic participants in the AADC is a barrier. We have worked with the Arizona Alzheimer Consortium to provide stipends to offset the burden to participants. Additionally, the length of study visits has been identified as a barrier. We have worked with our collaborators to develop study materials with Spanish translation that provides culturally sensitive, requisite information while limiting study fatigue.
10) While recruitment has been lower than expected, we attribute this to unanticipated restrictions from the COVID-19 pandemic. During this time, per our institutional guidelines, we were unable to conduct non-therapeutic research visits prior to widespread use of telehealth. We worked diligently and were successfully able to convert research study visits to televisits, but limitations in access to internet and comfort with this modality by participants was a major barrier. In addition, many intended and planned in-person outreach and recruitment events were canceled. We were able to convert some events to online, but our recruitment efforts were markedly slowed by this method. Despite this and while newly enrolled members are less than anticipated, we did recruit more individuals over the last year than the year prior. This is a testament to the work we have put in to develop the culturally appropriate programs and materials as noted above. With the programs in place and less pandemic related restrictions, we are able to establish a firmer presence in the local Hispanic community and, as such, anticipate improved recruitment over the long-term.

Project Progress Reports
Banner Sun Health Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking. Alireza Atri, MD, PhD, Kathy O'Connor, MS, Christi Belden, PsyD, David W Coon, PhD, Jessica J Powell, PsyD, Briana Auman, PsyD, Geidy Serrano, Thomas Beach, PhD, Michael Malek-Ahmadi. Banner Sun Health Research Institute; Arizona State University; Midwestern University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Clinical research phenotyping (adapted to 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;

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.

Background and Significance

Availability of these additional data and biospecimens will continue to create a synergistic effect of adding value and impact potential for an enhanced LCS database to possess a complete range of quality biopsychosocial data in a unique population, the older and the oldest old. The expanded dataset will provide a valuable resource that will be further leveraged to better understand biopsychosocial factors, their inter-relations, and their dynamics that are associated with successful aging, neural resistance and cognitive and functional resilience and reserve.

Finally, validating clinical phenotypes, by assessing the global status of LCS participants, will improve recruitment of cognitively unimpaired subjects into the Brain and Body Donation Program (BBDP) and dual-enrollment. Increasing efficiency and quantity of dual enrollment between LCS and BBDP serves to support continued enrollment of cognitively normal elderly, particularly the oldest old, into the BBDP, provides critical cross-validation between these programs, and allows additional opportunities for exciting and impactful science to be undertaken in the subset of dually-enrolled participants who are highly characterized by psychometric, bio, clinical, psychosocial, and, ultimately, pathological data.

Preliminary Data

The LCS has 641 active participants (enrolled 1489 since inception). Prior to COVID-19 physical distancing measures, approximately 45-60 visits are conducted per month, and new participants are enrolled to offset attrition, which is 4.5% per year (annualized over the 13-years; mostly due to death and moving from AZ). Approximately 68% of participants are female, and of 681 active participants, 382 are ≥80 years of age, 242 are ≥85, 117 are between 90-99, and 7 are 100 years or older. Publications below (Refs 1-10) provide exemplars of the diversity of LCS research, and of the PI's research on explicating factors related to cognitive reserve (Refs 11-14). LCS annual assessments, instruments and questionnaires administered include those assessing cognition (e.g. MMSE, MoCA, TICS, eCog); daily function (ADL/IADL), mood (CESD), worry/anxiety (Penn State Worry, GAI), quality and valuation of life (VoL, WHOQoL), coping, social support, leisure time, life event changes, fall risk (FRQ), physiological/physical activity/movement (BP, BMI, RAPA, grip strength, gait speed), and medications and medical conditions. Additional

assessments are administered non-annually years or at the baseline visit (e.g. Cognitive Reserve Index-CRIq). Some ApoE-genotype data via AAC-related collaboration with TGen.

During the 2019-2020 funding period, we required that all new enrollees into the LCS have a study participant partner in order to undergo the CDR interview. We also asked previously enrolled participants who did not meet high thresholds on cognitive testing and trajectory (e.g. Montreal Cognitive Assessment, MoCA, scores of 27 or higher regardless of age and no decline in score of two or greater points compared to a previous score) to provide a study partner to undergo the CDR interview. Through February 2020, 300 of 371 (80.8%) eligible new or previously enrolled LCS participants were classified: 218 via CDR assessment (120 in LCS and 98 who are dually enrolled in LCS and BBDP) and 86 via achieving high cognitive assessment test scores and identifying as being independent on activities of daily living. Seventy-one participants did not undergo CDR or in-person (MoCA) cognitive assessment: 33 declined or were not able to provide a study partner to undergo the CDR interview and 38 underwent telephone on in-residence abbreviated assessment only. As expected, the vast majority of active LCS participants (>96%) are thus far being 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 >40% are above age 84 years. We were successful to enroll 62 new participants in to the LCS in the 8 months prior to COVID-19 measures and restrictions in March 2020.

Response to requesting LCS participants to opt-in to donate ~30 cc of plasma for aliquoting, banking of plasma and sending the buffy coat to TGen for ApoE4-typing (per collaboration supported by a previous AARC grant to TGen) has been outstanding. We had aimed for ~65% of participants opting in to donate plasma, however, to the credit of the participants, 91.8% of eligible participants have donated a plasma sample – from July 2019 through February 2020, 323 samples were collected (225 LCS participants and 97 LCS and BBDP dually enrolled participants).

Experimental Designs and Methods

Aim 1: Clinical Phenotyping (adapted to COVID-19 measures and restrictions; see C19PDM restrictions and sequelae below) - 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 physical distancing measures and restrictions (C19PDM) in place, and precautions and sequelae to be expected through summer and fall of 2020 and, possibly, some portions of 2021, we will develop and adapt study procedures, questionnaires and testing to tele/video assisted and other formats; this will include remote (not in person) informed consent procedures, CDR assessment and cognitive testing, and potential use of on-line platforms to augment current assessments and testing. To account for attrition under C19PDM and sequelae we will enroll ~50 new participants (~30-50/year expected attrition rate under C19DPM). Additionally, active participants deemed to be at higher risk of cognitive impairment will be identified the algorithm, that includes risk factors, self or informant report, MoCA score of <26 at baseline, or a ≥2 point drop in MoCA from any previous score, to undergo CDR assessment (N~180-200). We will obtain CDR of ~100 active participants dual-enrolled in LCS and BBDP. All participants will be assigned a global stage (e.g. cognitively unimpaired, subjective cognitive decline, MCI, mild dementia) based algorithm criteria or the CDR (N~300).

Aim 2: Banking of plasma (N~250 in FY20 adapted to C19DPM restrictions and sequelae) expect ~60% of participants to be able to donate 30 cc for plasma aliquoting (per BBDP processing); buffy coat sent to TGen for ApoE4-typing.

Proposed One-Year and Long-Term Outcomes

The substantial progress in FY 2019-20 is detailed above; we expect to add to this progress by further clinical phenotyping of all participants; by adapting study procedures and measures to remote and electronic formats (due to C19DPM restrictions and sequelae); and by collection, characterization and biobanking of N~250 additional plasma samples (added to the 323 samples collected through February 2020). NIH grant submission in 2021 on biopsychosocial determinants of cognitive resilience and reserve in the older old that utilizes a latent class analysis approach integrating manifest variables from demographics (age, education, gender), ApoE-status, clinical phenotype, blood biomarkers (e.g. ß-amyloid and p-tau (AD), neurogranin (synaptic injury), NfL (axonal injury)), and LCS psychosocial, cognitive and physical variables. We will also leverage this expanding rich dataset with biosamples for collaborative projects and funding sources for clinico-biomarker correlations discovery and as a basis for growth opportunities as a major AZ-based biorepository, biomarker instrumentation and integrative bioinformatics center.

Year End Progress Summary:

The LCS has 585 active participants (enrolled 1,502 since inception). Prior to COVID-19 physical distancing measures, approximately 45-60 visits were conducted per month, and new participants were enrolled to offset attrition, which is 4.4% per year (annualized over the 14-years; mostly due to death and moving from AZ). Approximately 70% of participants are female, and of 585 active participants, 348 are ≥80 years of age, 218 are ≥85, 109 are between 90-99, and 4 are 100 years or older.

During the 2020-21 funding period, we continued to require that all new enrollees into the LCS 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 of 27 or higher 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. Through March 2021, 404 CDR have been performed in the LCS (not including those of BBDP co-enrolled participants, N=98), 294 participants have one CDR assessed, 110 have had 2 CDR assessments, and 2 participants have had 3 CDRs done. Including BBDP co-enrolled participants we have at least one CDR value on 392 LCS participants (>92% of eligible participants). As expected, the vast majority of active LCS participants (>96%) are thus far being 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.

Response to requesting LCS participants to opt-in to donate ~30 cc of plasma for aliquoting, banking of plasma and sending the buffy coat to TGen for ApoE4-typing (per collaboration supported by a previous AARC grant to TGen) has been outstanding. We had aimed for ~65% of participants opting in to donate plasma, however, to the credit of the participants, >90% of eligible participants have donated a plasma sample – through March 2021, 401 samples have been collected. ApoE4-typing results on 237 are known (4 e4/4, 52 e3/4, 4 e2/4, 139 e3/3, 36 e2/3, 2 e2/2).

In 2021 we also had one manuscript from the LCS accepted for publication (Melikyan et al. Norms and equivalences for MoCA-30, MoCA-22, and MMSE in the oldest-old. Aging Clinical and Experiment Research, in press, Ref 15) which contributes to providing normative data and measures to assess cognitive performance and to detect potential cognitive impairment in the oldest-old (90+ year-olds); an area that has been devoid of good normative data.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Developing a Shared Resource of Cerebrospinal Fluid, Plasma, Serum, and Peripheral Blood Mononuclear Cell (PBMC) Samples from Arizona's Longitudinal Brain and Body Donation. Thomas G. Beach, MD, PhD, Alireza Atri, MD, Danielle Goldfarb, MD, Geidy Serrano, PhD, Lucia Sue, Richard J. Caselli, MD, Charles H. Adler, MD, Donald Saner, Eric M. Reiman, MD. Banner Sun Health Research Institute; Mayo Clinic; Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims

1. To develop a repository of cerebrospinal fulid (CSF), plasma, and PBMC samples, linked to brain imaging and neuropathology data from well characterized, longitudinally assessed, and consenting participants in Arizona's Brain and Body Donation Program.
2. To provide a shared resource of CSF, plasma, and PBMC samples and data linked to brain imaging and neuropathology data to researchers inside Arizona and around the world.

Background, Significance and Preliminary Data

The Arizona Brain and Body Donation Program (BBDP) provides an invaluable scientific resource of longitudinal cognitive, motor, clinical, and genetic data from >900 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 AD Core Center (ADCC), research participants with the clinical features of Parkinson's disease (PD) and related disorders and cognitively and neurologically unimpaired older adults. The BBDP has provided an invaluable resource of data, brain tissue and DNA to researchers around the world. CSF and blood samples would enhance the value of the BBDP in several ways, including a) the chance to clarify whether the participants have CSF evidence of amyloid-β and tau pathology (biomarkers of AD), b) the chance to evaluate and further develop emerging CSF and blood-based biomarkers in terms of the extent to which they predict subsequent clinical decline and the neuropathological diagnosis of AD, PD, and other disorders, and c) the chance to use CSF- and blood-based measurements to further help in the clarification of disease mechanisms and risk factors.

Experimental Design and Methods

During the one-year funding period, we propose to further develop the infrastructure to conduct lumbar punctures (LPs), acquire up to 30 ml of CSF and 40 ml of blood and process CSF, plasma, and buffy coat (for PBMCs) samples from BBDP participants at BSHRI to process, aliquot and store samples using standardized procedures, and to establish a repository of these samples at BSHRI. This year, we propose, at a minimum, to acquire CSF samples in 15 new BBDP participants at BSHRI who consent to LPs; and we propose to acquire, at a minimum, blood samples in 300 returning BBDP participants.

CSF Samples. LPs will be acquired by trained and experienced personnel standardized procedures established for other longitudinal cohorts. We propose to acquire up to 30 ml of CSF, which will then be centrifuged at 1,500 rpm for 10 min at 24°C. The supernatant will be collected, placed into 0.25 ml aliquots, and stored at -80°C. One (1) ml of CSF from each subject will be

sent to a commercial lab for standard analyses on cell count, protein and glucose levels, and hemoglobin levels.

Blood Samples. We propose to acquire up to 40 ml of venous blood in EDTA tubes. Blood will be centrifuged at 1,500 rpm for 15 min at 24°C to separate plasma and red blood cells. The plasma will be collected and placed into 1.7 ml microcentrifuge tubes and then centrifuged again for 5 min, 4°C at 14,000 rpm. From blood samples collected at BSHRI, the buffy coat will be further refined using standard methodology to provide purified peripheral blood mononuclear cells (PBMC), which, along with the plasma aliquots, will be stored at -80°C.

Fluid Repository. All samples from Specific Aims 1 and 2 will be stored at BSHRI in ultra-low temperature freezers protected with redundant temperature-activated alerts, banks of emergency CO2 tanks, redundant air conditioning units and backup diesel alternate power supply. BBDP staff are on constant call to respond to freezer alerts. A biological sample distribution committee involving the BBPD Program PIs will evaluate all research proposals involving the use of shared biological samples.

Proposed One-Year and Long-Term Outcomes

Our one-year goal is to collect, process and store the samples as described. Our long-term goals are to extend this effort to all consenting participants in the BBDP, incorporate relevant information about these samples in a centralized database, secure NIH funding to support the longitudinal acquisition of CSF and blood samples in all subjects within this invaluable cohort, provide a shared resource of biological samples to researchers inside and outside of Arizona, and use these samples to make significant contributions to the scientific study of AD, related disorders and cognitive aging.

Year End Progress Summary

Blood samples. Since funding began in 2015, we have obtained and stored in-house 42,147 blood samples from 1005 participants on 1,975 different appointments, from which 278 already came to autopsy and 218 were collected this funding period (as of July 1, 2020). In addition, we collected 2,467 blood samples from 170 individuals who received or are eligible to receive MR, 18F Flortaucipir PET and 11C PiB PET scans, these samples are currently stored at NIH for further multi institutional collaborations. By clinical diagnosis, the collected blood samples are from 794 non-demented controls, 126 subjects with mild cognitive impairment, 62 subjects with a clinical diagnosis of dementia due to possible or probable AD, 140 subjects with PD and 51 with other diagnoses.

Due in part to this initiative, we were able to share blood samples from individuals that have undergone an autopsy and have a final clinicopathological evaluation with 9 different scientist groups. These samples have already resulted in high impact publications in Nature Medicine and JAMA Neurology and one additional important publication that is currently in preparation.

CSF Samples. To date since 2015, we have obtained 1,771 CSF samples from 79 participants, from which 7 already came to autopsy and 17 were collected in this funding period (as of July 1st, 2020). In addition, we collected 406 CSF samples from 29 individuals who were also received or who are eligible to receive the above-mentioned scans, these samples are currently stored at NIH for further multi institutional collaborations.

Fluid Repository. All samples from Specific Aims 1 and 2 are stored at BSHRI in ultra-low temperature freezers protected with redundant temperature-activated alerts, banks of emergency CO2 tanks, redundant air conditioning units and backup diesel alternate power supply. BBDP

staff are on constant call to respond to freezer alerts. A biological sample distribution committee involving the BBPD and APOE4 Gene Dose Program PIs will evaluate all research proposals involving the use of shared biological samples.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Patient-based postmortem fibroblast banking for translational research. Lih-Fen Lue, PhD Thomas Beach, MD, PhD; Rita Sattler, PhD, Geidy Serrano, PhD; Suet Theng Beh, PhD. Banner Sun Health Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims

1) To build on what we have already established in the last two years to bank and characterize more scalp tissue-derived fibroblasts from donors with neurodegenerative diseases or without neurodegenerative diseases. The goal is to increase the number of autopsy cases with cryogenically-preserved cells and to preserve cells for each apolipoprotein E genotype and from both Alzheimer's disease (AD) and non-AD cases.
2) To bank human iPSC lines generated from four of our banked cases: one from an ALS C9 expansion case, one from an ApoE4/4 AD case, and two from ApoE 3/3 cases (one with an AD diagnosis and the other from one that was cognitively normal).

Background and Significance

AD is a major neurodegenerative disease in the aging population. Although tremendous progress in understanding and diagnosis of the disease has been made in the last three decades, there is still no effective disease-modifying treatments. Many researchers have agreed that improved experimental models are needed to better recapitulate the sporadic AD disease pathways in human brains, as animal models carrying mutated genes identified in familial AD may not be adequate for sporadic AD. To create better research models for AD, human neural cell or organoid cultures generated from stem cell technologies have been increasingly used. These models can be made from procedures that generate somatic cells from inducible pluripotent stem cells (iPSCs) or procedures directly transforming somatic cells to other somatic cells.

Skin fibroblasts are the most frequently used somatic cell types for the stem-cell based procedures. At BSHRI, the Brain and Body Donation Program (BBDP) banks postmortem tissues from 50-60 autopsy cases a year. Since the program has access to scalp tissues at autopsy, it can be leveraged as an invaluable source of skin samples to make fibroblasts. Importantly, the participants of BBDP were enrolled in the longitudinal aging study while they were alive and received clinical and neuropsychological assessment yearly. The validation of their clinical diagnosis was made by neuropathological examination of the postmortem brain tissues. Taken together, these could provide valuable information to understanding cases with sporadic AD, whose phenotypes might be affected by co-presence of other neurodegenerative diseases.

In the last two years, we collaborated with the BBDP's Autopsy Brain Removal Team to obtain scalp tissues for fibroblast banking at BSHRI's Human Cells Core for Translational Research (HCCTR). We have established a workflow which is suitable for routine processing of autopsy tissues to produce enough cell numbers for cryogenic storage. We anticipate that our ongoing efforts will result in banking of 35-40 additional cases.

In this new grant period, we will provide cryogenic fibroblasts from the appropriate autopsy cases that we had banked in the last funding period as well as more cases in new funding period to research community. Providing these cells to AAC researchers as well as those in the greater AD research community will help move towards our mission for translational research.

Proposed One-Year and Long-Term Outcomes

During the proposed funding period, we will aim to bank fibroblasts and scalp tissues from a total of 35-40 autopsy cases. This is 3-4 cases each month for 10 months as each case takes approximately 2 months to maintain. We will use the last two months to complete characterization. As the cases selected for iPSC generation have already been banked, we will be able to start immediately. We anticipate that they will be completed 6-8 months into the project. Our long-term goal is to be able to build a large patient-based fibroblast and iPSC banking program for both familial and sporadic neurodegenerative disease research.

Year End Progress Summary

During this funding period, to avoid the culturing of fibroblasts from the autopsy tissues that carried SARS-CoV2, we needed to modify our regular procedure. That delayed the processing of postmortem scalp tissues until the SARS-CoV2 PCR test confirmed the absence of the virus. Therefore, since July of 2021, the number of autopsy cases used for isolation of the fibroblasts was reduced as well as the success rate due to the prolonged wait time for the test results. In a total of 30 months since the establishment of the HCCTR, we have banked 1121 cryogenic vials of well characterized scalp-derived fibroblasts. The HCCTR has published a paper describing the program and characteristics of the cells in a peer-review journal “Cells” in 2020. The reprogramming of the banked cells had successfully generated pluripotent stem cells (in collaboration with Dr. Brafman in Arizona State University). The HCCTR currently has a contract with Baylor Medical College Human Stem Cell Core to reprogram fibroblasts from an ALS patient who carried a C9 expansion mutation. The iPSC clones from this case will be expanded and banked at our facility. Continuing banking of iPSCs from special cases will be the goal of HCC in next phase. During this funding period, we have also discovered that some of the cases have scalp progenitor cells in the cultures. Development of a method to harvest and characterize these progenitor cells could have the potential to lead to a different and unique collection of such cells.

Description of the Progress:

Aim 1: To increase the number of cryogenic cells in each apolipoprotein E genotype from Alzheimer’s disease (AD) and non-AD cases. Since March of 2021, we changed our procedure to safeguard our staffs from exposure to the SARS-CoV2. We have observed significantly compromised viability of the autopsied scalp cells due to the delay from initial collection to receiving diagnostic SARS-CoV-2 results.

(A) Since established in September of 2018, we have successfully banked fibroblasts from 47 scalp tissues out of 72 donor cases that we processed. The success rate has been reduced from 73% to 54% due to the COVID-19 test holding time in the pandemic year (from March of 2020 to March of 2021). The means of the delay in hours are 14 ± 9.55 prior to the pandemic versus 158.73 ± 62.24 during the pandemic.

(B) Another key component to a successful culture is the adherence of the explants in the culture. We determined whether the interval of tissue processing delay affected the cell outgrowth from the explant cultures in the cases that yielded fibroblasts. We found that the duration from plating explant to cell outgrowth significantly correlated with the delay of autopsy tissue processing. The Pearson’s correlation coefficient was 0.71, $P<0.001$. Thus, the longer the delay for processing, the longer the time to take for cells to grow out of the explants.

(C) We characterized fibroblasts by the expression of a panel of fibroblast markers by qPCR. These genes included fibroblast activation protein (FAP), fibronectin (FN1), Thy-1 cell surface

antigen (THY1), and Vimentin (VIM). We found that FN1 and VIM were expressed more abundantly than the housekeeping gene GAPDH, whereas FAP and THY1 genes were expressed less abundantly than GAPDH expression.
(D) To further validate the identity of the banked cells, we characterized cells at passage 3 by a panel of antibodies to detect, by immunofluorescence, the fibroblast expressing proteins, including fibroblast surface protein (FSP), fibroblast activation protein (FAP), fibronectin, alpha smooth muscle actin (α-SMA), and vimentin. A positive control of fibroblasts and a negative control of keratinocytes from a commercial source were included in the study. An antibody for cytokeratin was used as the marker of the keratinocytes. Based on immunofluorescence intensity and morphological features we confirmed that all our banked cells were consistent with the features of the fibroblasts.

(E) The APOE genotypes and disease classification are two important features of our banked cells. From 33 cases for which the neuropathological diagnoses have been completed, there are 3 APOE 2/3 cases (1 AD, 1 AD/PSP, and 1 ALS), 20 APOE 3/3 cases (2 AD/DLB, 2 AD/PSP, 3 MCI, 6 normal controls, 1 PD, 2 PD with dementia not otherwise specified, 1 PD/PSP/MCI, and 1 VAD), 7 APOE 3/4 cases (2 AD, 1 AD/DLB, 1 MSA, 1 normal control, and 2 PD/AD), and 3 APOE 4/4 cases (1 AD, 1 AD/DLB, and 1 AD/VAD).

(F) During this funding period, we have provided to AAC research scientists fibroblasts derived from AD and AD/DLB cases with TDP43+ immuno-positivity by neuropathological examination. In addition, there are two other groups of external scientists who inquired about cells from specific APOE genotype, gender, and disease category. Scientists in the biomedical field have also been inquiring about our banked cells.

Aim 2: To bank human iPSC lines generated from our banked cases. The banked fibroblasts have been shown successful in producing iPSCs from an APOE3/3 case (Dr. Brafman, Arizona State University). During this funding period, we sent one ALS case with known C9 mutation to Baylor Medical College Human Stem Cell Core for generation of induced pluripotent stem cells (hiPSC) cell lines. As their operation of iPSC service has also been affected by the COVID-19 pandemic, the iPSC clones from this ALS case will not be received until July of 2021. Under the contract, we will receive three clones from the case. Once the clones are received, we will expand the clones at appropriate generations and cryo-preserve the vials for researchers to request.

Conclusion: The HCCTR will continue to bank postmortem human fibroblasts from APOE genotype- and neuropathologically characterized cases. As the program becomes more known to the research community, we anticipate increase in the demand for the banked cells in the coming years.

Publications:

1. Human Autopsy-Derived Scalp Fibroblast Biobanking for Age-Related Neurodegenerative Disease Research. Beh ST, Frisch C, Brafman DA, Churko J, Walker JE, Serrano GE, Sue LI, Reiman EM, Beach TG, Lue LF. Cells. 2020 Oct 30;9(11):2383. doi: 10.3390/cells9112383. PMID: 33143239.
2. Human microglia isolation from neuropathologically diagnosed cases in the single-cell era. Lih- Fen Lue, Douglas G walker, Suet Theng Beh, Thomas Beach. Book chapter in Methods in Molecular Biology on “Alzheimer’s Disease: Methods and Protocols”. Editor: Jerod Chun. 2021, Springer Nature.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

A Human Brain Single-Cell Suspension Resource. Geidy Serrano, PhD, Thomas G. Beach, MD, PhD, Lih-Fen Lue, PhD, Matthew Huentelman, PhD, David Brafman, PhD and colleagues from each of the participating Alzheimer's Consortium sites. Banner Sun Health Research Institute**;** Translational Genomics Research Institute**;** Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims

1. To provide the foundation of a shared resource of separated cells to researchers within and outside Arizona.
2. Phenotpically and Biochemically characterize single cells and phenotypically-specified populations of cells from single-cell suspensions created with an optimized standardized method (from Specific Aim 1).

Background and Significance

Biochemical analysis of human neurodegenerative brain tissue, especially from Alzheimer's disease (AD) and Parkinson's disease (PD) patients, has produced much of what is known about these conditions, and has led to the major FDA-approved therapies. The typical approach has been to homogenize whole pieces of brain tissue and separately characterize the proteins, RNA, DNA and other macromolecules within. While this has been sufficient to identify large changes, there is very little ability to identify small changes, or changes in small subsets of cells. Furthermore, neurodegenerative disease often leads to massive losses of the targeted and disease-relevant cells, for example the entorhinal cortex layer II stellate neurons or substantia nigra pigmented neurons. Whole-homogenate analysis of such brain regions can give completely misleading results, as any biochemical constituent that is selectively localized to the depleted cells will appear to be "down-regulated", whereas in fact it has most likely been lost only as an "innocent bystander". Also, a relevant loss or increase might be completely missed, if the biochemical entity is found in many cell types, diluting the 'lost" signal from the cell of interest, especially if that cell type is uncommon or rare. To effectively investigate the biochemistry of neurodegenerative disease in the brain, with its thousands of different cell types, we must first separate the cells, and study them as phenotypically-defined populations and even as individuals. In recent years, methods have been developed that allow an initial creation of single-cell suspensions from solid tissue followed by analysis of phenotypically-defined cells sorted on the basis of cell-type identifying proteins or RNA expression. Some groups have already published intriguing results from AD brain cells, but as yet there has not been a comprehensive exploitation of these novel technologies utilizing postmortem human brain. This set of experienced neuroscience investigators, together with a unique rapid-autopsy brain tissue resource, are well-suited to apply these methods on a large scale to AD and other neurodegenerative brain diseases.

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. She published a methodology paper on Med Archive, which is now under revision on PLSO ONE. Additionally, Dr. Serrano recently obtained two competitive grants from the Michael J Fox and PSP foundations to perform analyses on Parkinson's, PSP and control cells isolated with her methods.

To date, 361 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 128 subjects has been used to generate WSDS. The BBDP continued their operations during the COVID pandemic and in the current funding year (beginning July 1, 2020) performed 71 autopsies. However, due to the high percentage of COVID positive cases in the community, and therefore our participants, we only performed cell suspensions from 7 of those autopsies. All autopsies were screened for SARS- CoV-2 and none of the 7 suspensions were positive for SARS- CoV-2

Experimental Designs and Methods

Single cell suspensions are generated from frontal cortex obtained at autopsy. Approximately fifty grams of grey matter are dissected out from fresh frontal lobe slices bilaterally. The samples are then immediately processed to produce single-cell suspensions. The method uses enzymatic digestion with Accutase for 4 hours at 4^{o}C of fresh tissue minced with a razor blade, followed by mechanical disruption by repetitive pipetting. Myelin, neuropil and other cellular debris is removed by Percoll density gradient centrifugation. Final suspensions are then aliquoted for cell banking in cryopreservative solution and stored at -80°C for later experimental usage and quality control (QC) assessments (method manuscript in preparation).

Phenotypic characterization by H & E staining and Immunohistochemical staining confirms the presence of these cell types with antibodies specific for neurons (NeuN), astrocytes (GFAP) and microglia (Iba1). Once cell types are identified using the most suitable antibodies, cells are sorted with fluorescence-activated cell sorting (FACS) or magnetic beads. RNA from sorted cells is extracted, and 100 ng from each sample is used for qPCR. βactin is used as a housekeeping gene, and probes for MAP2, GFAP and IBA1 are used to confirm the presence of cells of interest and to estimate their enrichment compared to the remaining cell population. Manual bar coding using SplitBio technology allow single cell sorting. Further analysis of cell suspensions using next generation RNA sequencing (RNA-Seq) is used to analyze sorted cell-specific population or single cells.

Specific Aim 1: To provide the foundation of a shared resource of separated cells to researchers within and outside Arizona.

Over the last couple of years, we have collected enough evidence to show WSDS generated at the Banner BBDP are suitable for multiple experiments that could lead to better understanding of single cell or population changes in aging and neurodegenerative disorders associated with aging. We are now actively promoting this resource on our website and in meetings. A methodology paper was already published in Med Archives and a modified version is under revision on PLSO ONE.

In addition, more high-profile projects were undertaken to further establish the importance of the general approach and to increase awareness of the resource among the neurodegenerative disease scientific community. The resource is providing single cells suspension for studies independently funded by the MJFF and PSP foundations aiming to studies transcriptome sequencing from enriched human cell-specific populations and single cells. A summary of our results will be posted in each foundation websites and therefore contribute the resource promotion.

Specific Aim 2: Phenotpically and Biochemically characterize single cells and phenotypically-specified populations of cells from single-cell suspensions created with an optimized standardized method (from Specific Aim 1).

During this funding year we have done multiple FACS and magnetic beads experiments with different antibodies aiming to improve cell enrichment. We have used different cell specific markers to allow us to sort different cell populations (astrocytes and neurons). We have sorted a total of 50 cases and the RNA from the enriched populations was isolated and sent for RNA sequencing (RNA-Seq). The analysis results are pending, but preliminary data suggest that we should be able to correlate brain pathology with multiple disease-regulated transcripts such as aquaporins and glutamate transporter in astrocytes.

Another methodological approach that we are continuing to work on is using WSDS for single cell RNA-Seq that could potentially be the method that will give the greatest advances in the understanding of cell-type-specific gene expression changes. Unfortunately, the most common approach, using a 10X Genomics droplet-based platform, seems not be appropriate for human WSDS because the cells appeared to be damaged by the process. We hypothesized that cell size and the neurite presence in the suspension is our major challenge with this approach. We are now trying new approaches that will be gentler approaches for single cell sequencing, such as manual bar coding using SplitBio technology. This year we were able to create successful sequence libraries on over 80,000 cells from a total of 6 donors. Complete analysis results are pending.

Year End Progress Summary

1. Over the last couple of years, we had collected enough evidence that show WSDS generated at the Banner BBDP are suitable for multiple experiments that could lead to better understanding of single cell or population changes in aging and neurodegenerative disorders associated with aging. We are now actively promoting this resource in our website and meetings.
2. During this year two more high-profile projects were undertaken to further establish the importance of the general approach and to further awareness of the resource among the neurodegenerative disease scientific community.
3. Further analysis of cell suspensions using next generation RNA sequencing (RNA-Seq) will be done using gentler approaches such as manual bar coding using SplitBio technology and magnetic beads covered with a surface epoxy group for manual cell separation. Both approaches seem very promising and we are already in the process of testing the protocols

Laying the Groundwork for Prodromal Lewy Body Dementia Research in REM Sleep Behavior Disorder. David Shprecher, DO, MSci Thomas G. Beach, MD, PhD, Charles H. Adler, MD, PhD, Shyamal H. Mehta, MD, PhD, Holly Shill, MD, Nan Zhang, MS, Joyce Lee-Iannotti, MD**.** Banner Sun Health Research Institute**;** Mayo Clinic**;** Barrow Neurological Institute; Banner University Medical Center-Phoenix; Arizona Alzheimer's Consortium.

Specific Aims

1. To enroll subjects with polysomnogram-confirmed RBD into the following key observational research cohorts at Banner Sun Health Research Institute:
    a. The NIH-funded North American Prodromal Synucleinopathy (NAPS) Consortium
    b. The Brain and Body Donation Program (BBDP), a longitudinal clinicopathological study of normal aging and neurodegenerative disease in Sun City, Arizona.
2. To determine feasibility of using the Sleep Profiler device in place of gold standard sleep laboratory polysomnogram to diagnose RBD in a patient's home.

Background and Significance

Idiopathic REM sleep behavior disorder (iRBD) is a harbinger of neurodegenerative disease in the elderly. A definite diagnosis requires the presence of dream enactment behavior, absence of a secondary cause (such as medications, brainstem lesions in tracts mediating REM atonia, or neurodegenerative disease) and polysomnogram (PSG) confirmation (demonstrating REM atonia and the absence of an RBD mimic such as nocturnal frontal lobe epilepsy or arousals related to sleep apnea.) Over the last 15 years, evidence from multiple research groups world-wide has indicated that over 50% of those with iRBD will develop either parkinsonism or dementia within 10 years, with 80% or more phenoconverting after 20 years. Autopsy studies have shown that the great majority of those dying with RBD have a brain disorder characterized by the accumulation of a protein called alpha-synuclein and are hence termed "synucleinopathies." The major synucleinopathies are Parkinson's disease (PD) and dementia with Lewy bodies (DLB). After stratifying by predictive factors (olfactory or color vision dysfunction, subtle motor slowing, age over 54, non-use of antidepressants), iRBD subjects at 65% risk of phenocoversion within 3-years can be identified. There are currently no preventative treatments for PD or DLB, and prevention trials in iRBD have not been feasible for two reasons. First, recruitment of iRBD subjects is challenging due to relatively low rates of diagnosis at academic centers and cost/inconvenience of polysomnogram for diagnosis. Second, lack of biomarkers (particularly autopsy tissue) from iRBD subjects to elucidate the mechanism of disease progression (from a sleep disorder to a neurodegenerative memory or movement disorder). The NAPS Consortium is a multicenter prospective cohort study of iRBD subjects preparatory to prevention trials against PD and DLB (under NIH award R34AG056639, "Neuroprotective treatment trial planning in REM sleep behavior disorder.") Co-enrollment of these participants into the BBDP puts BSHRI in a unique position to address the need for autopsy tissue from these subjects, while also contributing to international, multicenter prospective clinical-biomarker research.

Preliminary Data

The principal investigators are recognized experts in the clinical and neuropathological evaluation of synucleinopathies and have published multiple studies of preclinical markers including RBD. As of spring 2020, a total of 7 individuals with probable iRBD completed research PSGs. Of these, two were not found to have RBD. The remaining 5 were given a PSG-confirmed diagnosis of iRBD. As of March 2020, we were fully contracted and activated to enroll subjects into the NAPS Consortium. Subjects will continue to be enrolled into the NIH funded NAPS Consortium through

May 2021. NIH funding has not covered the cost of the research PSG for these participants and our AAC funding has been leveraged to support these costs at our site.

We have completed our initial pilot study of the Sleep Profiler device (presented in abstract form at the International Lewy Body Dementia Conference, Las Vegas, June 2019 and the International RBD Study Group meeting in Copenhagen, October 2019.) Plans are already in place to pool our data with collaborators at Mayo Rochester (PI Erik St-Louis) to publish the manuscript.

Experimental Design and Methods

Specific Aim 1: To enroll subjects with polysomnogram-confirmed RBD in parallel into the following key observational research cohorts at Banner Sun Health Research Institute: The NIH-funded North American Prodromal Synucleinopathy (NAPS) Consortium and the Brain and Body Donation Program (BBDP).

Specific Aim 2: To determine feasibility of using the Sleep Profiler/Night shift devices in place of gold standard sleep laboratory polysomnogram to diagnose RBD in a patient's home.

Proposed One-Year and Long-Term Outcomes

By the end of the funding year, we expect to:

1. Complete research PSG and Sleep Profiler/Night Shift testing on a total of least 8 additional pRBD subjects (for a total of 20 overall since funding began), and refer them to participate in the NAPS Consortium and/or BBDP.
2. Publish our pilot study comparing the home Sleep Profiler device to in-laboratory polysomnogram.

By the subsequent year, we expect to

1. Participate with NAPS Consortium investigators to apply for the anticipated NIH U19 award "Prodromal Synucleinopathies Consortium" due June 2020. This will include large-scale validation of clinical, genetic, and imaging biomarkers necessary to guide prevention trials in these cohorts. Successful receipt of this grant will cover cost of future research polysomnograms.

Begin participation in a sub-study of tissue-based biomarkers (including skin biopsy) in these cohorts.

Year End Progress Summary

Specific Aim 1: Our enrollment progress was significantly impacted by COVID-19 with many anticipated in-person study visits delayed and/or cancelled. While all efforts were made to transition clinical visits to a virtual setting, the polysomnogram requires our participants to be seen in person. Since 7/1/2020, a total of 4 individuals have completed research PSGs. One individual did not have sufficient REM sleep captured during the first PSG and completed a second research PSG (for a total of 5 research sleep studies thus far.) We expect to schedule at least 3 additional research sleep studies in April 2021. Thanks in large part to the referrals from this project, a total of 12 individuals have been consented for enrollment in the NAPS Consortium at BSHRI. Each of these individuals will be invited to co-enroll in the BBDP.

Specific Aim 2: Data has now been compiled including participants from BSHRI and a separate cohort from Mayo clinic comparing the home Sleep Profiler/Night Shift device to full PSG and is being prepared for publication. In addition to this primary study, the PSG data will also be utilized to publish additional research on non-REM sleep without atonia in this population. The initial

manuscript, titled “Non-REM Sleep with Hypertonia is Associated with Synucleinopathy Neurodegeneration” has been submitted for publication to a high impact peer-reviewed journal. Two abstracts on this topic have also been accepted for presentation at the virtual American Academy of Neurology meeting in April 2021:

1. “Normal and Abnormal Stage N3 Sleep in Patients with Cognitive Impairment and/or Neurodegenerative disease”
2. “Non-REM Sleep with Hypertonia: a Potential Prodromal Biomarker For alpha-Synuclein Related Neurodegenerative Disease”

Additional Long-Term Successes: The NAPS Consortium investigators have received a notice of award for an NIH U19 grant, "Prodromal Synucleinopathies Consortium” with a funding date in 2021. This includes large-scale validation of clinical, genetic, and imaging biomarkers necessary to guide prevention trials in these cohorts. This grant will cover cost of future research polysomonograms. We received a favorable review for the Arizona Alzheimer’s Disease Core Center (AADCC) pilot grant, “Idiopathic REM Behavior Disorder as a Predictor of Neurodegenerative Disease” in 2020. PI Joyce Lee-Iannotti has resubmitted this proposal under the March 15, 2021 Arizona Alzheimer’s Consortium/AD Research Center (ADRC) Pilot Project Grant Request for Applications (RFA). This will, if funded, support biomarker sub-studies for the BSHRI NAPS participants of alpha-synuclein skin biopsy and plasma neurofilament light chain.

Advancing the Use of Lumbar Puncture in Alzheimer's Disease and Related Disorders Research. Danielle Goldfarb, MD, Alireza Atri MD, PhD, Daniel Viramontes, BS, Michael Callan, BS, Gene Alexander, PhD, David Weidman, MD, Po Tsai, MD, Marina Reade, DNP, Carolyn Liebsack, BSN, Teresa Wu, MD, Jason Grimsman, MD, Michael H. Malek-Ahmadi, PhD Eric M. Reiman, MD. Banner Sun Health Research Institute; Banner Alzheimer's Institute; University of Arizona College of Medicine-Tucson; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:
Aim 1. Train 8-12 Arizona Alzheimer's Consortium clinicians on ultrasound-guided lumbar puncture (Us-LP) techniques to implement Us-LP into their research practices.
Aim 2. Preliminarily assess the feasibility and utility of Us-LP implementation in ADRD research studies by a pilot program that measures clinician confidence, performance ratings and adverse events rates in Us-LP before and after clinician training and pre- and post-procedure.
Aim 3. Develop print and video materials for clinicians and the public on the importance, utility, and safety of LPs in order to enhance the perceived value; mitigate fears and misconceptions; and increase the likelihood of participation and referral for LPs.

Background and Significance: While ADRD neuroimaging biomarkers, including amyloid and tau PET, have evolved dramatically in recent years, high costs and lack of accessibility remain barriers to widespread use. Obtaining cerebrospinal fluid (CSF) via LP represents a widely available and safe approach to accurately diagnose AD for inclusion in ADRD clinical trials. 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.

The preponderance of evidence supports the utility of LPs for diagnosis of numerous neurological conditions, and LPs as safe and well-tolerated with low AE rates when performed correctly.5 Yet, various patient-, provider-, and procedure-related factors contribute to lower success rates. The major barrier to LP uptake identified in cross-sectional studies is the perception of procedure invasiveness. Other reasons included patient concerns, limited capacity to test universally, and inconclusive results. The LP program aims to proactively address these factors, specifically considering our older population, through education of patients, families and dementia specialists and referring clinicians.

Ultrasound technology is not yet used routinely with LPs. Studies have shown variable benefit for improving LP success rates, particularly in obese individuals; however, most studies evaluated Us-LP in emergency department and pediatric settings. Ultrasound is indicated for LP when bony landmarks are difficult to palpate and when congenital or chronic spine issues are present6. A recent review and meta-analysis3 reported Us-LPs were associated with higher success rates, fewer traumatic LPs, shorter time to success, fewer needle passes, and lower pain scores. They concluded that ultrasound should be considered for all LPs, particularly in individuals with difficult anatomy.

Successful implementation of this innovative pilot program will set the stage for dissemination to other ADRD centers in AZ and the US. These educational efforts could substantially impact ADRD outreach and research by mitigating barriers related to knowledge and stigma associated with LPs, and improve willingness to participate, advocate and refer.

Experimental Designs and Methods:
Aim 1: In the summer of 2019, 8-12 Arizona Alzheimer's Consortium clinicians interested in incorporating Us-LP into their research practices will complete a course led by expert faculty at the Banner Simulation Laboratory, Phoenix, AZ.
Aim 2: Implementation of a pilot program to assess pre- and post-Us-LP training outcomes on LPs performed at BAI and BSHRI ADRD-related research including observational cohorts, diagnostic and biomarker studies, and clinical trials. Participants will be consecutively enrolled in the proposed study whenever an LP is considered for diagnostic, research or clinical trial purposes. Following the training, questionnaires will also be administered (60 LPs), and pre- and post-LP (pre/post within LP method) comparisons including patient and clinician characteristics and attitudes; details of the LP procedure; use of ultrasound; and pre- and post-training clinician confidence, LP performance, and LP-related AE's will be measured.
Aim 3: We will develop print and video educational materials on the nature, value, safety and tolerability of LPs along with the availability of ultrasound technology. Targeted materials will be developed for patients/families, referring clinicians, and the community at large and will be incorporated in community outreach including lectures, newsletters, articles, and local and regional campaigns. Patient, family and referring provider surveys and focus groups will assess pre- and post-education attitudes about LP and referral rates.

Proposed One-Year and Long-Term Outcomes: Outcomes data (clinician confidence and attitudes regarding LP and Us-LP; patient, family and referring clinician attitudes and likelihood to participate or refer for LP; LP AE's; LP clinician and patient experiences) and findings from the proposed project will be analyzed and presented at scientific conferences and in peer-reviewed manuscripts. These pilot data will support applications for funding through NIH, industry and philanthropic organizations to enhance global efforts to increase capacity for ADRD fluid biomarker acquisition. A long-term goal of this program is to provide a foundation for a future training program for a LP proceduralist8 that can be a mid-level practitioner or RN in order to vastly expand capacity to obtain CSF in an effective, efficient and scalable manner.

Year End Progress Summary:
Aim 1. Train 8-12 Arizona Alzheimer's Consortium clinicians on ultrasound-guided lumbar puncture (Us-LP) techniques to implement into their research practices.

Very good progress was made on Aim 1 – six LP clinicians were trained on Us-LP techniques and implemented Us-LP into their research practices.

Two ultrasound-assisted lumbar puncture (Us-LP) courses convened and were led by Banner expert ultrasound faculty Dr. Teresa Wu (Associate Professor of Emergency Medicine, UA College of Medicine Phoenix, Banner Simulation Curriculum Director) and Dr. Jason Grimsman (Assistant Professor of Emergency Medicine). Course descriptions are as follows: (1) Introduction to Ultrasound-Assisted Lumbar Puncture and Advanced Us-LP. The introductory course (Two hours on 8/22/2019) was completed by six dementia specialist clinicians (5 neurologists and one advanced practice nurse from two Banner sites-Banner Alzheimer's Institute (BAI) and Banner Sun Health Research Institute (BSHRI)), during which time, Drs. Wu and Grimsman provided a didactic session following by simulation opportunities using the hand-held ultrasound equipment on two human volunteers and on simulation models. Needles were not inserted on human volunteers. For the advanced Us-LP course (3 hours on 11/21/2019), four of the six above clinicians complete the advanced training which demonstrated the use of an ultrasound cart system in conjunction with the hand-held tablet ultrasound devices on study participants undergoing lumbar puncture.

<u>Aim 2.</u> Preliminarily assess the feasibility and utility of Us-LP implementation in ADRD research studies by a pilot program that measures clinician confidence, performance ratings and adverse events rates in Us-LP before and after clinician training and pre- and post-procedure.

Table 1. Participant Characteristics	No Ultrasound	Ultrasound-Guided LP	p-value
No. Subjects	21	37	na
Age, mean (SD)	70.10 (9.84)	72.14 (9.01)	0.43
Sex (M/F)	15-Jun	14/23	0.48
BMI, mean (SD)	25.8 (2.51)	27.7 (4.79)	0.18
h/o chronic pain, n (%)	3 (14.2%)	8 (12.6%)	0.86
h/o chronic headache, n (%)	4 (19.0%)	6 (15.8%)	0.74
Fearful of LP pre-procedure, n (%)	11 (52.4%)	15 (39.5%)	0.38
Successful CSF flow, n (%)	20 (95.2%)	31 (81.6%)	0.2
Cognitive Status (Unimpaired/Impaired)	21/2	35/2	0.41
Any post-LP complication, n (%)	5 (23.8%)	15 (39.5%)	0.23

Excellent progress has been made on Aim 2 – 58 LP participants have been enrolled through March 2020; LP clinicians have completed Us-LP study questionnaires; and data on adverse events has been collected. Related abstracts have been accepted for the 2020 Arizona Alzheimer's Consortium Scientific Meeting and the 2021 Alzheimer's Association International Conference.

BMI	n	Conventional LP	Ultrasound-Guided LP
18-24.9	21	43%	57%
25-29	27	37%	63%
30-	10	20%	80%

Table 2. Frequency of LP type by BMI

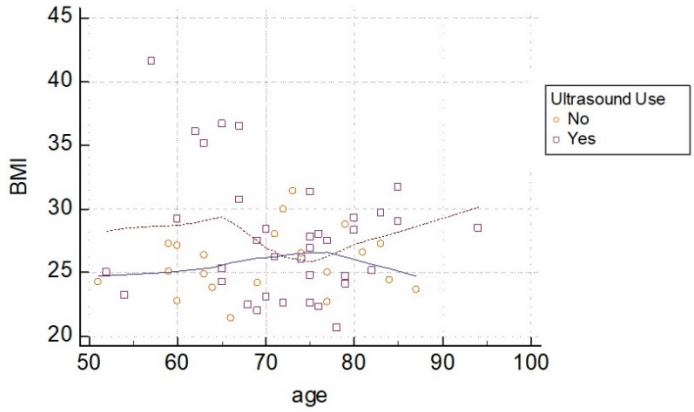
Age	n	Conventional LP	Ultrasound-Guided LP
<65	14	57%	43%
65-74	19	32%	68%
75-84	21	29%	71%
84-95	4	25%	75%

Table 3. Frequency of LP type by age

Study investigators reached an agreement with the company Philips to use their Lumify hand-held tablet ultrasound equipment for this AAC-funded study. Philips provided two tablets with two corresponding transducers (linear and curved). After IRB approval in August 2019, the study was initiated at BAI and BSHRI. All study participants who agreed to lumbar puncture for various observational and clinical trials at BAI and BSHRI were consented and enrolled sequentially (n=58). LP participants characteristics are listed in Table 1. For each LP completed, the LP clinician had the option to use ultrasound assistance. After the procedure, the LP clinician completed a post-procedure questionnaire about clinician background, use of ultrasound, and procedure performance. LP participants were contacted by the research coordinator within five days to identify adverse events. The research coordinator entered all questionnaire data into RedCap. The design (content and timing) of the questionnaires (clinician surveys) was modified from pre-/post-LP to post-LP based on input from LP clinicians, and consideration of Us-LP training, IRB approval and grant timelines.

Following training, four clinician-researchers implemented Us-LP into their practices. Between August 2019-March 2020, 58 research participants (Table 1) underwent LP. Clinician-researchers used Us-LP on 37/58 (64%) participants. Compared to conventional-LP, Us-LP choice was associated with higher/highest BMI and older/oldest age categories (Tables 2,3). A U-shaped relationship between BMI and Age in Us-LP choice was noted (Figure 1). Us-LP was also 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

Figure 1. Relationship of Age and BMI to Ultrasound Use



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.

Aim 3. Develop print and video materials for clinicians and the public on the importance, utility, and safety of LPs in order to enhance the perceived value; mitigate fears and misconceptions; and increase the likelihood of participation and referral for LPs.

Excellent progress has been made on Aim 3. Study investigators reached an agreement with medical animation company, AXS Studio, to develop an animated, educational video about lumbar puncture in ADRD research. The two-minute video highlights the significant value of CSF for enhancing ADRD knowledge and also demystifies the LP procedure experience, depicting a theoretical ADRD study participant undergoing the procedure in a calm and controlled environment. The video has been well-received by the Arizona Alzheimer's research community, and BSHRI provides the video for viewing to research participants who are considering LP. The study team continues to make plans to disseminate the video to a broader, national and international audience.

Lumbar Puncture Explained: Unlocking the Mysteries of Alzheimer's Disease

Long Term Goals:

Preliminary results suggest that Us-LP is feasible to implement in an AD/ADRD clinical research setting. We continue to partner with Philips to with imminent plans to further evaluate LP research clinician decision-making related. Upon study completion and based on our findings, we plan to apply for additional funding through NIH, industry and/or philanthropic organizations to develop enhanced efforts to increase the use of lumbar puncture and fluid biomarker acquisition in ADRD research. We continue to anticipate that this study will provide a foundation for a future training program for a LP proceduralist that can be a mid-level practitioner or RN in order to vastly expand capacity to obtain CSF in an effective, efficient and scalable manner. Enhancing ADRD LP capabilities is increasingly relevant with the possible approval of AD disease-modifying treatments on the horizon.

Project Progress Report
Mayo Clinic Arizona

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Normal and Pathological Aging (Preclinical Alzheimer's Disease). Richard J. Caselli, MD, Dona E.C. Locke, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

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.

1. 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:
    a. Mentation (neuropsychological measures of cognition and behavior; subjective assessments by observers and self; sleep parameters)
    b. Brain Imaging (structural brain changes [MRI], functional [FDG-PET], amyloid-PET, tau-PET)
2. To correlate longitudinal changes on each of these measures with clinical outcomes (mild cognitive impairment, Alzheimer's dementia, non-Alzheimer's dementia)
3. To characterize the influence of other demographic, genetic, epigenetic, and health factors on cognitive aging trajectories
4. To create a biobank of serum, plasma, DNA, frozen viable lymphocytes, and immortalized cell lines of this cohort.
5. To function as a core resource collaboratively supporting other investigators
6. 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 855 individuals including 479 APOE e4 noncarriers, 263 e4 heterozygotes, and 104 e4 homozygotes (APOE results pending in 9) with follow-up durations of up to 25 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

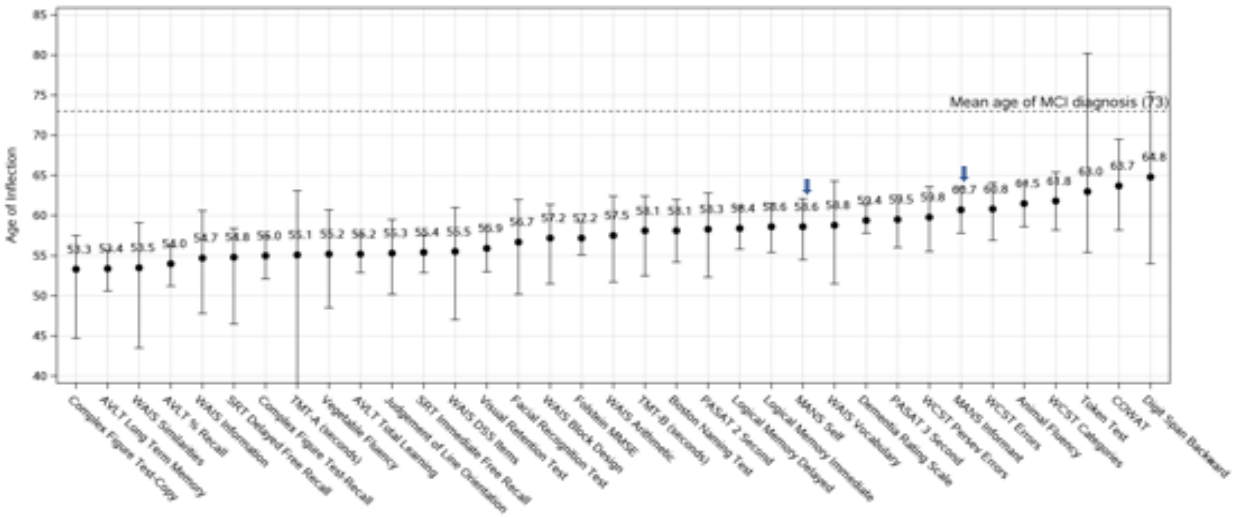
immortalized cell lines established including all with brain imaging. We have completed whole genome sequencing in 537 participants and have ongoing MRI enrollment with 167 completed to date. Among our many accomplishments, we established cognitive aging trajectories for each of 3 APOE genotypes (1-3), 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 fiscal year include:

1. Maintain continuity of follow-up testing of our established cohort.
2. Expand enrollment as our more limited budget will permit with an emphasis on increasing diversity
3. expand our biobanking efforts to include all those with young onset Alzheimer's disease
4. Use supporting funds to expand the scope of our work to include whole genome sequencing that will:
    a. Establish an ongoing resource for future research efforts
    b. Support an initial study examining the correlation of genomic diversity with cognitive aging trajectories and clinical outcomes
5. Use supporting funds to include MRI studies of cohort members that will:
    a. Establish an ongoing resource for future research efforts
    b. Support an initial study examining the correlation of APOE genotype with inter-hemispheric patterns of symmetry of functional MRI resting state in memory and Alzheimer's disease-sensitive regions of interest that reflect areas of early tau and amyloid deposition respectively
    c. Provide a training and educational opportunity for young investigators
6. Provide collaborative support for other scientists

Year End Progress Summary:

1. The results of our cognitive and behavioral aging trajectories contrasting individuals who developed incident MCI with those remaining clinically normal showed that the earliest cognitive changes predate incident MCI diagnosis by 20 years (figure), rivalling the earliest biomarker changes and implying that current pathophysiological models which posit a linear sequence of change with cognition lagging are in need of revision (7).



2. Based on our work to date and related studies from the scientific literature we published the amyloid homeostasis hypothesis, an alternate interpretation of the role of amyloid in the pathogenesis of Alzheimer's disease, one that better accounts for the critical physiological roles played by amyloid precursor protein and its various fragments, including abeta peptide and the continued failure (and relative inefficacies) of amyloid targeted clinical trials (8).

3. We are providing collaborative support to multiple investigators at Arizona State University (Yalin Wang, David Brafman, Michael Sierks, William Tyler, Molly Maxfield, Li Liu), USC (Berislav Zlokovic), Mayo Clinic (Oana Dumitrascu, Otto Pedraza, Leslie Baxter, Cynthia Stonnington), and Banner Alzheimer Institute (Eric Reiman and his team).

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Project Progress Reports
Midwestern University

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Identification and culture of microbes in brain tissue from Alzheimer's disease patients and controls. Garilyn Jentarra, PhD, T. Bucky Jones, PhD, Fernando Gonzalez, Doug Jones, PhD, Kathy Lawson, PhD, Vanthida Huang, PharmD, Pamela Potter, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1:
The goal of this aim is to obtain and use 16S rRNA gene sequencing data from brain tissue to validate and expand previous data and to provide antibody staining targets in brain tissue.
Aim 1.1: Perform 16S rRNA gene sequencing on DNA extracted from human brain tissue samples. Identify the most prominent bacteria in each sample.
Aim 1.2: Cut tissue sections from additional tissue cores from each sample and perform antibody staining of a few of the most prominent bacteria in each sample as identified by 16S rRNA gene sequencing.

Specific Aim 2:
The goal of our second aim is to attempt to culture microbes from cores of frozen brain tissue using growth media and conditions appropriate for aerobic, facultative, or anaerobic bacteria, and fungal organisms.
Aim 2.1: Obtain tissue core, gently homogenize, and apply homogenate to bacterial and fungal growth media, under various conditions
Aim 2.2: Evaluate any microbial growth that occurs and seek to isolate and identify any microbes cultured.

Background and Significance:

Many researchers over the last 20-30 years have proposed that various microbes play a role in the development of Alzheimer's disease. These include microbes such as *C. pneumoniae*, various spirochetes, *P. gingivalis*, HSV-1, HHV-6, and *Candida* species. In general, what these studies find is that whatever microbe they look for is found in both AD patients and controls, but more frequently in AD patients or at higher levels in AD patients. The implication of this is that it is not wholly unusual for there to be microbes present in the brain (at least in the older individuals studied). In addition, researchers, including ourselves, have performed 16S rRNA gene sequencing (for bacterial sequences) on DNA extracted from AD patient brain tissue. These studies have identified DNA sequences from many different kinds of bacteria in the samples of all individuals, both AD patients and controls, with some indication that there may be a larger number of sequence reads or variations in the predominant types of bacteria in the AD patients. However, as in our previously referenced studies, contamination at the time of autopsy, as well as contamination of lab reagents and plastics, is a major issue when analyzing these low microbial biomass samples.

We are attempting to address this contamination issue in various ways so that we can move past it and identify which microbes can be confirmed to originate from the brain tissues and which are contaminants. The experiments in this proposal will help us to validate our findings in a new set of subjects as well as to further advance this line of research. We will be conducting 16S rRNA gene sequencing for bacteria after fully decontaminating the outer surface of the tissue. We will

also attempt to culture microbes directly from the frozen tissue to evaluate whether the gene sequences represent living microbes.

Preliminary Data, Experimental Design and Methods:

We performed many experiments in our attempts to determine whether microbes are present in the brain and whether they contribute to the development of AD. Our first experiments involved 16S rRNA gene sequencing, to evaluate what types of bacteria might be present in the brain. Somewhat to our surprise, we found DNA sequences from hundreds of different bacteria, albeit with the caveat that there is still a concern that some of those sequences may result from autopsy or lab contaminants.

As a follow up to the sequencing data, we tested levels of lipopolysaccharide (LPS - gram negative bacteria) and lipotechoic acid (LTA - gram positive bacteria) in the brain tissue of the same subjects (by ELISA) and found substantial levels of both in almost all subjects, in three different brain regions (data not shown). Levels of LPS were particularly high (30,000-300,000 pg/ml from 400mg of tissue), indicating accumulation of a gram negative bacterial product. As the largest portion of bacteria found by sequencing in all four subject groups were the gram negative phylum Proteobacteria (61.6-77.2%), LPS results appear to support the sequencing data.

Aim 1.1: DNA extraction and purification:

Frozen brain tissue was obtained from the Banner Sun Health Research Institute (BSHRI). In an attempt to thoroughly remove potential contaminating microbes introduced during the autopsy and initial dissection process, we will first clean the outside surfaces of the tissue with 10% bleach to kill microbes and degrade any free DNA present. Subsequently, we will carefully trim outer surface layers off using sterile, DNA-free scalpel blades, and finally we will use sterile, DNA-free punch biopsy tools to take a core sample of the tissue. This procedure will be done under sterile conditions in a biosafety cabinet.

DNA extraction will be then be performed using the Qiagen Powersoil DNA Isolation Kit will be and the NEBNext Microbiome DNA Enrichment kit.

Bacterial DNA analysis: Analysis for the presence of bacterial DNA will be performed on the purified DNA by pathogen and microbiome experts at TGen North. They will perform nextgen 16S rRNA gene sequencing, which involves amplicon production and creation of tagged libraries of DNA fragments. Primers targeting the V4 region of the 16S rRNA genes are as published by Caporaso *et al*.

Aim 1.2: Antibody staining for microbes

16S data from Aim 1.1 will be used to select a small set of bacteria (~5-6) common to the majority of the samples and highly represented by sequencing read number. We will stain specifically for these bacteria in additional sterile tissue cores used to create frozen sections, and mounted on slides for antibody staining.

Aim 2.1: Culturing microbes from brain tissue

Cores of frozen tissue will be obtained from samples under sterile conditions as previously described. The tissue will be gently homogenized, diluted as necessary, and aliquots applied to various bacterial and fungal culture media in an attempt to establish whether live microbes can be recovered from brain tissue.

Aim 2.2 Identification of microbes successfully recovered from brain tissue

If any microbes are successfully cultured from any of the tissue samples, we will follow up by isolating the microbes and using either standard microbiological procedures or DNA sequencing to identify them.

Proposed One-Year and Long-Term Outcomes:

We have accumulated a considerable amount of data that we are currently completing analysis of and drafting for publication. From the existing work, we can produce at least 2 publications. In addition, a collaboration with a metabolomics researcher at Arizona State University, which involved extracts we made from tissues of our first subject set, has already resulted in a draft publication that has been submitted for publication. We were recently awarded an NIH R21 to follow up on this metabolomics data. In the next 6 months, we intend to complete submission of multiple publications based on our existing data. Further, we will use that data for grant proposals to the Infectious Diseases Society of America (IDSA) Foundation, which has created a specific grant opportunity for studying the involvement of microbes in AD. We will also submit a new proposal to the NIH, which has a funding opportunity within the National Institute on Aging that designates the involvement of microbes in AD as a high priority topic of interest (PAR-19-070, "Research on Current Topics in Alzheimer's Disease and Its Related Dementias (R01 Clinical Trial Optional)).

Year End Progress Summary:

Collectively, we anticipate that experiments in Aim 1 and possibly in Aim 2 will support and strengthen our previous data, helping us to determine more definitively whether or not living microbes are present in the brain in the numbers suggested by sequencing, proteomics, and ELISA data. The ultimate goal of this research is to identify the events that trigger AD pathology and, in doing so, open up new and more effective treatment options. The establishment of amyloid beta, a key pathogenic molecule in AD, as a likely anti-microbial peptide supports the need for further work in this area.

Due to issues with allowing lab personnel to safely work on campus during the pandemic, we experienced significant delays in starting the research in this proposal. It also took longer than expected to acquire the necessary tissue from BSHRI due to high autopsy volumes they were experiencing, which were in part pandemic-related. However, the research is now fully underway in the laboratories of our investigators.

We have acquired the necessary tissues from BSHRI. This includes 20 subjects in each experimental group: AD, mild cognitive impairment, high-pathology controls, and non-demented controls. We are currently in the process of sterilely obtaining cores from the tissues for the purpose of DNA extraction and subsequent sequencing. We are simultaneously taking cores for the purpose of attempting to culture living microbes from the tissue. The need for absolute sterility on the outer surfaces of the tissue makes these procedures very labor intensive. However, our goal is to complete the DNA extractions by the end of April, and immediately send the samples for 16S rRNA gene sequencing so that a portion of the work can be completed by the end of June. At the same time, another one of the principal investigators on this proposal will be performing the culture work outlined in the proposal. We are hopeful that work can also be completed by the end of June. The antibody staining described in Aim 1.2 is contingent on the receipt of this sequencing data and will be completed later in the summer. All of the supplies necessary to successfully complete Aims 1.1 and 2.1 have been purchased. The antibodies needed for the immunohistochemical studies will be purchased after we have obtained sequencing results, but we will move forward with those studies as soon as possible.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Reversal of diabetic obesity with dietary modifications and/or exercise results in improved cognitive ability, inflammation, senescence and thus mitigation of AD-like pathology. Layla Al-Nakkash, PhD, Thomas Broderick, PhD, Minsub Shim, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

1. Determine ability of genistein and exercise to reverse Alzheimer's-like pathology and synaptic markers in diabetic-obese mice.
2. Determine the effects of genistein and exercise to reverse inflammation in diabetic-obese mice.
3. Determine the impact of genistein and exercise to reverse senescence in diabetic-obese mice.

Background and Significance:

Obesity resulting from ingestion of high energy foods such as high-fat diet (HFD), results in loss of learning and memory function. In male C57BL/6J mice, HFD induced cognitive deteriorations mediated via neuronal insulin resistance and brain mitochondrial dysfunction. Hippocampal neurogenesis is impaired following consumption of HFD, this is important since this region of the brain plays a role in learning and memory, specifically of flexible memory (the ability to use previously learned information in a new situation). Metabolic syndrome is a major contributor towards cardiovascular disease, type II diabetes, insulin resistance and inflammation, which are all risk factors for Alzheimer's Disease (AD) and dementia. It has been postulated that, with such dietary habits, cognitive infractions are correlated with increased deposition of amyloid beta, increased formation of neurofibrillary tangles and reductions in synaptic plasticity. Clinically, overweight women are predisposed to cognitive dysfunction. Therefore, given the epidemic of obesity in the US, this proposed study is timely. Although the adverse effects of obesity are well-known, its underlying mechanisms remain to be determined. For many chronic diseases including AD, aging is the greatest known risk factor. There is a connection between aging and cellular senescence, for example, the number of senescent cells increases with age in mammalian tissues with osteoarthritis and atherosclerosis. It has been recently shown that HFHS induces senescence in mice. Given the strong association between senescence and aging, this finding suggests that senescence may contribute to obesity-associated neurocognitive decline. Genistein is a naturally occurring isoflavonic phytoestrogen found in high concentrations in soy products. In our previous studies the optimal concentration of genistein we feed mice is 600 mg genistein/kg diet, which yields serum genistein levels of 4-8 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 I_{sc}) is increased by a 4-week dietary genistein period in lean mice, and in ob/ob mouse jejunum. Genistein has been shown to alleviate neuroinflammation, amyloid beta deposition and to reduce oxidative stress in HFD-fed ApoE$^{-/-}$ mice. It is reasonable to predict that genistein administration would have beneficial effects on systemic inflammation and gastrointestinal-brain health in the current study. Exercise is commonly recommended by physicians to assist in reversing obesity. Of relevance to this proposal, exercise has been shown to improve hippocampal-dependent learning and memory in older individuals. Indeed, voluntary wheel running has been shown to ameliorate some of the memory dysfunction in HFD female C37BL/6J mice. From a cardiovascular perspective, there is some gathering evidence that AD is associated with risk of cardiovascular complication. Our

group has recently demonstrated that exercise training (along with resveratrol) provided benefits in cardiac function and aortic elastin morphology in the 3xTg mouse model of AD.

Preliminary Data, Experimental Design and Methods:

We utilized 60 male *C57BL/6J* mice were purchased from Charles River Labs (aged 4-weeks), acclimated for 1-week, and then fed high fat diet containing: 60% fat, 20% protein and 20% carbohydrate from Dyets Inc) along with 42g/L liquid sugar (sucrose and fructose combined) for 12-weeks (HFHS diet induced diabetic obesity at 12 weeks). The mice were then randomly divided into 5 groups: HFHS, HFHS+genistein, HFHS+exercise, HFHS+genistein+exercise, Standard chow and regular water, and comparisons made to a group fed standard chow and water for the entire 24 week duration, i.e. lean controls (n=10/group). From time 13-24 weeks mice were assigned to one of those 6 groups. Genistein supplement was added to the HF diets (Dyets Inc, Bethlehem, PA) at a concentration of 600 mg genistein/kg diet. Importantly, we have found that this concentration of genistein incorporated in the diet is sufficient to produce significant beneficial modifications in intestinal function and bone health. Exercise duration was set at 30 min/day for 5 days/week, for the study duration of 12 weeks. Exercise intensity was 12 meters/min (i.e. the American Heart guidelines for 30 minutes of moderate activity, for a total of 150 minutes/week). Comparison of sex-dependent effects and variances of mechanism(s) of action are fundamental to our long-term research objectives. Moreover, NIH guidelines require studies to utilize sex-dependent comparisons of animal models, thus proposing sex-dependent mechanisms, along with convincing preliminary data in future grant applications will be key. Mice were euthanized and tissues harvested and maintained at -80^{o}C until use for these studies.

Proposed One-Year and Long-Term Outcomes:

We hypothesized that administration of genistein or exercise would improve outcomes in the HFHS-fed diabetic-obese mice. We predicted that both genistein supplementation combined with regular exercise would have additive beneficial effects. We predicted that we would reverse the detrimental effects of diet-induced obesity on cognitive dysfunction and AD–like pathology.

Year End Progress Summary:

Aim 1-Determine ability of genistein and exercise to reverse Alzheimer's-like pathology and synaptic markers in diabetic-obese mice. This aim was on hold due to space constraints with individuals in the lab this past year.

Aim 2-Determine the effects of genistein and exercise to reverse inflammation in diabetic-obese mice.

We evaluated serum cytokines and found that levels of TNFα, MCP1, IL2, IL-10 were all significantly increased by high fat high sugar diet. Elimination of high fat high sugar diet (i.e. switching to consumption of standard chow and water) significantly reversed levels of TNFα and MCP1. Addition of genistein-diet or genistein plus exercise to the HFHS diet similarly reversed the significant increase in TNFα returning them to lean-like levels. Exercise reversed the increase in IL-10. Of note, we found no HFHS-induced changes in the following cytokines: IL-1a, IL-1B, IL-4, IL-5, IL-7, KC, MCP2. We plan to assess levels of inflammation in brain and intestine (Il-6 and TNFα).

Aim 3- Determine the impact of genistein and exercise to reverse senescence in diabetic-obese mice.

We evaluated cellular senescence in intestinal tissue using western blot methodology. We found that high fat diet induced significant increases in pH2AX (expression in jejunum and this is significantly decreased by elimination of fat and sugar from the diet, inclusion of genistein to the HFHS diet, and with genistein plus exercise added to the HFHS diet regimen (n=6-7/group). We

found no change in expression of p53 protein in the intestine from these same groups. We plan to evaluate these and other senescent markers in brain tissue.

Future grant applications, publications and collaborations that arose from the research:
Publications: one publication was recently submitted to Molecules 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.
The PI's (Al-Nakkash, Shim and Broderick) on the project have a second manuscript in preparation aiming to address the role of genistein and/or exercise on inflammation and senescence.

The role of vitamin B12 deficiency on stroke outcome and mechanisms in old aged male and female mice. Nafisa Jadavji, PhD, Volkmar Weissig, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:
The aim of this proposed study is to investigate the role of vitamin B12 deficiency on stroke outcome and mechanisms in old-aged male and female mice.

Background and Significance:
Stroke is one of the leading causes of morbidity and mortality globally, more than 80% of strokes are ischemic, therefore due to an obstruction of arteries (1). In the US by 2030, the number of stroke affected patients is predicted to increase by 3.4 million. There is a higher prevalence of stroke in older age individuals (> 65 years). The proposed research is both timely and much needed, as the population in the US and globally are aging and the prevalence of stroke is predicted to increase. Several studies have established that nutrition is now considered as a modifiable risk factor for vascular dysfunction and ischemic stroke.

Importance of adequate nutrition on stroke risk and outcome: Adequate nutrition reduces the risk of ischemic stroke. One-carbon (1C) metabolism revolves around folic acid, vitamin B12, and other B-vitamins. One-carbon is metabolic network that integrates nutritional signals with biosynthesis, redox homeostasis, and epigenetics, and plays an essential role in the regulation of cell proliferation, stress resistance, and embryo development. Through methylation, 1C reduces levels of plasma homocysteine. Increased levels of homocysteine are a risk for stroke, by increasing endothelial dysfunction and atrial fibrillation.

Vitamin B12 deficiency increases risk of stroke and impacts outcome: As we age, our metabolism and absorption of nutrients, including vitamins also change. Approximately 40% of older adults (> 60 years old) have a vitamin B12 deficiency. In a longitudinal cohort study of 725 stroke cases, increased dietary intake of vitamin B12 was statistically significantly associated with a decreased risk of ischemic stroke in men aged 40-75 years old.

Patients with a vitamin B12 deficiency during an ischemic stroke have been reported to have worse outcome afterwards. In patients with first lacunar stroke, low vitamin B12 levels were associated with more periventricular white matter lesions. The role of vitamin B12 on outcome was also describe in a case of recurrent stroke in a 35-year-old male patient. The patient suffered two ischemic stroke incidents within a 3 month span and was recorded as having relatively low levels of vitamin B12, as well as high homocysteine levels . **The mechanism through which low levels of vitamin B12 lead to decreased outcome after stroke requires more investigation.**

In the brain, after a stroke, there are several cellular signalling cascades that occur, one of which includes apoptosis. Mitochondria are the powerhouses of the cell and play major role in supplying energy in the form of ATP to cells, they also contribute to the development of apoptotic and necrotic cell death after ischemic stroke. Furthermore, vitamin B12 plays an essential role in mitochondrial energy production and cellular function. The impact of vitamin B12 deficiency after stroke on mitochondrial function requires more investigation. Mitochondrial function will be studied in this proposed research with the support of Dr. Volkmar Weissig (Co-I). His research has focused on assessment of mitochondrial function and has the expertise required to contribute to the proposed research, therefore the proposed research will have a multidisciplinary approach.

Preliminary Data, Experimental Design and Methods:

Ischemic Stroke Model

Dr. Jadavji's (PI) laboratory has developed and established a working protocol to induce ischemic damage to the mouse brain using the photothrombosis (PT) model, which relies upon an intraperitoneal injection of a photoactive dye (e.g. Rose Bengal), after which the intact skull is irradiated using a light beam at 532 nm, resulting in sensorimotor cortical damage. The damage is a result of singlet oxygen and superoxide formation, which results in endothelial injury, platelet activation, and aggregation. This reliable method has been standardized over the past decade in mice, and the major advantage of this model of ischemic stroke is that it results in highly reproducible damage within a localized region of the brain, there is also minimal surgical intervention involved. This stroke model shows brain characteristics reminiscent of the clinical circumstance and is being adopted by several laboratories around the world. In our work, we target the sensorimotor cortex, as shown by representative images of cresyl violet stained brains in. Using the PT model, we have previously demonstrated functional impairment in the animals after damage.

Stroke Outcome in Vitamin B12 Deficient Adult Male and Female Mice

At Midwestern University AZ campus, Dr. Jadavji's (PI) laboratory has induced ischemic stroke in 1-year-old male and female mice on a vitamin B12 deficient diet. The male mice on a deficient diet had reduced coordination and balance when their functional outcome was assessed on the accelerating rotarod task. Four weeks after PT damage, the males could not stay on the accelerating rotarod for as long as females ($F_{(1, 32)} = 5.52$, $p < 0.05$) and fell off the rotarod at low rotations per minute (RPM) (Diet main effect, $F_{(1, 32)} = 6.573$, $p < 0.05$; Sex main effect, $F_{(1,32)} = 4.89$, $p < 0.05$). Dr. Jadavji's (PI) laboratory has the equipment and expertise to conduct the proposed research.

In collaboration with Dr. Weissig (Co-I), Dr. Jadavji (PI) has established an immunofluorescence protocol to measure cytochrome c levels within the damage area of brain tissue after ischemic stroke. Cytochrome c is a heme protein that is localized in the compartment between the inner and outer mitochondrial membranes, it functions to transfer electrons between complete III and complex IV. When a cell receives an apoptotic signal, cytochrome c is released to trigger programmed cell death [46]. Our preliminary data suggests that there are increased levels of cytochrome c after ischemic damage in mice with a genetic deficiency in one-carbon metabolism

Proposed One-Year and Long-Term Outcomes:

The proposed work will be completed in one year following this timeline. By month two we expect recieve IACUC approval. Experimental work will take place from months 2 to 10; data analysis will take begin in month 5 and continue to month 11. In month 12 we will begin drafting the manuscript and preparing it for submission. One graduate student enrolled in the Master's in Biomedical Science (M.B.S.) program will contribute to the proposed research program. The graduate student will be actively involved in data collection, data analysis, and manuscript preparation for submission to a scientific journal for peer review. Dr. Jadavji (PI) and the Research Assistant will work on the mitochondria functional measurements. This data collection and analysis will be performed under the direct supervision of the *Drs. Jadavji (PI) and Weissig (Co-I)*. For the proposed project, on a weekly basis *Drs. Jadavji (PI) and Weissig (Co-I)* laboratories will meet regularly to discuss the latest scientific research, as well as the experimental data generated in the lab, brainstorm new ideas, and tackle experimental challenges.

Planned outputs: We plan to publish the proposed research in a high impact peer-reviewed journals, such as the *Journal of Nutrition, Experimental Neurology, Nutritional*

Neuroscience, or Neurobiology of Disease. It is expected that the proposed research plan will result in one publication, the manuscript will outline the impact of vitamin B12 deficiency on stroke outcome and mechanisms.

It is also expected that the results of the proposed project will be presented in regional and national meetings. In addition to publications, the research team will present the research at local, national, and international meetings. The graduate student will also have the opportunity to present their research findings at a scientific meeting to enhance their training and research skill acquisition. No travel funds are being requested, university funds (e.g. travel funding or start-up) will be used to cover travel of the student and Dr. Jadavji (PI).

Year End Progress Summary:

We have completed the *in vivo* portion of this proposed work. In aged female mice maintained on a vitamin B12 deficiency we observed impaired coordination and balance after ischemic damage. Deficient females also had an impaired neuro-deficit score. The PI and Agnes Pascal (Senior Research Specialist) have completed sectioning brain tissue and are currently working on measuring damage volume.

There are several Midwestern University students involved in this research project. Currently, we are analyzing ladder beam walking task. This is being completed by a research assistant (Neha Kwatra, College of Dental Medicine student). Joshua Poole, College of Osteopathic Medicine student is analyzing the forepaw placement task and will be continuing assessing neurodegeneration and mitochondrial function in brain tissue. We anticipate completing this analysis by early Spring 2021.

We are also measuring metabolites in the cecum samples and brain samples collected at the completion of the *in vivo* studies with our collaborator Dr. Haiwei Gu at Arizona State University. Blood and liver one-carbon metabolites are being measured by another collaborator, Teodoro Bottiglieri at the Baylor Scott and White Research Institute. These data will provide important insights into the mechanisms through which a dietary vitamin B12 deficiency is reduces stroke outcome.

We anticipate writing up the results from this study and submitting for peer review by the Fall of 2021. The data collected from this research will also be included in future funding application.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

The role of phosphorylation on the function of the telomere protection protein RAP1. Mark J. Swanson, PhD, Nancy S. Bae, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1. **Generate mutant versions of the RAP1 protein that replace serine residues known to be phosphorylated with alanine or aspartic acid.** The *working hypothesis* for this aim is that these mutations will mimic non-phosphorylated RAP1 (alanine substitutions) and phosphorylated RAP1 (aspartic acid substitutions).

Specific Aim 2. **Determine effects of the RAP1 mutations on its functions in the cell.** The *working hypothesis* for this aim is that post-translational modifications are required to cause RAP1 to leave the telomere in the nucleus to interact with GFAPε and PS1 in the cytoplasm.

Specific Aim 3. **Test specific kinases for their ability to interact with RAP1 as a target.** The *working hypothesis* for this aim is that specific kinases will phosphorylate RAP1, which may be predicted by the amino acid sequence of the RAP1 protein.

Background and Significance:

The shelterin protein complex protects telomeres. The RAP1 subunit is recruited to telomeres by TRF2. RAP1 has also been shown to have functions independent of telomeres. To understand the roles of RAP1 in the cytoplasm, a yeast two-hybrid (Y2H) screen was performed, in which we identified an isoform of glial fibrillary acid protein (GFAP), GFAPε, as an interacting protein of RAP1. Altered GFAP expression is associated with a variety of neurological diseases. There are ten GFAP isoforms, and the GFAPε isoform is expressed by neurogenic astrocytes in the sub-ventricular zone. Increased GFAPε expression occurs near amyloid beta plaque deposition in Alzheimer's disease (AD) brains. GFAPε is the only isoform that interacts with presenilin protein, PS1. Mutations in the genes coding for amyloid precursor protein (APP) and the presenilins (PS1 and PS2) are frequently seen in familial AD.

Cells must respond immediately to signals or imminent danger. The functions of many proteins are regulated at the post-translational level, which provides for a rapid response. Phosphorylation occurs on hydroxyl groups of serine, threonine or tyrosine in proteins. Under conditions of oxidative stress, RAP1 was found at high levels in the cytoplasm of human cells. How RAP1 dissociates from TRF2 and telomeres, and how it gets into the cytoplasm are unknown. RAP1 is phosphorylated on six serine residues. We predict that phosphorylation of these residues leads to RAP1 leaving the telomere to enter the cytoplasm to interact with GFAPε and PS1.

Preliminary Data

RAP1, GFAP epsilon and PS1 interact in the Y2H system. The Y2H system is a simple yeast method for detecting protein-protein interactions. Using this system, we found that GFAPε interacted with RAP1. Using a modified system that includes expression of a third protein, we found that the interactions among GFAPε, RAP1 and PS1 are cooperative.

RAP1 is predicted to be phosphorylated by kinases associated with Alzheimer's disease. RAP1 is known to be phosphorylated on six serine residues by mass spectrometry. We used the NetPhos3.1 software to predicted specific kinases that may phosphorylate RAP1. Among the predicted kinases, Cdk5, p38MAPKs (MAPK11 and MAPK14), and GSK3 (α and β) have been implicated in AD. These kinases are predicted to target the serine residues of RAP1 at positions 36, 154 and 203, which may be relevant for AD.

Experimental Designs and Methods

Specific Aim 1. **Generate mutant versions of the RAP1 protein that replace serine residues known to be phosphorylated with alanine or aspartic acid.**

We will mutagenize serines at positions 36, 154 and 203, converting them to alanine to generate non-phosphorylatable mutants. We will also change them to aspartic acids to mimic phosphorylated serines that cannot be dephosphorylated. Each serine will be mutated individually then we will combine two or all three positions as alanines or aspartic acids.

Specific Aim 2. **Determine effects of RAP1 mutations on its functions in the cell.**

We will test the effects of serine mutations on RAP1 functions, including interactions with TRF2 and GFAPε/PS1, localization in human cell lines, and effects on yeast γ-secretase activity.

Specific Aim 3. **Test specific kinases for their ability to interact with RAP1 as a target.**

We will clone the genes encoding the kinases Cdk5, the p38MAPK proteins MAPK11 and MAPK14 and the two GSK3 kinases (α and β) into Y2H vectors to determine whether they interact with RAP1 and to determine whether the kinases alter the interaction between RAP1 and GFAPε or between RAP1 and TRF2.

Proposed One-Year and Long-Term Outcomes:

We anticipate this work will show RAP1 is regulated by phosphorylation. We are studying three known phosphorylation sites on RAP1 that are predicted to be phosphorylated by several kinases associated with AD. Yeast are eukaryotes, and RAP1 may be phosphorylated at these same sites in the Y2H strains. The use of serine to alanine mutations, which generate non-phosphorylatable versions of RAP1, will be important to determine specific effects of the post-translational modifications on interactions. We will also use proteins expressed in *E. coli* cells for interactions since *E. coli* will not phosphorylate the proteins. We predict RAP1 phosphorylation is necessary for dissociation from TRF2 and the telomere. Combining immunofluorescence and cellular fractionation of human cells expressing different RAP1 mutations should allow us to determine how phosphorylation affects cellular localization. Phosphorylation of RAP1 may affect its formation of a tripartite complex with GFAPε and PS1, which may affect γ-secretase activity.

The studies outlined in this proposal will be sufficient for publication and lead to more in-depth studies on RAP1 and its kinases using human cells. The yeast system has benefits of ease of use, powerful genetics for manipulation and introduction of various mutations. Thus, the work done in yeast will streamline what needs to be verified using human cells. These data will also form the basis of an external grant application to the National Institutes for Aging and/or other institute or foundation as appropriate.

Year End Progress Summary:

Specific Aim 1. **Generate mutant versions of the RAP1 protein that replace serine residues known to be phosphorylated with alanine or aspartic acid.** We have generated all six single mutations, and each has been verified by sequence analysis. We have recombined these to create several double mutations. The remaining double mutations and the triple mutations are currently being cloned. The various constructs are being cloned into a several plasmids to test functions that will be described in the next section.

Specific Aim 2. **Determine effects of the RAP1 mutations on its functions in the cell.** All of the RAP1 serine mutants (single, double and triple) will be cloned into a variety of plasmids, many of which have already been constructed. These include:

- Yeast two-hybrid plasmids to test interactions of the RAP1 mutants with TRF2 and separately with GFAPε and PS1.
- *E. coli* expression vectors that include affinity tags for additional interaction tests.
- Human expression vectors to determine the localization of RAP1 mutants in human cells.
- We have created two yeast strains that can be used to analyze γ-secretase activity. On the chromosome, we have integrated a target for γ-secretase that is an APP fragment consisting of the carboxy-terminal 99 amino acids (C99), the natural target for γ-secretase. At the carboxy-terminus of the C99 fragment, we fused the yeast GAL4 transcriptional activator protein. If the C99 is not cleaved by γ-secretase, then GAL4 will remain at the plasma membrane. If the C99 fragment is cleaved, GAL4 can translocate into the nucleus and activate reporter genes with GAL4 binding sites near their promoters. In this system, we have been able to detect γ-secretase activity. We have data showing that when GFAPε and RAP1 are both expressed, there is a four-fold increase in γ-secretase activity. Currently, we are cloning the RAP1 mutants into the system plasmids, and we will test them alone and with GFAPε.
- We will also clone the RAP1 mutants into a bacterial one-hybrid system. Recent work in our lab has used a bacterial one-hybrid system to detect DNA binding by RAP1. Most of the data in the literature indicate that RAP1 is not able to bind to DNA. We have found that RAP1 can bind DNA weakly using the bacterial system. The advantages of this system are that there is not protein purification required, and specific conditions for protein-DNA binding do not need to be laboriously determined. We have found that the full length RAP1 protein does not bind to DNA very strongly, and we get a much stronger binding when the carboxy-terminal half of the protein is deleted. These data indicate that there is most likely an inhibitory domain in the carboxy-terminus that prevents RAP1 from binding to DNA until it is required by the cell. We believe that the phosphorylation state of RAP1 may play a role in the control of DNA binding. We are currently cloning all of the RAP1 mutants into the bacterial one-hybrid plasmids to determine if these phosphorylation sites play a role in controlling DNA binding.

Specific Aim 3. **Test specific kinases for their ability to interact with RAP1 as a target.** Using polymerase chain reaction, we amplified the genes encoding the five kinases that may target the RAP1 serine residues of our interest. Each was verified by sequence analysis. The kinases were cloned into the Y2H system, and they were tested for interaction with the RAP1 wild type protein. Our data for interaction were negative. Though it is possible that none of the kinases interacts with RAP1, it is also possible the interaction is too weak to detect, or the interaction requires an accessory protein. We are considering additional approaches to test the latter two possibilities.

Overall, we are developing a story about RAP1 in neuronal cells. The RAP1 protein seems to respond to oxidative stress. Once it has left the telomere, it appears to have some potential function as a transcriptional regulator in the nucleus. In the cytoplasm, RAP1 may regulate γ-secretase activity with GFAPε. RAP1 function may be regulated by post-translational modifications (phosphorylation). Although the data we have are not yet ready for publication, we do believe that our preliminary data are strong enough for a grant application (NIA R15) that we believe will be competitive.

Project Progress Reports
Northern Arizona University

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Toward establishing causality of the gut microbiome via the gut-brain axis in Alzheimer's Disease. Emily K. Cope, PhD, J. Gregory Caporaso, PhD. Northern Arizona University; Arizona Alzheimer's Consortium.

Specific Aims:

The primary goal of the proposed study is to determine the microbial species and strains, including bacterial, fungal, and viral communities that are altered in the GI tract in Alzheimer's Disease (AD). *The central hypothesis governing this proposal is that alterations in the gut microbiome contribute to microgliosis, astrocyte activation, tauopathy, and amyloid deposition in susceptible individuals.* Therefore, we propose the following Specific Aims:

Specific Aim 1. Determine the microbial species and strains that change as key pathologies emerge in 3xTg-AD, APPSWE, and Tau (JPNL3) mice compared to their genetic backgrounds using shallow shotgun metagenomic sequencing. In addition, we will determine the microbial strains that engraft in young 3xTg-AD and B6129SF2/J mice receiving FMT from aged 3xTg-AD mice. *This work will provide a higher resolution view into the microbial taxa that are suspected to be associated with AD.*

Specific Aim 2. Determine whether shallow shotgun metagenomic sequencing outperforms bacterial 16S rRNA gene sequencing as predictors of AD progression, measured by tauopathy, amyloid deposition, microgliosis, and reactive astrocytes in a longitudinal assessment of 3xTg-AD, APPSWE, and Tau (JPNL3) and in an interventional study of FMT from 3xTg-AD mice. *We expect that the findings from this aim will have methodological implications for all sequencing-based AD microbiome projects.*

Background and Significance:

The human body is host to trillions of microorganisms (bacteria, fungi, archaea, and viruses) collectively termed the human microbiome.[7] Emerging studies of the healthy human microbiome have demonstrated that niche-specific microbial communities play a key role in metabolism,[8,9] mucosal barrier integrity,[10,11] and development and maintenance of host immune function.[8,12,13] Several recent studies have linked gut microbiota to neurodegenerative diseases, including Parkinson's Disease[14] and Alzheimer's Disease (AD).[15] Bidirectional communication between the gut microbiota and the brain, termed the gut microbiota-brain axis, is highly relevant in AD. Changes in gut microbiota composition and diversity during aging can drive age-associated inflammation; recent studies in *Drosophila*[16] and in murine models[10,17] suggest that alterations to the gut microbiota in late life drive intestinal permeability and increased systemic inflammatory markers. Since neuroinflammation is a key feature of Alzheimer's Disease (AD), understanding the aging gut microbiome is critical to understanding AD progression. Mechanistically, bacteria in the GI tract can produce significant amount of amyloids (aggregated, insoluble proteins exhibiting β-pleated sheet structures), LPS, or other pro-inflammatory metabolites that can prime the immune system during aging, contribute to Aβ plaque formation, and increase AD risk.[18–20]

Our proposed study addresses important limitations of prior research in the nascent field of gut microbiota-brain interactions relevant to AD. We propose to use a novel sequencing method, shallow shotgun metagenomics,[21] to resolve species and strains of bacteria, fungi, and DNA viruses in longitudinal fecal samples from three strains of AD mice and their genetic backgrounds. Strain-level taxonomic assignments will be used to predict neurological markers, such as amyloid deposition, tauopathy, reactive astrocytosis, microgliosis, and neuroinflammatory gene expression. Current mouse and human studies of the gut microbiota in AD are based on amplicon

sequencing of the 16S rRNA gene. While valuable, 16S rRNA gene surveys exclude other microbiota community members (fungi, viruses) and typically result in taxonomic resolution to the genus level. By contrast, shallow shotgun metagenomics recovers more accurate strain-level profiles of bacteria, fungi, and DNA viruses than 16S rRNA gene sequencing.[21] Three studies in human AD patients showed alterations in the abundance of genus *Bacteroides* using 16S rRNA gene sequencing.[15,22,23] Vogt and colleagues demonstrate strong correlations between *Bacteroides* and *Phascolarctobacterium* and levels of phosphorylated tau and Aβ42/Aβ40 ratio in the CSF.[15] However, since these studies are based on amplicon sequencing, the species of *Bacteriodes* associated with AD could not be resolved. Our preliminary results also suggest increasing relative abundance of *Bacteroides* in 3xTg-AD mice. ***Completion of this innovative project will result in a higher resolution of gut microbiota associated with AD markers in the brain, and will contribute to the emerging field of microbiome-based therapeutics or diagnostics aimed at the gut-brain axis.***

Preliminary Data, Experimental Design and Methods:

With support of the AAC, we have established colonies of wild-type B6129SF2/J, 3xTg-AD, APP-SWE tg/wt, APP-SWE wt/wt, and JPNL3 mice. Fresh fecal pellets are collected weekly for microbiome analysis and mice are sacrificed at 8, 24, and 52 weeks for analysis of amyloid-β deposition in the gut and brain. **Our preliminary results show a distinct gut microbiota in 3xTg-AD mice when compared to WT mice** (n=130 mice, n=1500 total fecal samples). Using Random Forest machine learning regressors we can accurately predict the week that each sample comes from given only its microbiome composition (r-squared: 0.80; p=1.744259e-76). Longitudinal analysis demonstrates a temporal trend of increasing relative abundance of the genus *Bacteroides* in 3xTg-AD mice, while other taxa such as *Lactobacillus* exhibit more stability over time. APP-wt, APP-Tg, and Tau (JPNL3) mice demonstrated altered microbiome composition in the GI tract relative to WT mice. Interestingly, different members of the Bacteriodales family seem to drive differences in community composition in AD mice, despite being on different genetic backgrounds.

A subset of n=10 3xTg-AD and n=20 B6129SF2/J mice underwent fecal microbiota transplants. All fecal transplant material was collected from aged (12-19 month) 3xTgAD mice. All mice began the FMT trial at 8 weeks old, receiving oral gavage treatment for five consecutive days, followed by maintenance doses fortnightly for six months. The gut microbiota of wild-type mice receiving FMT had more similar GI microbiota to 3xTg-AD mice and increased relative abundance of *Bacteroides* over time, indicating at least partial engraftment of the AD-associated gut microbiota. We are in the process of assessing if this transplant speeds the onset or increases the severity of AD pathologies. ***Together, these studies suggest increased* Bacteriodes *relative abundance as AD progresses. The proposed study will determine which* Bacteriodes *species and strains increase in relative abundance in AD, in addition to evaluating the potential role of fungal and viral microbiota in AD.***

Proposed One-Year and Long-Term Outcomes:

This project may ultimately lead to early markers of pre-Alzheimer's patients, and to potential approaches to Alzheimer's prevention through alteration of the gut microbiome. In future studies, we plan to collaborate with AAC clinicians to obtain human fecal samples from patients with mild cognitive impairment and AD. As a result of our funding in the AAC, we have submitted proposals to the NIH (two R21s and an F31), Alzheimer's Association, and the Infectious Disease Society of America. A third year of funding will support an R01 to the NIH and we have identified two relevant funding opportunities: PA-18-876 *(Advancing Mechanistic Probiotic/Prebiotic and Human Microbiome Research)* and PAR-19-070 (*Research on current topics in AD and related dementias*). We also expect that new open source software will be developed and released

publicly as part of MPI Caporaso's team's work to support the analyses reported here. This will support other groups doing research on the AD microbiome, as well as microbiome research more generally. Finally, we plan to publish the findings from our first two years of funding this year, and expect that the results from this third year of funding would lead to an additional publication.

Year End Progress Summary:

1) *Progress made toward Specific Aim 1 and key findings.* We have prepared shallow shotgun metagenomic sequencing libraries from 3xTg-AD and B6129SF2/J from fecal samples of (n=10/strain, n=20 total), 24 week (n=10/strain, n=20 total), and 52 week (n=10/strain, n=20 total). This sample size will allow us to detect significant differences at 90% power with a moderate effect size (Cohen's D: 0.55). Specimens have been pooled, and 40 have been sequenced on the Illumina NextSeq500 using a high output reagent kit, so we can reach sample depth of approximately 500,000 sequences/sample. This sequence depth will enable species and strain level resolution of taxa with equivalent or improved coverage compared to 16S rRNA gene sequencing.[21] We are currently analyzing these data using the QIIME 2 plugins q2-shogun and q2-metaphlan2.[6,24] In the very near future, we will be preparing shallow shotgun sequencing libraries from single transgenic (APP-Wild Type, APP-SWE, Tau) strains and from mice (3xTg-AD and B6129SF2/J) receiving a fecal microbiome transplant from aged 3xTg-AD mice (n=10/group, 50 total). In addition to shallow shotgun metagenomics, we have performed metabolomics on 32 fecal specimens from 3xTg-AD, B6129SF2/J, APP-Wild Type, APP-SWE, and Tau. We will integrate these data with species profiles as recently described in a pre-print from PI Caporaso's laboratory.[25]
2) *Progress made toward Specific Aim 2 and key findings.* We have performed 16S rRNA gene sequencing on n=1703 fecal samples, collected fortnightly from 176 mice (3xTg-AD, B6129SF2/J, APP-Wild Type, APP-SWE, and Tau) aged to 52 weeks. We have recently analyzed the gut microbiota of wild-type B6129SF2/J and 3xTg-AD mice to determine whether there are unique temporal gut microbiome signatures of AD progression. Analysis of the single transgenic strains are ongoing. In 3xTg-AD and B6129SF2/J, we observe striking differences in the abundance trajectory of gut microbiome taxa between our wild-type and 3xTg-AD mice over time. Gut microbiome composition in our mice changes predictably with time, such that using Random Forest machine learning regressors we can accurately predict the week that each sample comes from given only its microbiome composition (r-squared: 0.49; p=0.000002).[26,27] These Random Forest models identify specific taxa that are changing with time, and therefore with progression of 3xTg-AD mice through disease. *Bacteroides* sp. increases in relative abundance over time in 3xTg-AD mice but not wild-type mice, and therefore may be a potential indicator that they may be drivers of AD progression. Other common GI taxa do not change over time between the strains (e.g. *Lactobacillus*). In addition, we have performed immunohistochemistry (IHC) for amyloidosis with anti-Aβ reactive deposits [α-Aβ(6E10), α-Aβ(1560) IgG] in n=3 mice/group. Finally, we have performed gene expression analysis using a custom qPCR array. Markers for Th1/Th17 (*il2, il1beta, il-6, il-8, ifn-gamma, tnf-alpha, il17a*), astrocyte reactivity (*GFAP, STAT3, vimentin*), and M1/M2 macrophage activation/microgliosis (*ccl2*, *il1β, il4, arg1, iNOS, cd206, il-10,* and *il-12*) were profiled in the colon and hippocampus of 3xTg-AD and B6129SF2/J mice at three timepoints (n=8-10 mice/group at 8, 24, and 52 weeks). Gene expression analysis for the single transgenic strains are ongoing. Both B6129SF2/J and 3xTg-AD mice exhibited age-related increases in inflammatory markers in the hippocampus and colon. 3xTg-AD mice had significantly increased NFK-β in the hippocampus at 52 and 24 weeks compared to 8 weeks (Mann Whitney p=0.031), and elevated NFK-β in the colon of 3xTg-AD mice compared to B6129SF2/J at 8 weeks (Mann

Whitney p=0.024). There were no significant age-associated increases in B6129SF2/J mice at 24 or 52 weeks (Mann Whitney p>0.05). As expected GFAP gene expression, indicating astrocyte activation, was elevated in the hippocampus of 3xTg-AD mice at 24 and 52 weeks compared to B6129SF2/J mice (Mann Whitney p=0.024 at 24 weeks, and 0.007 at 52 weeks). For the remainder of this funded period, we will use colon and hippocampus inflammatory markers, IHC, pathology stage/age, and strain as variables in predictive models using amplicon and shallow shotgun metagenomic strain-level designations to determine which microbial features are important to predict AD pathologies.

3) *Challenges.* Our progress on this proposal is consistent with our timeline. However, we did experience slight delays in our sequencing pipeline due in part to the ongoing COVID-19 pandemic. Sequencing of SARS-CoV-2 genomes necessarily gained priority during a portion of this funding period, slightly delaying non-critical sequencing runs. We anticipate completion of this study within the proposed timeline.
4) *Publications, grants, and collaborations.* We have one publication in preparation that is a culmination of the progress we've made in Years 1 and 2 of support from the AAC, which will be submitted to a top-tier journal. We have submitted an R21 to PAR 19-071, to develop a novel tool to study host-associated microbiomes in AD, which scored in the 11th percentile (payline 28th percentile). The AAC has facilitated collaborations between Dr. Haiwei Gu (ASU, metabolomics) and Dr. Jonathan Lifshitz (UA, neuroinflammation/neuropathologies). These collaborations have helped to train students and young researchers in AD and microbiome ecology, and have expanded our understanding of the role of the gut microbiome in AD. Two undergraduates (George Testo and Kathryn Conn) presented a poster on this study at our institutional undergraduate research symposium (UGRADS) and the ASM regional conference in April 2021.

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Project Progress Reports

Translational Genomics Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Common genetic polymorphisms associated with exceptional verbal memory performance in aging. Matt Huentelman, PhD, Lee Ryan, PhD. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to identify the genetic factors that may be associated with exceptional age-related performance on the MindCrowd paired associates verbal learning (PAL) task. We will draw on our already recruited MindCrowd cohort and analyze the genetic polymorphisms present in the top 2% of individual performers based on their age-related scores on the PAL task. Additionally, we will utilize existing samples from MindCrowd from individuals with self-reported first-degree family history of Alzheimer's disease (FHAD). In this sample set we will attempt to identify genetic factors that may modify the effect of FHAD on PAL.

Background and Significance:

Much of the genetic contributors to learning and memory performance are still left to be elucidated. Our MindCrowd study, which has been recruiting since 2013, has amassed a cohort of ~50,000 individuals who have agreed to be re-contacted for additional scientific research. MindCrowd assesses cognition via two tasks – a simple visual reaction time test and a verbal memory task known as paired associates learning (PAL). PAL is a form of episodic memory, a key memory type that is notably influenced by Alzheimer's disease and is typically one of the first memory forms that are affected by the disease process. We have successfully collected and analyzed DNA from the MindCrowd cohort using self-collected dried blood spots (DBS) and we have already collected DBS from hundreds of the top performers in MindCrowd. In this project we propose to utilized a new technique – termed genotyping-by-sequencing – to rapidly and cost effectively assess the genome-wide polymorphisms that may be linked to exceptional performance on the PAL test by sampling those individuals in the top 2% of performers for their respective age group.

Preliminary Data, Experimental Design and Methods:

We have already collected DBS from over 200 individuals in the top 2% of performance. We have isolated DNA and analyzed it for the APOE allele – a common polymorphism with known association to Alzheimer's disease. The APOE E4 variant is known to be a risk factor while the E2 allele is a known protective factor at this locus. Interestingly, individuals in the top performing category are enriched for the E2 allele suggesting that this allele may also be associated with enhanced cognitive performance in addition to being protective for AD. During this project we will assess the millions of other common genetic changes in this group to examine for other factors that may be associated with exceptional cognitive performance.

We will utilize our already collected, isolated, and purified DNA from the top 2% performers by age. Additionally, we will continue to request and collect samples from the top 2% in MindCrowd during the grant period. Genotyping will be performed by low coverage sequencing and imputation across the human genome by leveraging public data. Association will be performed using a case:control design by comparing allele frequencies in the top 2% cohort with known allele frequencies in the general population. This will result in candidate SNPs associated with PAL performance and to confirm these variants we will assess a random sampling of MindCrowd that will cover the entire PAL scoring spectrum.

Proposed One-Year and Long-Term Outcomes:

By the end of the grant period we expect to have our candidate list in hand based on the top performers. These data will be utilized in a Federal NIH grant to pursue validation genotyping and more extensive genotyping of the MindCrowd cohort. This grant will include additional collaborations within the State of Arizona to investigate the putative biological implications of the associations – including organoid, cell culture, and animal behavior experiments.

Year End Progress Summary:

We were able to genotype by sequencing ~800 participants from MindCrowd – 4X more than originally proposed. The assay was a success with an average of 30 million genotypes determined for each person. We then performed the following comparisons, for the top 2% of performers in MindCrowd we searched for alleles that were enriched in this select cohort by comparing their allele frequencies with a large database of non-selected individuals. This analysis didn't yield statistically compelling results for any of the tested common genetic variants. This finding is still significant as it suggests that a different approach may be necessary in this group and we plan to employ a rare genetic variant search approach that will utilize whole genome sequencing in the future.

The second group we examined were individuals with a first-degree family history of Alzheimer's disease (FHAD). We have shown previously that the presence of FHAD was associated with statistically lower performance on the MindCrowd PAL test and this effect spanned the aging spectrum from 20-65 years of age. Using the genotyping data generated here we searched for genetic alleles that may modify this FHAD effect. We identified two significant loci. At these loci we found common genetic variants that were associated with an increased risk for even lower performance on the PAL task. In short, the combination of FHAD with variants at these loci placed that individual into a higher risk class for an even larger negative effect of FHAD on PAL performance.

The two loci identified encode for the genes KNIP4 and NEDD9. KNIP4 encodes Kv channel interacting protein 4 and belongs to a family of voltage-gated potassium channel-interacting proteins that may regulate neuronal excitability in response to intracellular calcium changes. KNIP4 also interacts with Presenilin, a known familial Alzheimer's disease causal gene. Six SNPs in the KNIP4 gene correlate with decreased PAL scores across all ages. NEDD9 is a neural precursor cell expressed developmentally downregulated protein. The protein is an intermediate in several critical signaling pathways relevant for proliferation, survival, and migration and has been previously linked to Late Onset AD (LOAD). Four SNPs in the NEDD9 gene correlate with increased PAL scores across all ages. These findings are suggestive of biological links between the identified loci and AD-related molecular pathways. Future work will explore these genes and variants in a larger FHAD cohort.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Identification of RNA modifications altered in Alzheimer's disease (AD) and Down's Syndrome (DS). Kendall Van Keuren-Jensen, PhD, Elliott Mufson, PhD. Translational Genomics Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Cellular mechanisms underlying cognitive decline in Down syndrome (DS) remain largely unexplored. DS is a developmental genetic condition caused by trisomy of human chromosome 21 (HSA21) (Hassold and Sherman, 2004). DS is estimated to affect approximately 350,000 people in the USA, with an about 5000 infants per year born with DS (Murthy, et al., 2007) and affects 5-8 million people word-wide (Hanney et al., 2012). Trisomy results in triplication of the amyloid precursor protein gene (*APP*) and an age related deposition of amyloid-beta (Aβ) plaques in DS (Head et al., 2016; Schupf 2002). Although Aβ accumulation in the form of amyloid plaques typically occurs after 30 years of age (Brookmyer et al., 2018), diffuse plaques occur in the teens and 20's in DS brain (Head et al., 2012) and accumulates progressively. In addition, the appearance of intracellular Tau-bearing neurofibrillary tangles (NFTs) begin after age 40 in DS. NFTs strongly correlated with dementia in AD compared to plaques. A crucial, but often overlooked observation is that not all people with DS develop clinical symptoms of dementia (Millis et al., 2013; Garcia et la., 2019) despite exhibiting AD-like lesions. Interestingly, we have shown that amyloid plaque load is similar in DS with (DS+D) and without dementia (DS-D) and that there are significantly greater numbers of NFTs, which exhibit more advanced tau type lesions in the frontal cortex (FC) in DS+D (Perez et al., 2019).

This proposal builds on tool development from previous funded AARC projects. We have been building the expertise to do long read RNASeq to investigate RNA modifications, differential transcript usage, and changes in splicing associated with disease. There are significant genetic similarities between AD, DS with dementia and DS without dementia, but there is a lack of information on the neurobiological mechanism(s) that underlie dementia onset in these groups. Of interest are observations that the stability of the RNA plays a crucial role in gene regulation and converting precursor messenger ribonucleic acid (pre-mRNA) into mature mRNA. We hypothesize that one of the molecular mechanisms underlying the neuropathology associated with dementia, are changes in RNA splicing and transcript usage. Data derived from the proposed studies, headed by Dr. Mufson and Dr. Van Keuren-Jensen, are crucial for the development of therapeutic interventions to slow the onset of cognitive decline in DS and also contribute to knowledge of the cellular neuropathobiology and treatment of DS and AD. We will further investigate the hypothesis that NFT formation is associated with splicing errors that underline dementia associated with AD and DS. These innovative investigations may elicit the discovery of unexpected mechanisms and allow the determination of the widespread influence of RNA and RNA binding proteins on neurofibrillary tangle (NFT) formation.

Aim – Drs. Perez and Mufson (*Perez et al, Acta Neuropathol 2019*) demonstrated a greater number of NFTs compared to amyloid plaques in frontal cortex (FC) layers V and VI of DSD+ compared to non-demented DS (DSD-) individuals. However, the cellular and molecular mechanisms that underlie the increase in tau pathology between these two groups remain unknown. We will correlate NFTs with changes in RNA spicing and differential transcript usage. We will also assess these change in correlation with dementia. We plan to assess 5 HC, 5 AD, 5 DS + dementia and 5 DS (–) dementia.

We have been developing an analysis pipeline to assess the abundance of transcripts in these tissues. We will also use publicly available data for additional mining. These data will provide us with information for a small paper and pilot data for an R21 or R01 grant application.

Year End Progress Summary:

We purchased a higher throughput version of the ONT system. Doing them one flowcell/sample per time was slow and would potentially introduce more noise. The GridION can do 5 samples at one time, allowing us to add samples from each condition and reduce batch effects. Unfortunately, due to COVID, the installation of this piece of equipment was significantly delayed. All parts are currently up and running, however we are behind in collecting and analyzing the sequencing data. While delayed, we hope to have one of the first real examinations of long read data and accurate splicing analysis for AD and DS. We have been moving forward with the bioinformatic pipeline and streamlining the analysis. We look forward to completing these data and writing a small paper and a grant with Dr. Mufson.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Single nuclei RNA sequencing of the posterior cingulate in Alzheimer's disease. Kendall Jensen, PhD, Ben Readhead, PhD, Joel Dudley, PhD, Geidy Serrano, PhD, Thomas Beach, MD, PhD, Diego Mastroeni, PhD, Eric Reiman, MD. Translational Genomics Research Institute Arizona State University; Icahn School of Medicine at Mount Sinai**;** Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Perform single nuclei RNA sequencing (snRNAseq) of the posterior cingulate from Alzheimer's disease (AD) and healthy elderly donors.

Background and Significance:

We have an ongoing study funded by the Nomis Foundation to generate a region- and cell-specific transcriptomic characterization of brain regions differentially impacted by Alzheimer's disease (AD) for the scientific community. These regions include the entorhinal cortex, hippocampus (HIP), posterior cingulate (PC), superior frontal gyrus (SFG), and primary visual cortex. We have completed snRNAseq of the SFG across 46 AD and control subjects and are expanding these analyses to a larger cohort of 100 AD and control subjects across the PC, HIP, and SFG. We propose to complete snRNAseq of the PC for approximately 25 subjects to identify cell populations and novel sub-populations in this metabolically-affected brain region in AD.

Experimental Design and Methods:

1) Perform tissue dissociation of fresh frozen PC specimens collected from neuropathologically-verified AD and control subjects, provided by Dr's Beach and Serrano from the BSHRI Brain and Body Donation Program. Dissociation will yield single nuclei suspensions that will be used to generate libraries.
2) Generate snRNAseq libraries using the 10x Chromium platform and perform paired-end sequencing of libraries on the Illumina NovaSeq 6000.
3) Perform preliminary analyses to transcriptomically characterize nuclei and identify cell populations and sub-populations that may differentiate AD and control subjects.

Proposed One-Year and Long-Term Outcomes:

1) Complete sequencing of PC snRNAseq libraries from approximately 25 AD and control subjects.
2) Identification of cell populations and sub-populations in the PC of AD and control subjects.

Year End Progress Summary:

We have received the tissues and we are in the process of going through these samples. The proposal changed slightly so that we are focusing on 100 samples from the SFG and 50 PC samples. We are approximately halfway through but focusing on completing these samples.

Project Progress Reports

University of Arizona

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Behavioral Biomarkers in Brain Aging and Alzheimer's Disease Risk. Gene Alexander, PhD, David Raichlen, PhD, Thomas Beach, MD, PhD, Richard Caselli, MD, Yi Su, PhD, Matt Huentelman, PhD, Yann Klimentidis, PhD, Steve Rapcsak, MD, Eric Reiman, MD, Lee Ryan, PhD, Ted Trouard, PhD. University of Arizona; University of Southern California; Banner Sun Health Research Institute; Mayo Clinic; Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

We will address the following specific aims: 1) to determine how physical activity (PA) and sleep quality influence cognitive performance in older adults with differential risk for Alzheimer's disease (AD); and 2) to develop, evaluate, and implement novel methods for processing and analysis of PA and sleep quality data to identify new behavioral biomarkers for age-related cognitive decline and AD risk. Additionally, we expect this study will provide important added value with key pilot data to: 1) evaluate wearable technologies as novel biomarkers for the Arizona ADCC Brain Imaging and Fluid Biomarkers (BIFB) Core, 2) create a unique dataset to support cognitive aging and AD research across Arizona, 3) explore how brain imaging and genetics relate to PA and sleep in older adults; 4) evaluate how PA and sleep ultimately relate to post-mortem brain pathology, and 6) support 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 and it will be essential to respond to the associated growth in AD across Arizona and nationally. Whereas genetic (e.g., APOE ε4) and cerebrovascular health factors increase AD risk, exercise can improve cognition in aging and may reduce AD risk, yet the mechanisms underlying these benefits are not well understood. High PA levels are associated with greater brain volume and connectivity. Studies in older adults are critically needed to identify how PA supports healthy brain aging, while reducing AD risk. Sleep quality is another critically important part of our daily activities that may impact brain aging and the risk for AD.

Preliminary Data, Experimental Design and Methods:

We previously found that young adult, endurance athletes had increased functional connectivity compared to non-athletes, suggesting PA can enhance brain function in young adults (Raichlen et al., *Front Hum Neurosci*, 2016). We applied a new analysis method for tracking PA with actigraphy in the CDC NHANES dataset, ages 6 to 85+. We found less consistent PA was associated with increasing age and greater mortality (Raichlen et al., *J Gerontol: Biol Sci Med Sci*, 2019). We have also shown that different PA measures are associated with preferential brain effects, with larger hippocampal volumes related to more moderate to vigorous exercise and greater cardiorespiratory fitness associated with larger total brain volumes (Raichlen et al., *Brain Imaging Behav*, 2019).

This project proposes to leverage a unique cohort of healthy older adults enrolled in the Brain and Body Donation Program (BBDP) led by Dr. Tom Beach, with complementary support at BSHRI and the Arizona Alzheimer's Disease Core Center (ADCC). BBDP participants already receive annual cognitive assessments and have agreed to post-mortem donation of their brain and body to support AD research. Additionally, over one third of the cohort will be recruited to the NIA ADCC BIFB Core to receive structural MRI scans and brain PET measures of amyloid and tau. We will collect PA and sleep quality data on cognitively unimpaired BBDP participants during their annual

cognitive assessment. Participants will be outfitted with an actigraph wrist monitor and self-report measures of PA and sleep quality will be completed. All materials will be sent to Dr. Alexander's Lab by mail. We will continue to develop and test new actigraphy methods as behavioral biomarkers for aging and AD risk. We will also obtain dried blood spots as a novel, low-cost sample for AD blood biomarker assays.

Proposed One-Year and Long-Term Outcomes:
This work will be leveraged to support complementary projects investigating effects of PA and sleep quality on cognition and brain structure and function, as well as in relation to AD genetic risk. These studies reflect collaborations focused on developing externally funded grant proposals, as part of a multi-disciplinary, collaborative research program, to study how differing levels of PA and sleep quality impact brain aging and preclinical AD risk. The proposed research will provide unique and rich data to publish findings to advance our understanding of brain changes associated with health and lifestyle factors that may reduce the risk for dementia and cognitive decline. Importantly, this work will provide critical pilot data to support new proposals for external NIH funding. Specifically, this project will provide key data and methodological developments to support planned grant submissions, including our NIA ADCC renewal application and an NIA proposal to study how exercise/PA and sleep quality influence brain aging and cognitive function, as well as the interactive effects of AD risk on brain aging.

Year End Progress Summary:
We have made significant progress, with numerous publications and new grant funding in the past year, with our studies on health factors and lifestyle characteristics for brain aging and the risk for AD. Data collection for PA and self-report measures in the unique Arizona cohort of the BBDP in collaboration between the UA, BSHRI, TGen, and the Banner Alzheimer's Institute is well established, providing a valuable resource for AD and aging research. In this project, we have demonstrated the feasibility of acquiring high quality actigraphy and self-report data on PA, as well as collection of blood spot samples from healthy community dwelling older adults in Arizona. Additionally, we have now collected these samples on over 200 cognitively unimpaired BBDP participants. It is expected that continuing our efforts to build this dataset will provide a key cohort to support the submission of future collaborative grant proposals by Arizona investigators, and we have already begun to leverage this collaborative work to support new grant submissions, including our pending NIA Alzheimer's Disease Research Center grant renewal.
In support of this project, we have published articles this year showing how PA is related to brain structure (Raichlen et al., *Brain Imaging and Behavior*, 2020), showing how PA can enhance cognitive function during dual-task walking (Raichlen et al., *BMC Geriatrics*, 2020), and showing the effects of aging and physical frailty in a novel cross-cultural cohort of East African foragers and pastoralists (Sayre et al., *Phil Trans Royal Soc B*, 2020). We also showed how age and self-reported PA influence white matter lesion load in brain aging (Franchetti et al., *Front Aging Neursci*, 2020), how differences in hypertension status influence the mediation of subjective memory complaints by hippocampal atrophy in healthy aging (Van Etten et al., *Neurobiol Aging*, 2020), and how white matter lesion load interact with genetic risk for AD to influence hippocampal volume in healthy aging (Van Etten et al., *Hippocampus*, 2021). We published articles demonstrating the effects of brain aging in a translational rodent model (Alexander et al., *Front Aging Neurosci*, 2020), investigating frontal brain structure and working memory in aging (Evangelista et al., *Cerebral Cortex*, 2021), evaluating differences in executive cognitive functions in healthy aging (Glisky et al., *Aging, Neuropsychology, & Cognition*, 2020), identifying how differences in hippocampal volume relate to cognitive aging (Hardcastle et al., *Front Aging Neurosci*, 2020), investigating the effects of cognitive aging on resting state functional connectivity (Hausman et al., *Front Aging Neurosci*, 2020), and identifying the neural correlates of decision making performance in older adults (Kraft et al., *Front Aging Neurosci*, 2020). In addition, we were

invited to publish an article highlighting our evolutionary-neuroscience model of PA and brain aging (Raichlen and Alexander, *Scientific American*, 2020), which was featured on the cover of the January 2020 issue of Scientific American. We have also submitted articles for publication investigating the potential impact of pollution on brain structure in an aging cohort (Furlong et al., submitted) and evaluating the effects of white matter lesions on frontal cortex and executive functions in healthy older adults (Boutzoukas et al., submitted).

This AAC project has also directly supported methodological developments and data collection to advance our wearable/digital biomarker efforts for our ongoing $3.8M NIA grant to supplement our NIA Arizona Alzheimer's Disease Center (ADC), which established a collaborative Brain Imaging and Fluid Biomarkers Core (Core Leader: Alexander; Co-Investigators: Reiman (ADC PI), Atri, Beach, Chen, Kuo, Trouard, Ryan, Su, Stokes) to provide enhanced access and expertise for the use of MRI, PET, CSF, and blood biomarkers in combination with measures of PA to foster collaborative AD and aging research across Arizona. Furthermore, we incorporated these state-of-the-art PA lifestyle measures as additional cutting-edge technology-based biomarkers into our newly submitted $5M Biomarker Core (Core-Leader: Alexander; Co-Core Leaders: Atri, Su), as part of our overall $15.7M NIA Alzheimer's Disease Research Center renewal grant application (ADRC PI: Reiman), to provide expanded biomarkers for preclinical AD risk.

In the past year, a new $3.6M NIA R01 grant was awarded to University of Arizona investigators to study enhancement of hippocampal plasticity using transcranial magnetic stimulation in those at risk for AD dementia (PI: Chou; Co-Investigators: Alexander, Barnes, Bedrick, Chen, Fisher, Mohler, Rapcsak, Ryan) and a new $300K NIA supplement grant was awarded to develop methods for measuring cognition and PA in a novel animal model of age-related cognitive decline and dementia (PI: MacLean; Co-Investigators: Alexander, Raichlen). In addition, a new $760K NIA R56 grant was awarded to evaluate markers of physical activity in relation to cognition and brain health in those at risk for Alzheimer's disease (MPIs: Alexander, Raichlen). We also received new Covid supplement grant funding of $150K to the University of Arizona to evaluate how the Covid19 pandemic has affected participants in our ongoing multi-site transcranial direct current stimulation intervention study with the University of Florida, Gainesville (MPIs: Woods, Cohen, Marsiske; UA Sub PI: Alexander). Additionally, a new $3.07M NIA R01 grant was submitted (MPIs: Alexander, Raichlen, Klimentidis) to evaluate the effects of low levels of PA on cognition, brain aging, and the risk for AD; and a new $4.9M NIA R01 was submitted to evaluate the effects of cerebrovascular disease and extracranial carotid atherosclerosis on the risk for AD (PI: Weinkauf; Co-Investigators: Alexander, Altbach, Nikolich-Zugich, Stokes).

Work from this AAC project also continues to support the development of new methods and complements ongoing studies of PA and sleep quality assessment of healthy oldest old adults funded by the McKnight Brain Research Foundation (MPIs: Alexander, Cohen, Visscher, Rundek) to evaluate how lifestyle factors influence cognition and brain aging in older adults, ages 85 to 100+. This complementary effort continues to be underway and reflects ongoing collaborations between the University of Arizona, University of Florida, University of Alabama, and the University of Miami. Initial findings from this work have shown that, among oldest old adults, engaging in more moderate activity is associated with greater brain volume in regions of frontal and other cortical regions. Dr. Alexander will present these findings at the McKnight Brain Institute's Inter-institutional meeting, Miami, FL, April, 2021. In addition, Dr. Alexander was invited to present findings from his work on PA, brain aging, and the risk for AD at the Fellows meeting of Adult Development and Aging, Division 20 of the American Psychological Association, Washington, DC, 2020 and at Loma Linda University Medical Center, Loma Linda, CA, April, 2021.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Why is the glass half-full? Sources of the positivity effect in healthy aging and AD risk.
Jessica R. Andrews-Hanna, PhD, Matthew D. Grilli, PhD, Matthew Huentelman, PhD, Matthias Mehl, PhD, Lee Ryan, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) To test the hypothesis that older adults who show better memory for positive compared to negative stimuli (known as the "positivity effect") are happier and less lonely, and exhibit more present-focused, positive, and socially-oriented everyday autobiographical thoughts.
2) To test the hypothesis that older adults who display a stronger positivity effect are more likely to employ successful emotion regulation strategies, especially involving emotional reappraisal.
3) To test the hypothesis that higher depressive symptoms and presence of the APOE4 allele are associated with reduced positivity effects, and that these relationships are mediated by increases in everyday repetitive negative thought and poor emotion regulation.

Background and Significance:

This project seeks to examine mechanisms underlying the well-known "positivity effect" in aging, and its alteration by two important AD risk factors: depression and the APOE4 allele. The pilot data we propose to collect will quantify the positivity effect in memory, validate a novel mood induction task, and use two mobile apps developed by our *Naturalistic Assessment Core* (NAC) to explore everyday manifestations of the positivity effect in healthy aging and AD risk. This pilot data will best position our team to apply for federal funding to measure, monitor, and thwart processes associated with AD risk to help ensure that one's later years of life remain as healthy and as productive as possible.

Preliminary Data, Experimental Design and Methods:

Preliminary data from a pilot study with Dr. Andrews-Hanna's *Mind Window* app reveals that older adults' everyday thoughts are consistent with age-related positivity biases and a prominent theory of emotional and social wellbeing in aging – the socioemotional selectivity theory. Older adults report more positive, "on-task" everyday thoughts, and greater perceived control over their thoughts. Preliminary data from a novel 'think aloud' task developed in a prior pilot grant provides supporting evidence for more positive and less negative spontaneous thought content in the absence of task demand. Here we seek to link these findings in the same group of people and relate such findings to positive biases in memory and emotion regulation following a mood induction. As has proven useful in prior years, we will leverage our existing collaboration in the context of the "ACHIEVE Study" (Aging, Cognition, and Health: Interdisciplinary, Ecologically-Valid Experiments). Forty cognitively normal older adults with variation in depressive symptoms and 20 gender, education, and clinically-matched younger adults will be recruited. As part of the ACHIEVE team, this project includes a Neuropsychology Core (PI Grilli), Naturalistic Assessment Core (PI Andrews-Hanna), and Neuroimaging Core (PI Ryan).

Proposed One-Year and Long-Term Outcomes:

1 year: This pilot project will yield critical behavioral, clinical and neuroimaging data which will significantly strengthen PI Andrews-Hanna's likelihood for success in collaborative grant resubmissions this year. *Long-term:* The project will yield multiple collaborative publications and generate valuable pilot data for the submission of new grant proposals, including a randomized clinical trial implementing an established web-based mindfulness-based cognitive therapy

treatment (for which PI Andrews-Hanna has implemented with success) to individuals with heightened risk for AD.

Year End Progress Summary:

Despite COVID-related setbacks, we have made considerable progress towards the completion of our pilot project. Although COVID-19 challenges have thwarted our ability to collect as many participants by this time as we had planned, we are still on track to complete our study by June 30, 2021. AAC pilot funding has also been critical for the success of two large federal grants and one planned submission this year, described below along with other progress.

We have spent considerable time adapting our study materials to an entirely remote data collection platform. This involves the use of "Zoom for Health" to administer the study and simultaneously video and audio-record participants' verbal responses on our tasks. We are also employing RedCap to collect trait-level and other behavioral data. We developed a novel remote emotional memory task for this study and have integrated the use of two smartphone apps into our study, including our lab's AAC pilot-funded *Mind Window* app, which was developed by a graduate student in Dr. Andrews-Hanna's lab. New dynamic scoring and analysis protocols have recently been developed and adopted for this study as well.

Since 07/01/20, our ACHIEVE team has screened 143 individuals, 82 of whom have met eligibility criteria for Neuropsych assessments. Of these, 19 individuals have enrolled in this particular pilot study (4 completed).

AAC pilot funds for the ACHIEVE project have been critical for the success of a collaborative R56 from NIH/NIA, titled "Tracking autobiographical thoughts: a smartphone-based approach to the detection of cognitive and neural markers of Alzheimer's disease risk." This is a collaborative, inter-disciplinary study involving Dr. Jessica Andrews-Hanna and Dr. Matt Grilli as Multiple PIs, Dr. Matt Huentelman as Co-I, Dr. Matthias Mehl as Co-I, and Dr. Eric Reiman as a Consultant. Award Date: 9/15/20–8/31/21, Total award = $642,211.

Pilot data from the current AAC project will be directly relevant for a planned R01 submission to NIA in November 2021 by Dr. Andrews-Hanna (MPI) and Dr. Grilli (MPI), which is a related collaborative study involving a collaboration with the ADCC Clinical and Biomarker cores.

AAC pilot funds for the ACHIEVE project have also been critical for the success of a collaborative R01 from NIMH in middle age adults, titled "*Connected Lives - Overcoming the Self through Empathy (CLOSE): A dyadic, multi-method study."* This study involves using the AAC-funded Mind Window app to measure ruminative thought – a risk factor for Alzheimer's disease – in real-world contexts. Dr. Jessica Andrews-Hanna and Dr. David Sbarra are Multiple PIs on the study. Award Dates: 04/01/21-01/31/26. Total Award = $2,925,543.

AAC pilot funds also supported the publication of recent collaborative manuscripts with Dr. Grilli in *Current Directions in Psychological Science, Frontiers in Human Neuroscience, Consciousness & Cognition, Memory & Cognition*, as well as additional manuscripts in preparation.

In the laboratory of Dr. Andrews-Hanna, data from the ACHIEVE studies have supported 1 graduate student (Eric Andrews), one post-baccalaureate study coordinator (Chris Griffiths), and numerous undergraduate Directed Research and Honors research projects. Many of these students are under-represented minorities in STEM fields.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Combining high resolution *ex vivo* magnetic resonance imaging with immunohistochemical labelling of neurovascular function in aged macaque monkey brains. Carol A. Barnes, PhD, Daniel T. Gray, PhD, Beth Hutchinson, PhD, Ted Trouard, PhD.
University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. To develop and optimize a quantitative MRI microscopy acquisition battery and analysis pipeline that uses diffusion MRI and relaxometry techniques to quantify brain microstructure in fixed brains from a colony of behaviorally-characterized aged macaque monkeys.
2. Perform regional assessments of brain microstructure to characterize each individual animal's unique anatomical pattern of age-associated microstructural change. These analyses will localize areas of age-associated microstructural change in each monkey in order to immunohistochemically study the neurovascular response to such structural alterations.
3. Immunohistochemically label and image myelin, vasculature, microglia, and reactive astrocytes in brain tissue immediately surrounding sites where age-associated microstructural changes emerge within a brain. This aim will determine the radiologic-pathologic correspondence between the local neural, vascular and glial responses and quantitative microstructural changes detected by MRI in aged brains.

Background and Significance:

A fundamental goal of neuroscience is to translate findings acquired in animal models using precise molecular and electrophysiological technologies into a more thorough understanding of the human brain. *Ex vivo* imaging, or MRI 'microscopy', is a relatively novel brain imaging approach that enables high-resolution quantitative measurements of microstructural tissue environments from fixed brain tissue post-mortem. The superior resolution (for T1 200 microns) of this imaging technique relative to what is obtainable *in vivo* provides the opportunity to study the radiologic-pathologic correspondence between microstructural changes observable with MRI and brain pathologies observable at cellular and molecular levels of analysis. This novel approach requires MRI and histochemical data to be performed within the same brains so that the data from both can be registered to the same space for analysis. The primary goals of this project are to first identify, using *ex vivo* MRI of aged monkey brains, sites of observable microstructural change. After these brains are serial sectioned and immunohistochemically stained, the MRI images and the images of the tissue sections will be registered into the same volume for analysis. This will enable us to identify what brain tissue changes are responsible for the microstructural changes observable in the MRI.

Preliminary Data, Experimental Design and Methods:

At the time this proposal was submitted (Spring 2020), we had obtained preliminary data demonstrating our ability to perform quantitative *ex vivo* MRI in fixed macaque brain tissue in one monkey. In a different population of monkeys (rhesus macaques), we have also recently demonstrated that we can immunohistochemically label brain vasculature, glia, and neurons in nonhuman primates. Finally, in another study, our laboratory has demonstrated the ability to align MRI images with digitized immunohistochemical images using diffeomorphic registration processes. Our progress over the past year has brought us significantly closer to the goal of applying all three of these methods to the same set of brains (see Year End Progress Summary section for details).

Proposed One-Year and Long-Term Outcomes:

1. To finalize the parameters of the quantitative MRI microscopy battery and optimize image registration for cross-modal registration of the quantitative maps collected in this study.

2. Create monkey-specific anatomical maps (in MRI space) of age-associated changes in white matter anisotropy (DTI maps), macromolecular content (BPF maps), and myelin water fraction (MWF maps).

3. Histologically prepare macaque tissue with markers of neurovascular function in brain sections adjacent to the sites of white matter structural change, then align MRI and histology data to create a cytoarchitechtonically-driven atlas of the neurovascular response associated with each change noted in MRI images.

4. Use these preliminary data to prepare an RO1. The first aim of the RO1 will consist of a thorough analysis of every quantitative map acquired in this imaging battery to isolate the areas in each monkey's brain expressing microstructural change. The second component of the grant will be to section and stain the remaining macaque brains, and further develop methods to align the histological sections and high-resolution MRI images.

Year End Progress Summary:

We have made substantial progress towards the proposed one-year outcomes since funding for this project began on 07/01/20.

Outcome 1: The first area of progress is in the optimization of parameters for 4 distinct imaging methods including high resolution anatomical (HRA) imaging, diffusion tensor imaging (DTI), multi-spin echo (MSE), and selective inversion recovery (SIR) imaging. From these methods we can create T1 and T2 images as well as bound pool fraction (BPF) and myelin water fraction (MWF) quantitative maps. Note that BPF and MWF maps provide more direct measures of myelin content than does DTI. After trying a number of different parameter approaches, we have settled on 600-micron resolution for BPF and MWF mapping since, particularly with these images, the signal-to-noise ratio is inversely related to the resolution. Using these parameters, we have successfully acquired all the quantitative maps that these 4 imaging methods provide in all 12 of the fixed macaque brains that are being used for this study. The age range of these animals at the time of perfusion was between 15 to 32 years. This optimally positions us to begin understanding what radiologic changes are associated with the transition from middle age to aged, and the histopathological correlates of these differences.

Outcome 2: With the DTI images acquired we have begun investigating the reliability with which we can detect white matter tracts that originate in the midbrain and brainstem and innervate cognitive regions in the neocortex and hippocampal formation using probabilistic tractography analyses. In particular, our preliminary investigations have utilized seed regions in subcortical neuromodulatory regions such as the dopaminergic ventral tegmental area and the noradrenergic locus coeruleus and target regions in the forebrain such as the hippocampus and dorsolateral prefrontal cortex. We have demonstrated the ability to detect and isolate these fiber pathways in one macaque brain using these high-resolution scans, which had not been demonstrated in monkeys previously. These sorts of analyses will allow us to quantify the myelin content (using BPF and MWF maps) of specific subcortical pathways important to cognition before aligning the MRI images to the histological sections (see outcome 3 below).

Outcome 3: Having completed the battery of MRI scans on all 12 macaque brains, we have begun the process of preparing these brains for histological analysis. Jeff Bennet, our longtime collaborator with ample experience in macaque neuroanatomy has begun the process, in 2 monkeys, of serial sectioning the brains into 30 micron thick coronal sections and preparing individual-animal brain atlases by Nissl staining every 4th section cut. These individualized

atlases will allow us to 1) precisely find brain regions of interest for immunohistochemical analysis, and 2) align the MRI images and the histology images to allow observations acquired from both techniques to be analyzed within the same space.

Our laboratory recently purchased a 3D image visualization and analysis software package named AMIRA from ThermoFisher Scientific (Waltham, MA). AMIRA is a sophisticated software package that uses artificial intelligence and diffeomorphic registration algorithms to quantify complex cellular structures and map these data into common template spaces derived from multiple imaging modalities. In the present study, AMIRA will provide us the ability to systematically quantify markers of neurovascular/glial cell function from the immunohistochemical analyses and align these data with the *ex vivo* MRI images acquired for each animal.

Outcome 4: We have obtained a sizable amount of preliminary data that will aid us in applying for funding through other sources. Critically, once the first macaque brain is cut and serial sectioned we will immunohistochemically prepare sections from this brain and write the necessary AMIRA macros to quantify this data and align it with the MRI images. We anticipate that we will obtain these data from the first monkey, and be partway through the second, by the end of summer 2021.

Transcranial Magnetic Stimulation for Mild Cognitive Impairment (Year 2). Ying-hui Chou, ScD, Lee Ryan, PhD, Nan-kuei Chen, PhD, and Steven Rapcsak, MD. University of Arizona; Banner University Medical Center; Arizona Alzheimer's Consortium.

Specific Aims:

4) To determine the behavioral effects of hippocampal rTMS on memory function
5) To verify hippocampal rTMS effects on brain functional connectivity

Background and Significance:

Current treatment options for mild cognitive impairment (MCI) are limited and there is an urgent need to develop more effective therapies that can either prevent or attenuate the ongoing neurodegenerative processes. Recent evidence from numerous Alzheimer's disease (AD) models suggest that dysfunction of hippocampal synaptic plasticity and network disorganization underlie progression of cognitive impairment during prodromal stages of AD[6,7]. Therefore, it is crucial to provide an early intervention in individuals at high risk of developing AD (e.g., MCI) to attenuate neurodegeneration before it becomes medically refractory.

In this project, we aim to enhance hippocampal plasticity and reorganize hippocampus-related networks in individuals with MCI through the application of theta burst stimulation (TBS). Previous human studies using intra-cranial recordings have shown that regions within the hippocampus exhibit neuronal synchrony and phase locking at theta frequencies during rest and during performing memory tasks[8-12]. The non-invasive human TBS paradigm is a highly efficient rTMS variant[13]. Conventional rTMS procedures typically last for 40 minutes per session whereas TBS can be completed in as little as 40 seconds with similar effects on brain activity. In addition to its improved efficiency, the TBS paradigm that resembles the endogenous activity of the hippocampus is expected to be more effective in modulating hippocampal activity[14].

Preliminary Data, Experimental Design and Methods:

Participants with MCI will be enrolled in this double-blind, randomized, sham-controlled, crossover study with three protocols: excitatory TBS, inhibitory TBS, and sham TBS. The MCI diagnosis will be supported by the measures of general cognitive function using (1) MMSE 24-27; (2) MoCA 18-26; and (3) CDRS of 0.5. The inhibitory TBS paradigm consists of 3 pulses of 50 Hz stimulation repeated at 200-ms interval for 40 seconds. The excitatory TBS paradigm is also involved the appliction of 3 pulses of 50 Hz applied at 5 Hz. However, instead of applying these bursts continuously, a 2-second train of stimulation repeats every 10 seconds for 190 seconds[13]. A MagVenture sham TBS coil that is designed for use in blinded clinical trials will be used. All TBS sessions will be administered by the same research specialist who will be blinded to the condition of intervention. Individuals with MCI and investigators who perform the assessments will be blinded to the testing sequence. Each participant will complete 2 sessions of each protocol (yielding a total of 6 sessions for each participant), which will be separated by at least 1 week to avoid carry-over effects. Primary outcome measures consisting of memory and hippocampal functional connectivity will be acquired immediately before and after each TBS session.

Proposed One-Year and Long-Term Outcomes:

This project is approved by the IRB and we had recruited 9 individuals with MCI in Year 1 (i.e., 9x6 = 54 rTMS sessions in Year 1). We plan to enroll 9 individuals with MCI every year. This proposal is developed to collect data for the submission of an NIH R01 proposal in responding to the funding opportunity: *Non-Invasive Neurostimulation in AD* (PAR-19-298). The NIH proposal

we are planning to submit will involve implementing a double-blind, randomized, sham-controlled trial to 1) elucidate mechanisms of the rTMS effects, and 2) address heterogeneity of response to optimize the rTMS intervention.

Year End Progress Summary:

Based on the findings of pilot research projects supported by the Arizona Alzheimer's Consortium (AAC), we are awarded $3.4M from the NIH/NIA to develop personalized TMS treatment for individuals with MCI (R01 AG062543)! We are very grateful for the support for the AAC!

For this pilot project, 9 right-handed older adults with MCI aged between 65 and 74 years old (70 ± 3 years old, 5 females) participated in our study. All participants improved memory performance from single session of excitatory TBS, inhibitory TBS, or both. Specifically, 6 participants responded positively only to the excitatory TBS, 1 participant responded positively only to the inhibitory TBS, and 2 participants benefited from both TBS protocols. The average changes in memory score were 8.6 in excitatory TBS, -3.1 in inhibitory TBS, and -0.3 in sham TBS. The TBS effect on memory function was significant, $F = 4.47$, $p = 0.03$.

The effect of TBS was also significant on resting-state functional connectivity measures along the hippocampal white matter pathway. We found that functional connectivity along the left inferior longitudinal fasciculus was significantly increased due to single session of TBS ($p < 0.05$). The brain regions that exhibited increased functional connectivity include the frontal orbital cortex, posterior parahippocampal gyrus (PHG), putamen, occipital fusiform, and temporal pole (TP). Furthermore, individuals with a greater increase in functional connectivity between TMS stimulation site and subfields of the hippocampus (left CA1 and left left hippocampal fissure) showed a larger improvement of memory function ($r = 0.51$ - 0.68, $p < 0.05$).

Our novel image guided TMS approach significantly enhanced memory performance in individuals with MCI. According to previous studies (Maller et al., 2019), the temporal structures (e.g., PHG and TP) and the putamen were all structurally connected to the hippocampus via the inferior longitudinal fasciculus. Specifically, 40% of the hippocampal connections to other brain regions were through the inferior longitudinal fasciculus. The inferior longitudinal fasciculus is located inside the temporal and occipital lobes and includes the fusiform gyrus, which is an important brain region for face processing, face recognition and visual memory (Herbet, Zemmoura, & Duffau, 2018; Rossion, Schiltz, & Crommelinck, 2003; Uono et al., 2017). Findings from our study suggest that the image guided TMS approach might have an effect on the hippocampal subfields, the left CA1 and the left hippocampal fissure, and that the improvement of memory function might be due to the increased functional connectivity along the hippocampal pathway.

We are finalizing this manuscript and will submit it to *Functional Connectivity* for publication.

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Autobiographical memory, future thinking, and neuropsychology in Hispanics. Matthew D. Grilli, PhD, Jessica R. Andrews-Hanna, PhD, Matthias Mehl, PhD, Lee Ryan, PhD, Matthew Huentelman, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1. To reveal the type of memories and themes retrieved by Hispanics while creating autobiographical past narratives. H_1. Similar to White Non-Hispanics, we predict that young and older Hispanics will recall a mix of episodic and semantic autobiographical narratives, with episodic memories populated with both episodic and semantic details. **H_2** It is an empirical question whether Hispanics and White Non-Hispanics sample similar content and emotional/social themes, and if this differs as a function of age.

Aim 2. To determine whether older Hispanics, similar to White Non-Hispanics, show commonalities between past and future autobiographical narration.
H_1. We predict that young and older Hispanics will show similar episodic and semantic profiles for past and future narration. **H_2.** It is an empirical question whether Hispanics will tend to retrieve distinct types of themes relative to White Non-Hispanics while describing the future.

Background and Significance:

Between 2014 and 2060, the share of older adults in the U.S. with Alzheimer's disease (AD) and related dementias who are Hispanic is expected to rise from 8% to 21% (Matthews et al., 2019). While cognitive assessment remains an important tool in the diagnosis of AD symptoms and for pharmacological clinical trials, existing neuropsychological assessment approaches may be less precise at measuring AD-related cognitive decline in Hispanics (Weissberger et al., 2018). Therefore, there is a need for better cognitive markers of AD risk in Hispanics, taking into account factors relevant to this group, such as bilingualism.

Recent research suggests that episodic autobiographical memory (EAM), meaning memories for unique, personal life events, is one cognitive function that may be particularly sensitive to age-related cognitive decline and risk for AD. For instance, considerable research has revealed that relative to young adults, cognitively normal older adults' EAMs are more overgeneral, with older adults generating less episodic (e.g. specific) details when describing memories (Levine et al., 2002). Reduced EAM specificity is also a characteristic of genetic risk for AD, and prodromal and clinical AD (Addis et al., 2008; Grilli et al., 2018; Murphy et al., 2008). Additional age-related changes in EAM have also been described, including a positivity shift in emotion (Bernsten & Rubin, 2002). This suggests that EAM has the potential to be a sensitive measure of cognitive changes in normal and abnormal aging, and could help separate these two trajectories. Nevertheless, most EAM research comes from studies with samples that are predominately White Non-Hispanics. Thus, we know very little about EAM retrieval in Hispanic individuals. To address this gap in knowledge, the proposed study will examine EAM in Hispanics, hopefully moving closer to culturally appropriate tests that improve early detection of memory decline. We also will explore episodic future thinking, given the established commonalities between remembering and imagining, and the sensitivity of the latter to age.

Preliminary Data, Experimental Design and Methods:

In the proposed study, our goal is to examine autobiographical memory and future thinking in young and older Hispanics. We are asking participants, through remote video conferencing, to

complete an Autobiographical Interview (Levine et al., 2002) and a Future Thinking Task, which involves generating and narrating a series of memories and future thoughts. These autobiographical memories and future thoughts are scored using protocols for content/details and emotions. We are recruiting both Hispanics and White Non-Hispanics, although existing data in the lab on Non-Hispanics is available as well. The newly recruited sample includes adults across the adult age spectrum (18 to 85+). We screen for bilingualism. Participants must have minimal self-reported cognitive concerns or difficulty independently managing activities of daily living. Participants are screened objectively for abnormal signs of cognition using established telephone screens. With the autobiographical narratives, we will analyze the types of themes and details generated by Hispanics, and whether these differ by past or future, or by age. We also will investigate Hispanics vs. White Non-Hispanic differences in narratives. Finally, we will assess the relationship between autobiographical memory, future thinking, and our standard neuropsychological scores (i.e., telephone screening data).

ACHIEVE. This project builds on "Aging, Cognition, and Health: An Interdisciplinary, Ecologically-Valid Experiment" or ACHIEVE, which is a collaborative project on cognitive aging that brings together multiple labs in the Psychology Department at UA. This project includes a Neuropsychology Core (PI Grilli), Naturalistic Assessment Core (PI Andrews-Hanna), and Neuroimaging Core (PI Ryan). The Neuropsychology Core is responsible for screening and and cognitive testing for all AAC Projects in ACHIEVE.

Proposed One-Year and Long-Term Outcomes:

Our short-term goals include the following: 1) Improve our recruitment and enrollment of young and older Hispanics in the greater Tucson area and 2) Enroll at least 30 Hispanics (from across the adult age spectrum). Our long-term goals include the following: 1) Incorporate data from this project into an R01 application or supplement within two years. 2) Compare these in-lab autobiographical memory results with naturalistic assessment in a future project.

Year End Progress Summary:

1) We adapted to the COVID-19 pandemic and moved much of our research to online/remote testing (e.g., with virtual meetings using a HIPAA-compliant platform). Once these procedures were established, we resumed data collection and are on track to meet our goals.

2) We remain highly active in recruitment and enrollment in ACHIEVE. In the past year, the Neuropsychology Core has screened 149 individuals. We have completed neuropsychological testing for 86 of these individuals. These individuals have been directed to ACHIEVE projects based on study eligibility, with ongoing enrollment.

3) Consistent with our short-term goals, we are actively recruiting young and older Hispanics. From 7/1/2020 to 4/1/2021, we have enrolled 22 Hispanic individuals.

4) As MPIs, Dr. Grilli and Dr. Andrews-Hanna, along with Co-I's Dr. Mehl and Dr. Huentelman, were awarded an R56 from NIH/NIA that builds on ACHIEVE and will investigate the utility of naturalistic assessment of cognition and Alzheimer's disease risk in older adults.

5) With the help of 2019-2020 ACHIEVE data as key preliminary findings, Graduate Student Mónica Acevedo-Molina was awarded a Ruth L. Kirschstein National Research Service Award from the National Institutes of Health/National Institute on Aging.

6) In accordance with the overarching goal of this project, Dr. Grilli contributed to ACHIEVE-related projects published in *Frontiers in Human Neuroscience, the Journal of the International*

Neuropsychological Society, Current Directions in Psychological Science, Memory & Cognition, Frontiers in Human Neuroscience, Journal of Gerontology: Psychological Sciences, Cortex, and *Memory*.

7) Participants screened and tested through the Neuropsychology Core supported two dissertation projects in Dr. Grilli's lab, and one poster and one paper presentation at the International Neuropsychological Society Annual Meeting (February 2021). One poster presentation was awarded the Memory and Memory Disorders Research Award at the International Neuropsychological Society Annual Meeting (Acevedo-Molina et al., 2021).

8) Data collected through this year's project will support at least one R01 resubmission in Fall 2021 (MPIs: Andrews-Hanna and Grilli).

ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Developing an Alzheimer Drosophila model co-expressing TDP-43 and Tau. May Khanna, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

The goal of the project is to develop a Drosophila model co expressing two AD relevant proteins: TDP-43 and Tau.

Background and Significance:

Amyloid plaque and neurofibrillary tangles (NFTs) are two hallmarks of AD, and NFTs correlate with clinical symptoms. NFTs may include Aβ, Tau, and TDP-43. Cytoplasmic TDP-43 inclusions are associated with AD-type dementia and patients with mixed TDP-43, Aβ and Tau proteinopathies exhibit more severe AD-type dementia than patients with Aβ and Tau proteinopathies alone. TDP-43 has also been linked to Tau splicing and mRNA stability[3,4], suggesting that TDP-43 is involved in modulating Tau function. There is also evidence of cellular co-localization between Tau and TD-43 misfolded proteins, and it was suggested that common pathways or protein interactions facilitating misfolding of protein[5]. There has even been evidence of co-localization of Tau and TDP-43 in the same cells in the amygdala[6]. Thus, our overarching hypothesis is that TDP-43 and Tau directly interacts to promote AD pathology.

Preliminary Data, Experimental Design and Methods:

We validated the interaction between TDP-43 and tau, using Microscale Thermophoresis (MST), we tested the ability of TDP-43 to bind directly the 2N4R isoform of Tau, the largest size human brain Tau (purchased from R&D; 2N4R which includes all four R1-R4 tubulin binding domains) and able to assume pathological conformation and form aggregates. Excitingly, *we found a robust interaction between TDP-43 and Tau with a Kd of 435 nM*. A stable complex is also formed based on data obtained by Surface Plasmon Resonance (SPR).

Proposed One-Year and Long-Term Outcomes:

The one-year outcome will be to define if a genetic interaction occurs. If TDP-43 and Tau display a genetic interaction, we will observe a different phenotype when comparing double mutant animal to single TDP-43 mutant or single Tau mutant. TDP-43/Tau double genetic mutant could result in either a phenotype enhanced to a severity beyond expected (enhancement interaction) or a phenotype not observed in either single mutant (synthetic interaction). Should TDP-43 and Tau display any genetic interaction, our long-term outcome will be to target the Tau/TDP-43 interface using peptides and small molecules to modulate AD phenotypes for therapeutic development.

We proposed a scheme for genetic crosses between TDP-43 and tau. TDP-43 and tau were engineered to be selectively expressed in CNS and motor neurons.

Year End Progress Summary:

All the crosses were completed except for the last step. There seems to be an issue as it is not possible to obtain the cross between TDP-43 and tau when they are expressed in CNS and motor neurons. We have now adapted the genetics and are crossing just in CNS to define if the issue is with motor neurons defect that does not allow for the growth of normal TDP-43xTau interactions. We have also purchased an incubator from grant funds and are developing screens using machine learning to measure multiple parameters at once to screen for defects in behavior.

Assessing medial temporal lobe network integrity using high resolution fMRI. Lee Ryan, PhD, Arne Ekstrom, PhD, Matthew D. Grilli, PhD, Jessica Andrews-Hanna, PhD, Matthew Huentelman, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To determine whether selective decreases in the fidelity of PRC-hippocampal connectivity and increases in PHC-hippocampal connectivity underlie age-related impairments in object and scene processing using high-resolution hippocampal imaging.
Aim 2: To determine whether older e4 carriers show additional degradation in PHC-hippocampal circuitry and a decreased reliance on coarse processing.

Background and Significance:

A recent study by our group[1] demonstrated that cognitively healthy older adults who carry the APOE e4 allele provide fewer perceptual and spatial-temporal details when describing autobiographical events, despite performing similarly to non-carriers on conventional neuropsychological tests of memory. This finding suggests that the quality of memory retrieval may provide a particularly sensitive and specific marker of neural changes associated with preclinical AD. In a recent theoretical paper, we suggested that there are two parallel but relatively independent memory retrieval pathways, both relying upon contributions from PRC and PHC to the hippocampus – a "coarse" pathway that creates a global representation of the environment or context, and a "detail" pathway, providing information on the combinations of specific features of environment. Based on data from animal models and human studies, we hypothesized that the detail pathway is impaired in normal aging due to the deposition of tau pathology, while the coarse pathway remains intact. In contrast, individuals with preclinical Alzheimer's pathology results in increases in both tau and a beta deposition in regions that will damage the coarse pathway. Damage to the coarse pathway will likely result in a loss of easy access to the disparate components of an episode since retrieval of a single component of the memory will no longer lead to relatively automatic reinstatement of the rest of the memory.

A recent study in our laboratory demonstrated that older adults are impaired on visual "pattern separation" tasks (relying on the detail pathway) but utilize context to the same degree as older adults[3], suggesting that the coarse pathway remains relatively intact with age. However, behavioral studies cannot provide a direct assessment of these neural circuits. High-resolution fMRI offers significant advantages over conventional whole brain fMRI, including greater resolution and visualization of hippocampal subfields, and higher signal to noise ratio. One of our investigators (Ekstrom) has developed a whole brain high-resolution sequence that provides higher signal-to-noise across the whole brain, as well as within the hippocampus. We will employ this method to measure connectivity within MTL circuitry as well as prefrontal cortex, in older adults with and without increased risk for AD compared to young controls

Preliminary Data, Experimental Design and Methods:

Design/analysis: 15 young, 15 cognitively healthy older adult non-carriers, and 15 older adult e4 carriers will be included in the study. All participants will be presented with objects (fractals) and scenes (virtual reality backgrounds). While undergoing high resolution fMRI, participants will see two stimuli on the top of the screen and must determine whether a third object is the same or different. Stimuli will include feature and viewpoint differences to created matched levels of

discrimination performance between conditions. 80 object trials and 80 scene trials will be presented along with a visual control condition (squares of varying sizes). Among each trial type, half of the trials will be “easy” and half will be “difficulty”. All analyses will involve multivariate pattern/interaction analyses including searchlight analyses focusing on the following regions: PRC, PHC, CA1, CA3/DG (dentate gyrus), and bilateral PFC.

Proposed One-Year and Long-Term Outcomes:

1. We will collect imaging data for 45 participants – 30 older adults and 15 young adults.
2. An RO1 will be submitted in fall 2021, based on the pilot data obtained from the FY 2020 AAC project described here.
4. Long-term, we expect that the ACHIEVE project will result in a multiple PI longitudinal R01 to study preclinical markers of memory and cognitive changes utilizing naturalistic and laboratory-based cognitive tests.

Year End Progress Summary:

Despite a months-long research shutdown due to the COVID-19 pandemic, progress is being made on this project. The study is on track to complete data collection from 45 participants by June 30, 2021. The behavioral paradigm was developed and tested on young and older adults, half of each group carrying the e4 allele. The recognition results demonstrated that repetition of the scene context – either complex scenes or a white background – significantly increased recognition of objects relative to novel scenes for all groups. On average, younger adults outperformed older adults on correctly identifying similar objects, demonstrating that older adults have more difficulty overall in engaging in pattern separation processes. Older adults produced a specific kind of error, misidentifying similar objects as “old” more often than “new” compared to younger adults. This type of error was most pronounced when the scene was repeated. Together, these findings are consistent with the notion that older adults engage more in pattern completion, rather than focusing on the detailed analysis of the objects that are required for pattern separation. And, repetition of the context leads older adults to engage to an even greater extent in pattern completion. Interestingly, APOE status interacted with scene and age such that when the scene was repeated, younger e4 carriers produced fewer false alarms, while this finding was switched among older adults. Our results support an older age-related shift toward holistic pieces of information and away from subtle details. Additionally, the unique interaction between age, scene and APOE status in false alarms is consistent with Han and Bondi’s hypothesis that regards e4 as an antagonistic pleiotropy allele (Han & Bondi 2009; Tuminello & Han, 2011). Lower pattern separation false alarms among young carriers may reveal a subtle behavioral advantage in our task. This advantage is lost in aging, as older e4 carriers now produce more pattern separation false alarms. A manuscript with the results is in final stages of editing and will be submitted shortly (Palmer, J., Grilli, M., & Ryan, L.).

Due to delays in scanning, imaging results are not yet available for analyses. We expect data collection to be completed in the next two months and analyses will continue through summer, 2021.

Assessing the Impact of COVID-19 on Cognitive Functions. Lee Ryan, PhD, Meredith Hay, PhD, John Altin, PhD, Matthew Huentelman, PhD. University of Arizona; Translational Genomics Research Institute; Translational Genomics Research Institute North; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To identify a large cohort of individuals who have experienced COVID-19, confirmed by seropositivity.

Aim 2: To establish baseline measures of cognitive and immune functioning in the cohort to allow for longitudinal cognitive testing to determine the impact of COVID-19 on trajectories of cognitive aging.

Background and Significance:

SARS-CoV-2 is a highly pathogenic coronavirus that causes the acute, highly lethal pneumonia coronavirus disease COVID-19. The most characteristic symptom of patients with COVID-19 is respiratory distress. Some patients also show neurological signs including headache, nausea, vomiting, and alterations in consciousness. Increasing evidence suggests that coronaviruses are not always confined to the respiratory tract, but also invade the central nervous system. Although the exact route of transmission is unknown, the virus may spread to the brainstem and thalamus via mechanoreceptors and chemoreceptors in the lower respiratory system, or more directly via the olfactory nerve. In 2002 and 2003, autopsy studies of patients infected with SARS showed SARS-CoV particles in the brain, located almost exclusively in neurons. Although COVID-19 survivors may effectively "clear" the SARS-CoV-2 infection – as evidenced by RNA-based viral genome screening – it is currently unknown if the virus may maintain a chronically infectious state in solid tissues or if the acute viral infection altered physiological or cellular functions in a sustained manner. Whether or not SARS-CoV-2 has direct effects on brain function is unknown. However, it is increasingly clear that viral infections exacerbate age-related dysregulation of immune function and lead to increases in inflammation. Both of these conditions have been associated with increased risk for age-related cognitive impairment and for dementias, including Alzheimer's disease. Inflammation and immunity coexist in the same pathological process and they share the same cellular basis where inflammatory cells are also immune cells. We know that aging substantially affects immune system regulation resulting in defects in both rapid responses to infectious agents (the innate immune system) and the slower generation of antibodies to pathogens (the adaptive immune system). The most pronounced changes observed with aging are in the adaptive immune system characterized by a decrease in naive T cells and an increase in memory cells. These changes result in a low-grade chronic proinflammatory environment with increased production of proinflammatory cytokines. Age-related immune system changes are also accelerated by genetic predisposition, hormonal changes with decreased production of estrogens or androgens, mitochondrial function, and exposure to infections. However, relatively little is known about the cellular and molecular mechanisms controlling age-related changes in immune function, or the impact they have on risk for age-related cognitive impairment and neurodegenerative disorders.

Preliminary Data, Experimental Design and Methods:

We have previously shown the feasibility of obtaining dried blood spots through the mail from MindCrowd as well as demonstrated high participation rates (over 35%) for additional surveys and cognitive testing.

Participants and overview. MindCrowd.org is an internet-based study of adults, ages 18 to 90+ across the US. Approximately 50,000 individuals have completed cognitive tests assessing memory and processing speed, provided extensive information on health and lifestyle factors, and have agreed to be contacted for participation in additional studies of cognitive aging. We propose to send all MindCrowd participants a survey asking about COVID-19 symptoms over the past several months and whether or not they have had a COVID-19 diagnosis or negative test. We will then identify the highest likelihood individuals, ages 18 and over and send kits to 2,000 individuals to obtain blood spots. Participants will complete cognitive testing that includes the tests previously administered as well as additional tests that are known to be sensitive to age-related changes including other aspects of memory, executive functions, visual-spatial functions, and processing speed. A subset of participants (n=50) will be asked to wear a Garmin smartwatch for two weeks and keep a sleep diary over that period to measure daily activity and sleep quality.

Blood samples. Seropositivity testing will be performed using the PepSeq assay developed by our collaborator (Altin). This assay currently represents all (>300) viruses known to infect humans (as of early 2019) in the form of 244,000 30mer peptides, and is being supplemented with 100,000 additional peptides focusing exclusively on members of the *Coronaviridae* family, including SARS-CoV-2. The result of this is a personalized historical profile of an individual's exposure to viruses. Inflammatory markers will also be assessed using dried blood spots. Using the SISCAPA (Stable Isotope Standards and Capture by Anti-Peptide Antibodies) approach – which couples antibody-based enrichment of peptides followed by mass spectrometry quantitation – we can measure ten inflammatory markers in a single dried blood specimen.

Proposed One-Year and Long-Term Outcomes:

Given that the study cohort already exists and that we are able to begin sending study surveys immediately, we are confident that data collection can be completed within a year. We will apply for external funding from NINDS to expand the baseline cohort and follow these individuals longitudinally to determine changes in health status or cognitive functioning over time.

Year End Progress Summary:

In the first wave of the study, surveys have been obtained from 7,578 respondents across the U.S., before vaccinations were available. From those, self-report of a COVID diagnosis that was confirmed by a clinical PCR or antigen test in only 143 individuals, reflecting the difficulty of accessing COVID testing in early stages of the pandemic. However, among 2,778 individuals who self-reported three or more flu-like symptoms in 2020 but had no positive COVID test, 16% were positive for COVID antibodies. Even among individuals who self-report zero flu-like symptoms in 2020, 12% were positive for COVID antibodies. Cognitive testing is currently underway with all respondents. A second wave of surveys will be sent out in the coming weeks to larger numbers of individuals and to update information on all respondents.

We have also begun an in-person phase of the study investigating how the severity of respiratory dysfunction in older adults who were hospitalized for COVID-19 relates to cognitive functions and brain health following recovery. A cohort of older adults, ages 55-79, will be recruited. Assessments include cognitive testing, sleep quality, magnetic resonance imaging, genetic profiles, and biomarkers of immune function including a novel potential marker of brain damage, neurofilament light protein (NFL). Our group has already demonstrated that NFL is elevated in COVID-19 hospitalized patients, particularly within individuals with severe respiratory symptoms and neurological complications. These important findings from the study have been submitted for publication. We have begun to enroll participants into the behavioral/MRI study through the Banner Hospital system and from the community with the support of Dr. Parthasarathy. We anticipate that enrollment will continue over the next several months.

In addition to the publication submitted on NFL and its relationship to cognitive functioning in COVID-19 survivors, one NRSA fellowship has been submitted to NIA (Palmer) in April 2021 based on preliminary data from the study. An RO1 is planned for submission in fall, 2022.

ARIZONA ALZHEIMER'S CONSORTIUM
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Determining levels of tau protein in postmortem cerebral spinal fluid and serum samples.
Judith Su, PhD, Gene Alexander, PhD, Thomas Beach, MD, PhD. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:
1) Perform an ELISA assay for tau on 40 CSF postmortem patient samples from patients with varying degrees of AD severity.
2) Perform an ELISA assay for tau on 40 serum postmortem patient samples from patients with varying degrees of AD severity.

Background and Significance:
Our lab has developed a technique known as FLOWER (frequency locked optical whispering evanescent resonator) which is capable of ultra-sensitive and label-free detection of analytes down to the single molecule level. FLOWER is based on whispering gallery mode microtoroid optical resonator sensing technology.[1,2] FLOWER has achieved a signal to noise ratio of 5 using an anti-IL-2 antibody layer immobilized on a microtoroid to specifically capture IL-2. Direct detection of biomarkers such as amyloid beta is possible because the binding of proteins to antibodies on the surface of the microtoroid produces a detectable optical thickness change. Demonstrating the feasibility of our concept for ultra-sensitive detection of Alzheimer's biomarkers should impact early detection and prognosis and permit longitudinal studies involving various treatments and their corresponding effects on biomarker levels. One important part of demonstrating the feasibility of our technique is comparing our results to those obtained using an established technique, in this case ELISA. In addition, there is limited literature on the levels of tau in serum from AD patients.

Preliminary Data, Experimental Design and Methods:
We have used FLOWER to detect attomolar concentrations of amyloid beta in saline solution. In addition, we screened 80 postmorten patient samples for amlyoid-beta 42 using ELISA. We will use ELISA kits for ultrasensitive tau purchased from Invitrogen (RAB1085). All samples including standards will be done in duplicate according to the protocol suggested by the manufacturer. We have previously screened all samples for hemoglobin using a hemoglobin assay established a cutoff level as suggested by the literature (1.6 mg/mL)[3] above which we did not use the sample.

Proposed One-Year and Long-Term Outcomes:
FLOWER has achieved a signal to noise ratio of 5 using an anti-IL-2 antibody layer immobilized on a microtoroid to specifically capture IL-2. Direct detection of biomarkers such as amyloid beta is possible because the binding of proteins to antibodies on the surface of the microtoroid produces a detectable optical thickness change. Demonstrating the feasibility of our concept for ultra-sensitive detection of Alzheimer's biomarkers should impact early detection and prognosis and permit longitudinal studies involving various treatments and their corresponding effects on biomarker levels. One important part of demonstrating the feasibility of our technique is comparing our results to those obtained using an established technique, in this case ELISA. In addition, there is limited literature on the levels of tau in serum from AD patients.

Year End Progress Summary:
During 7/1/20 to current, we were limited in the number of experiments we could perform as we could only work on COVID-related projects for a period of time and we have also been restricted in terms of how many people can be in the lab due to COVID social distancing requirements.

Nevertheless, over this period of time, we detected tau protein in human samples via ELISA and FLOWER. In addition, we performed calibration data for FLOWER using Abeta 42 in buffer and screened patient serum samples using FLOWER.

We discovered that to obtain clean calibration data for Abeta 42, that the dilution buffer should be basic to inhibit aggregation as the peptide diffuses to the toroid surface. The calibration data that we took was in 5% human serum albumin. With regard to data from patient serum samples, while we have been able to obtain clean data using cerebral spinal fluid, we encountered some problems with the serum samples. Some problems encountered were that serum samples contain high amounts of proteins other than the proteins of interest (amyloid beta 1-42 and tau). We solved this by a combination of two approaches. We first treated the serum sample with CHAPS detergent and then filtered it through a 0.2 um membrane filter. When CHAPS is added to plasma samples, this releases any amyloid beta bound to proteins in the blood.[4] The filter helps to reduce large aggregates in the serum sample, but is large enough to allow amyloid beta to pass. Afterwards, we used an amyloid-beta sandwich method to improve the specificity of our approach. When combined, these two approaches gave us a clean calibration curve. To date, we have screened 15/30 patient serum samples. In the future, we are continuing to work on performing the same experiments using tau instead of Abeta 42. We plan to submit an R01 proposal on this topic and have a manuscript currently in preparation.

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ARIZONA ALZHEIMER'S CONSORTIUM
2020-2021 Scientific Progress Report

Novel Imaging in Rodent Models of Aging and Alzheimer's Disease. Theodore Trouard, PhD, Gene Alexander, PhD, Carol Barnes, PhD, Matt Huentelman, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Complete the processing and analysis of anatomical and diffusion MRI data of 114 rats collected within two NIH R01 grants. Processing and analysis will include comparison of behavior with regional brain volume as well as characterization of diffusion parameters within white matter tracts relevant for memory and AD.

Background and Significance:

Magnetic Resonance imaging (MRI) is an extremely valuable and readily translatable tool for assessing brain anatomy, function and stuctural connectivity in AD and age related dementias. Rodent models of aging and Alzhiemer'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. The grants that are supporting personnel to finish analysis of the imaging data are in a no-cost extension year and are expiring in March and May of 2020. It is critically important to be able to finish the analysis of this dataset as it will set up multiple labs to publish several papers and allow continued research in this area.

Preliminary Data, Experimental Design and Methods:

Anaotomical images will be analyzed with atlas-based approaches similar to those from our previous publications [Totenhagen, 2107; Shang, 2020]. Regional brain volumes will be compared with age and cognitive performance and will be compared to network analysis being done in Dr. Alexander's laboratory. Diffusion images have been collected with multiple directions and multiple b-values (1000, 2000 and 3000 s/mm^2) and will be preprocessed with the TORTOISE software developed at the NIH. Specifically, pre-processing of the raw images will be carried out using DIFFPREP and DRBUDDI algorithms that correct for motion, eddy current and EPI distortions.

Proposed One-Year and Long-Term Outcomes:

The completed processing and analysis of MRI data in the rat model of will allow comparison of neuroanatomical correlations with behavior and help elucidate neuro-correlates of healthy cognitive aging. This should result in ***one submitted manuscript***, on brain volume and white matter differences.

Year End Progress Summary:

To date, we have completed the generation of all preprocessing pipelines for the diffusion MRI datasets. Preprocessing includes motion and eddy current correction, bias field inhomogeneity correction, local principle compnent deniosing, and Gibbs ringing artifact suppression.

Through the preprocessing, three of the dMRI datasets were seen to have artifacts that prevented further analysis, bring the total numbe of datasets to 111. All of these datasets were run through the preprocessing pipeline.

From preprocessed images, several scalar diffsusion parameter maps were calculated using MRtrix software including the Apparent Diffusion Coefficient, ADC; Fraactional Anisotropy, FA).

Constrained Spherical Deconvolution (CSD) analysis was used to calculate Fiber Orientation Distribution Functions (FODs) which, in turn, are used to calcuated “fixels” at each voxel location [Raffelt, 2015; Raffelt, 2017]. Fixels represent single fiber populations with voxels and can be used to compare white matter microstructure.

FODs of individual animals were registered by symmetric diffeomorphic registration to create a study-wide FOD template for statistical analysis. Individual animals parameter maps, ADC, FA, FOD and fixel were warped to the template.

ANOVA has been carreid out on the parameter maps with age and cognitive score as main effects. Family-wise error correction was carried out to correct for multiple comparisons. There are several region in all parameter maps where the effect of age was statistically significant. The ADC showed differences in and near the ventricles. The FA showed differences in some white matter regions. Fixels showec the most significant differences and point to their utility in analyzing white matter microstructure. No statistical effect of cognitive status was seen on any of the parameter maps.

The results are currently being written up for publication and presentation at scientific meetings. The data are the most comprehensive study of aging in rodents and will be compared to histological and genetic information. We expect that a manuscript will be submitted by June 30, 2021 which will complete our one year outcomes.

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Cognitive Effects of Carotid Disease and Carotid Intervention. Wei Zhou, MD, Ted Trouard, PhD, Ying-hui Chou, PhD, Salil Soman, MD, Greg Zaharchuk, PhD, Chiu-Hsieh Hsu, PhD, Manoj Saranathan, PhD, Thomas Hastukami, MD, PhD. University of Arizona; Surgical Services Southern Arizona VA Health Care System; Harvard Medical School; Stanford University**;** University of Washington; Arizona Alzheimer's Consortium.

Specific Aims:

1) Identify the characteristics of SBIs that affect cognition
2) Determine the impact of CBF on SBIs and cognitive changes
3) Characterize high risk patterns of brain connectivity contributing to SBIs

Background and Significance:

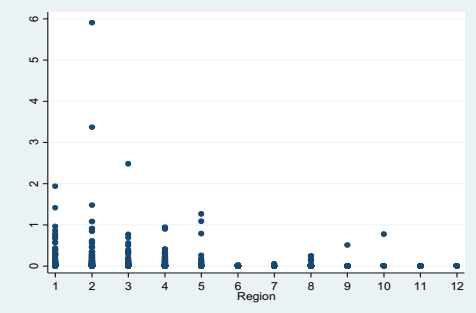
Carotid revascularization is a commonly performed procedure for stroke prevention, but procedure-related subclinical micro-embolization is common, occurring in 30-80% of patients. Majority of these micro-emboli do not cause clinically evident neurologic sequelae. However, we and others have reported their association with cognitive deterioration. Understanding these microembolization-related brain injuries has a significant impact in public health relating to cognitive impairment and risk of dementia in our aging population.

Our central hypothesis is that characteristics of micro-infarcts and baseline brain properties modulate cognitive impacts of procedure-related subclinical embolization. We propose to identify cognitively significant silent brain infarcts (CS-SBIs) through a multidisciplinary collaborative team at 4 institutions. By understanding these micro-brain injuries, this project will help to generate information for our long-term goal of understanding cognitive impairment in aging population. The proposal may also change our current clinical practice by identify 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. ***Size and location of SBIs***: Using the new semi-automated region-growing registration and algorithm program developed by Trouard's lab, we analyzed our previously recruited 157 subjects from 2012 to 2018. 77 subjects (49%) had procedure-related microinfarcts with an average volume of 762.90mm^3 (18mm^3 to 6892mm^3) related to carotid interventions. The locations of lesions were assigned based upon their coordination in the brain using an in-house MATLAB script. **T**he sum of total lesion burden across all subjects by lobe and by subcortical gray matter structure, defined using the Harvard-Oxford subcortical atlas was demonstrated in Figure 1. We have previously observed that changes in volumes of infarcts were significantly correlated to long-term changes in memory measured by MOANS ($P<0.05$) and executive function measured by the Trail Making Test ($P<0.05$).

2. ***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) (Figure 2, unpublished).



List of the regions

1 Frontal Lobe	2 Parietal Lobe	3 Occipital Lobe	4 Temporal Lobe	5 Misc.	6 Thalamus
7 Caudate	8 Putamen	9 Pallidum	10 Hippocampus	11 Amygdala	12 Accumbens

Figure 1: Distribution and volume of infarcts within 12 brain regions of the 77 subjects

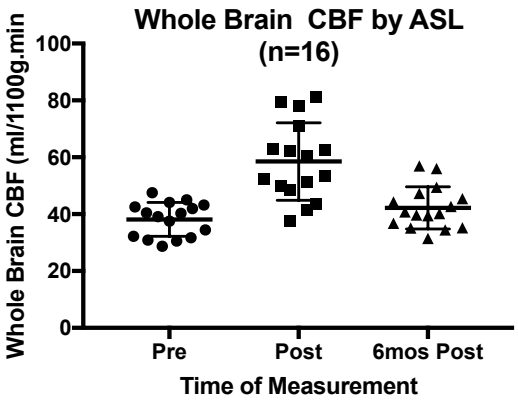


Figure 2: CBF changes of 16 subjects who underwent carotid interventions

Proposed One-Year and Long-Term Outcomes:

We expect to generate useful preliminary information on CBF and brain connectivity at one year. These preliminary data is critical for our NIH grant application in next 18 months. We hope to identify MRI-based prognostic imaging biomarkers for cognitive significant SBIs and procedure-related long-term cognitive decline in the future.

Year End Progress Summary:

1. Identify risk factors for SBI (Publication 1): We analyzed previously recruited 202 patients who underwent carotid stenting (CAS) or carotid endarterectomy (CEA) for severe carotid artery disease,. By comparing preop and postop MRI, we identified procedure-related SBI. We observed that patients undergoing CAS were more likely to have microemboli than patients undergoing CEA (78% vs 27%; P < .0001). For patients undergoing CAS, patency of the external carotid artery, lesion calcification (OR, 5.68; 95% CI, 1.12-28.79; P< .04), and lesion length were all found to be independent risk factors for perioperative embolization, particularly lesion calcification. These factors did not confer increased risk to patients undergoing CEA. The study provides valuable information for patient selection prior to carotid interventions.
2. Identify risk factors for larger volume SBI (Publication 2): 81% of CAS patients had procedure-related new infarcts with a mean volume of 388.15 ± 927.90 mm^3 compared with 30% of CEA patients with a mean volume of 74.80 ± 225.52 mm^3. In the CAS cohort, increasing age and obesity were positively correlated with infarct volume, whereas antiplatelet use was negatively correlated with infarct volume. For the CEA group, diabetes was identified as the only risk factor positively correlated with infarct volume, whereas increasing age was negatively correlated with infarct volume. This information helps with medical optimization and patient selection for clinical practice.
3. Develop semi-automated algorism to define SBI volume: Manually tracing SBI is labor intensive, subject to user fatigue and variability. Our investigator team has developed a semi-automated region-growing algorithm to define size and location of microinfarcts. We have worked with different users to optimize the program and determine the reliability and practicality for clinical use.

4. Standardize CBF analysis across different institution: We examined 107 brain images with ASL value to determine whole brain CBF and hemispheric CBF. The same brain images were also analyzed by University of Washington vascular imaging laboratory (Publication 3). We showed consistent CBF value across institutes (R^2=0.66, P<0.01). CBF values of several large brain regions have also been analyzed. We plan to determine whether preop CBF predicts large volumes of procedure-related SBIs or changes in cognitive function postop.

Project Progress Reports
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Detecting rod microglia, tracking inflammation, and rehabilitating cognitive impairment. Jonathan Lifshitz, PhD, Katherine R. Giordano, Luisa M. Rojas Valencia, L. Matthew Law, PhD, Emily Cope, PhD. University of Arizona College of Medicine – Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Health Care System; Northern Arizona University; Arizona Alzheimer's Consortium.

Specific Aims:

1. To validate phage-derived human domain antibodies to detect rod microglia by immunohistochemistry. *Hypothesis: The preliminary results from phage display will yield antibody tools with specificity to rod microglia in brain-injured rodent cortex*;
2. To develop protocols for spatial genomics of rod microglia in diffuse brain injury tissue in order to determine gene expression profiles unique to rod microglia;
3. To evaluate fecal microbiome abundance and diversity as a pharmacodynamic outcome that relates to peripheral inflammation after diffuse brain injury. *Hypothesis: The fecal microbiome diversity will shift proportionately to peripheral inflammation induced by diffuse brain injury in the mouse.* Diffuse brain injury by midline fluid percussion induces peripheral inflammation, which likely affects the fecal microbiome, which can become a pharmacodynamic outcome of injury and treatment.

Background and Significance:

Microglia heterogeneity and the differential roles in health and disease are at the forefront of understanding and then treating disease. One microglia variant, the rod microglia, was described a century ago, but has been overlooked due to the absence of molecular and cellular tools to isolate and distinguish them. Over the past few years, we have pioneered laser capture microdissection and phage display to identify HCDR3 domains unique to rod microglia. Cyclized synthetic antibodies have been generated to promote immunohistochemical and immunoprecipitation experiments on rod microglia. In the development of these tools, it is critical to validate them as specific and sensitive to rod microglia and then verify their utility across species and models, including post-mortem tissue. New tools will open new avenues to a more complete understanding of microglia in health and disease.

Isolated traumatic brain injury (TBI) has neuroinflammation as a hallmark of the disease process. More recently, it is evident that isolated TBI has far-reaching effects on the immune system, which can be measured in the periphery. Through blood flow cytometry, it is evident that monocytes and neutrophils represent inflammation processes. Additionally, the microbiome of the gastrointestinal system is affected by TBI and other neurological conditions. To advance the field, we pursue a reliable, non-invasive pharmacodynamic outcome measure to track disease processes. In particular, we propose that the inflammatory response disrupts the fecal microbiome abundance and diversity as part of the TBI disease process. Therefore, both peripheral inflammation and fecal microbiome can be used as disease and therapeutic biomarkers.

Preliminary Data, Experimental Design and Methods:

Preliminary ex vivo phage biopanning identified specific, high confidence biological motifs of rod microglia. Whole brain tissue was used as a negative screen to remove shared biological motifs in the domain antibody (dAb) phage library. In separate cohorts of brain-injured CX3CR1-eGFP mice, laser capture microdissected rod microglia were used in three positive screening rounds with the selective phage libraries biased towards rod microglia. To identify dAb biomarker candidates from the biopanning process, next generation sequencing (NGS) of the final library

identified the biological motifs fused to the phage genome, using commercial sequence alignment software. The ex vivo biopanning identified sequencing clusters, converted to amino acid sequences for the associated single chain variable fragment antibody that recognizes cellular expression on rod microglia over other microglia morphologies. Specificity in the results builds confidence for molecular tools to identify, isolate, and interrogate rod microglia in neurological injury and disease.

Aim 1 Approach: Phage-derived synthetic antibodies are biotinylated to permit histochemical and molecular biology protocols. Mice will receive mFPI or sham surgery (n=6/treatment), be perfused with aldehydes at 7 DPI, and used for immunohistochemistry (IHC) on 20 µm cryosections. Protocol refinement will include antigen retrieval and chemical sources to optimize dAb visualization of rod, without non-rod microglia, co-localized to the morphology of CX3CR1-eGFP microglia. Co-localization (%) of dAb and rod morphology will be quantified from confocal images and ImageJ analysis. We a priori set 70% as the expected co-localization threshold to identify rod microglia; rod microglia subtypes may exist and limit 100% detection. We do not expect rod microglia in sham or remote injured cortex.

Aim 2 Approach: The 10X Genomics spatial genomics platform will be used to identify rod microglia on nanodrops of RNAseq material. The investigators will work with the company to optimize rapid immunohistochemical protocols to label rod microglia within brain-injured cortex. Technical troubleshooting will aim to develop a reliable protocol to label rod microglia in a manner compatible with downstream spatial genomics.

Aim 3 Approach: Emily Cope (consultant) has provided guidance on preparing and analyzing fecal samples for microbiome analysis. The abundance and diversity of the fecal microbiome serves as a pharmacodynamic endpoint to monitor post-injury inflammation. From frozen fecal pellets, bacterial DNA will be extracted (DNeasy PowerSoil Kit, Qiagen) for PCR amplification of the 16S rRNA gene V3 region. Read sequences (Illumina MiSeq System) are analyzed (QIIME 2) for the richness and evenness of species as represented by the Shannon diversity index. Using flow cytometry, we track leukocytes (monocytes, neutrophils, B and T lymphocytes) as the population distributions (percentage) shift in response to injury, time, and sex. Repeated blood samples drawn from the submandibular vein (100 µl) is blocked with Fc block and then incubated with antibodies of interest (Cd45, Cd11b, Ly6c, Cd115, and Ly6g), as well as a dump channel (Cd3, B220, Nk1.1, Siglec F). Labeled cells are quantified as Cd11b+Ly6chigh monocytes, inflammatory Cd11b+Cd115+ monocytes, and Cd11b+Ly6g+ neutrophils as a percentages of the total population.

Proposed One-Year and Long-Term Outcomes:

The COVID-19 Pandemic challenged the determination of one-year outcomes, based on access to research space and research resources.

Ms. Giordano is the lead on Aim 1 to detect rod microglia with phage-derived synthetic antibodies and Aim 2 to develop spatial genomics protocols. We anticipate a successful protocol with two different recombinant antibodies to be used on rodent and human tissue.

Ms. Rojas is the lead on Aim 3 to track inflammation and microbiome diversity. She has been introduced to the techniques in Dr. Cope's laboratory and will resume animal experiments as soon as possible. It is anticipated that protocols are refined and samples are collected within 1 year and analysis then analysis protocols can begin. Longitudinal measures over 3 weeks are proposed to track changes in peripheral inflammation and microbiome diversity.

As the 2020-2021 proposals were reduced, the number of animals were reduced.

The long-term outcomes include a validated and verified set of molecular tools (antibodies, genes) for rod microglia. The goal is to apply these tools to diagnostic markers in the blood to

detect rod microglia presence in the course of disease. Similarly, the tools can be deployed in post-mortem tissue to aid in describing the neuroinflammatory processes across age-related degenerative disease. Secondly, in the treatment of injury and age-related neurodegenerative disease, pharmacodynamic biomarkers are necessary to evaluate therapeutic efficacy of treatment interventions. In particular, we propose to pursue probiotic interventions to modulate inflammation.

Year End Progress Summary:

The COVID-19 Pandemic challenged progress towards the proposed aims. Specifically, funding towards these projects was reduced to accommodate for the economics of the pandemic. Secondly, access to research space was limited to essential research, which prioritized the end-run of ongoing experiments. Further, research resources were more challenging to procure and obtain, as supply chain logistics were compromised for most of the year. Lastly, personnel comfort with open lab space was limited and therefore remote work and data analysis were prioritized over in-person experimentation.

The synthetic antibodies are based on proposed antibody structure, using the human dAb to promote specific antigen binding. To optimize success, the same tissue preparation procedures for phage display have been used to validate the antibodies. To date, none of the antigen retrieval, tissue preparation, tissue permeabilization, or solution concentrations have delivered specific results. In addition to new synthesized antibodies, new tissue preparation approaches are under development. Alternatively, the dAb selected by phage display may not be viable and additional motifs will be investigated.

The spatial genomics approaches require visualization of the anatomical feature of interest, while preserving mRNA for expression analysis. Protocol development continues to optimize short-run immunohistochemistry and/or transgenic reporter of microglia. As this is a novel approach for the laboratory and the company, shared insight continues to evolve protocols. Currently, the visualization protocols are not sufficient to identify rod microglia for downstream analysis. Ongoing grant submissions to the DOD, NIH, and VA are in constant revision to support the rod microglia studies.

The focus of peripheral immune monitoring was on flow cytometry. Concerns with equipment maintenance and calibration stalled initial experiments. Shortly thereafter, the analysis software was updated to permit improved compensation and unsupervised analysis. In a critical preliminary study, we evaluated the interaction between the rodent estrous cycle and peripheral immune responses to an LPS immune challenge. The results are emerging to show multiple, novel cell expression profiles using unsupervised analysis which expand our view of immune cell classes. The results will further develop our ability to include female rodents in studies and quantify peripheral immune responses. As far as the fecal microbiome, studies have recently resumed to validate the applied protocols received from Dr. Cope.

Two critical manuscripts were written and published during the pandemic. First, we reviewed the literature on sex differences in TBI clinical research and proposed that the binary categories for sex/gender significantly limit the ability to analyze the data. A proposal was made to use expansive definitions to define subject populations, including, for example, circulating sex hormones. Second, a comprehensive review article about rod microglia was written, which made a call to action for molecular tools that can describe a functional role for this morphological variant in aging, injury, and disease.

Outside the scope of the Arizona Alzheimer's Consortium project, our research program concluded a 3-year study on the chronic cognitive deficits associated with diffuse TBI in the rat, exploring cerebrovascular mechanisms. In this way, our model can reproduce the cognitive impairments in TBI survivors, which is associated with reduced cerebrovascular reactivity at 6 months after injury. These studies will continue under a new VA Merit Award to evaluate cardiovascular risk factors for vascular dementia after TBI.

2020 – 2021

Publications, Manuscripts, & Grants

2020-2021 Publications and Manuscripts

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Current and Pending Grants

Current Grants

Alireza Atri (Co-I; BSHRI Site PI) 5P30AG019610-21 (Reiman) NIH/NIA via Arizona State University Arizona Alzheimer's Disease Research Center – Clinical Core	07/01/2020-06/30/2022 $321,636 Total Annual
Alireza Atri (Co-I; BSHRI Site PI) 5P30AG019610-21 (Reiman) NIH/NIA via Arizona State University Arizona Alzheimer's Disease Research Center – Brain Imaging and Fluid Biomarkers Core	07/01/2020-06/30/2022 $8,948,605 Total Project
Alireza Atri (Co-PI) Gates Ventures via Banner Alzheimer's Foundation Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders	09/01/2020-08/31/2024 $3,085,720 Total Project
Alireza Atri (Project Co-PI) Arizona Alzheimer's Research Consortium (Reiman) AZ DHS CTR040636 via AARC (Beach) Developing a Shared Resource of CSF, Plasma, Serum, PBMC samples from Arizona's Longitudinal Brain and Body Donation and APOE4 Gene Dose Program	07/01/2020-06/30/2021 $89,074 Total Project
Alireza Atri (Project PI) Arizona Alzheimer's Research Consortium (Reiman) AZ DHS CTR040636 via AARC (Atri) Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking	07/01/2020-06/30/2021 $40,926 Total Project
Alireza Atri (Site PI) U24AG057437 (Aisen) NIH/NIA via University of Southern California Alzheimer's Clinical Trial Consortium	12/02/2017-11/30/2022 $896,667 Total Project
Alireza Atri (Site PI) R01AG053798 (Aisen) NIH/NIA via University of Southern California Global Alzheimer's Platform Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease	05/01/2019-04/30/2023 $60,000 Total Project
Alireza Atri (Site PI) Global Alzheimer's Platform Foundation	01/01/2020-12/31/2020 $100,000 Total Project

Ann Revill (PI) 01/01/2021-12/31/2021
NIH R25 $23,800
Effects of Chronic Intermittent Hypoxia on Cholinergic Modulation of Hypoglossal Motoneurons

Ann Revill (PI) 07/20/2020-06/30/2023
R15HL148870 $447,700
NIH/NHLBI
Cholinergic modulation of XII motoneurons and XII premotoneurons

Arne Ekstrom (PI) 07/01/2016-08/01/2022
BCS-1630296 $347,985 annual TC
National Science Foundation (NSF)
The Neural Basis of Human Spatial Navigation in Large-scale Virtual Spaces with Vestibular Input

Arne Ekstrom (PI) 07/01/2012-04/01/2023
R01 NS076856 $347,985 (current TC)
NIH/NINDS
Representation of Spatiotemporal Information in Human Episodic Memory and Navigation

Arne Ekstrom (PI) 09/01/2020-08/01/2022
R21 NS120237 (Ekstrom/Weisberg) $434,125 (current TC)
NIH/NINDS
Volumetric and Connectivity Measures of Navigation and Memory Skill Acquisition

Arne Ekstrom (PI) 06/01/2020-05/01/2025
R01 NS114913 $2,769,521 TC
NIH/NINDS
Precision and binding as two dimensions of medial temporal lobe amnesia

Ashley M. Stokes (Co PI) 07/01/2020-06/30/2022
P2-5021 (Saleem/Stokes) $25,000
Valley Research Partnership
A Highly Specific Inhibitor of Matrix Metalloproteinase-9 Abrogates Tissue Plasminogen Activator Mediated Hemorrhagic Transformation in Experimental Ischemic Stroke

Ashley Stokes (Co-I) 09/12/2017-08/31/2022
U01CA220378 (Swanson) $642,098
NIH/NCI
Quantifying Multiscale Competitive Landscapes of Clonal Diversity in Glioblastoma

Ashley Stokes (Co-I) 09/16/2011-07/31/2021
R01 CA158079 (Quarles) $207,500
NIH/NCI
MRI Assessment of Tumor Perfusion, Permeability and Cellularity

Ashley Stokes (Co-I) 07/01/2017-06/30/2021
R01 CA213158-01 (Quarles) $175,000
NIH/NCI
Establishing the validity of brain tumor perfusion imaging

Ashley Stokes (Co-I) 07/01/2018-06/30/2022
P30 AG019610-20 (Reiman) $1,229,916
NIH/NIA
Arizona Alzheimer's Disease Core Center - Brain Imaging and Fluid Biomarkers (BI-FB) Core

Ashley Stokes (Co-I) 04/01/2020-03/31/2025
UG3CA247606 (Quarles) $299,723
NIH/NCI
Structural and Functional Imaging for Therapy Response Assessment in Brain Cancer

Ashley Stokes (Co-I) 07/01/2020-06/30/2021
AZ Alzheimer's Disease Consortium (Prigatano) $50,000
Diagnostic and Potential Prognostic Value of Finger Tapping Abnormalities in Assessing Older Adults with Memory Complaints

Ben Readhead 04/15/2019-02/29/2024
R01 AG062500 (Velazquez) $366,845
HHS: National Institutes of Health (NIH)
S6K1 as a novel link between aging and Alzheimer's disease

Ben Readhead 03/01/2019-02/28/2022
1RF1AG058469-01A1 (Ehrlich) $65,536
NIH / Icahn School of Medicine at Mount Sinai
Integrated understanding of complex viral network biology in Alzheimer's Disease

Ben Readhead 09/01/2019-05/31/2024
1R01AG062514-01 (Darvas) $15,211
NIH / University of Washington
Modulation of Alzheimer's disease by Herpes simplex virus infection

Ben Readhead (Co-I) 07/01/2020-06/30/2021
CTR040636 (Coon) $130,000
Arizona Alzheimer's Consortium (AAC) FY21
Multiomic modelling of microbe-host interactions in the brain affected by late onset Alzheimer's disease.

Ben Readhead (Co-PI) 07/01/2017-06/30/2022
AGR 08/22/18 (Reiman/Liang/Beach/Readhead/Mastroeni/Dudley) $137,478
NOMIS Foundation via Banner Alzheimer's Institute
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

Ben Readhead (PI) 09/01/2018-08/31/2023
U01 AG061835 $2,492,682
HHS: National Institutes of Health (NIH)
Identification of the genetic and transcriptomic networks of cognitive and neuropathological resilience to Alzheimer's disease associated viruses

Ben Readhead (PI) 04/01/2019-01/31/2021
R21AG063068 $182,697
HHS: National Institutes of Health (NIH)
Investigation of chromosomally integrated Human Herpesvirus 6 as a risk factor for Alzheimer's disease

Ben Readhead (PI) 05/10/2019-05/10/2022
AGR 05/7/19 $67,501
Global Lyme Alliance
An interesting necroptosis angle: tick-borne disease and AD

Ben Readhead (PI) 09/01/2019-09/01/2021
2020-26 $75,700
Benter Foundation
Characterizing the microbiome of preclinical and early stage Alzheimer's disease and additional neurogenerative diseases.

Briana Auman (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $40,926 Total Project
AZ DHS CTR040636 via AARC (Atri)
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Carol Barnes (Co-I) 07/01/2016-06/30/2021
5 P30 AG019610 (Reiman) $15,945 Annual DC
NIH/NIA
Arizona Alzheimer's Disease Core Center Ad Hoc Review Program

Carol Barnes (PI) State of Arizona, DHS Grant Combining high resolution ex vivo magnetic resonance imaging with immunohistochemical labelling of neurovascular function in aged macaque monkey brains	07/01/2020-06/30/2021 $30,000 TC
Carol Barnes (PI) T32 AG044402 NIA/NIA Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease	05/15/2016-04/30/2021 $260,293 Annual TC
Carol Barnes (PI) R01 AG049465 NIH/NIA Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging	08/01/2014-03/31/2021 $734,176 Annual TC
Carol Barnes (PI) R01 AG003376 NIH/NIA Neurobehavioral Relations in Senescent Hippocampus	01/01/2016-11/30/2021 $734,165 Annual TC
Carol Barnes (PI) R01 AG050548 NIH/NIA Cell Assemblies, Brain Adaptation and Cognitive Brain	09/01/2015-05/31/2021 $516,626 Annual TC
Carol Barnes (PI) R01 AG072643 NIH/NIA NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease	04/01/2021-03/30/2026 $1,237,047 Annual DC
Carol Barnes (UA PI) P30 AG061421 (Stern) NIH/NIA/Columbia University Collaboratory on Research for Cognitive Reserve and Resilience	10/01/2018-09/30/2021 $18,945 Annual TC
Charles Veltri (PI) Center for Plant Science and Health Pharmacological and Phytochemical Investigations of Kratom (Mitragyna speciosa Korth.) in the Nematode Caenorhabditis elegans	12/01/2019-06/30/2021 $9,978
Christine Belden (Co-I) 5P30AG019610-21 (Reiman) NIH/NIA via Arizona State University Arizona Alzheimer's Disease Research Center – Clinical Core	07/01/2020-06/30/2022 $321,636 Total Annual

Christine Belden (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $40,926 Total Project
AZ DHS CTR040636 via AARC (Atri)
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Danielle Goldfarb (Co-I) 07/01/2020-06/30/2022
5P30AG019610-21 (Reiman) $8,948,605 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Core Center – Brain Imaging and Fluid Biomarkers Core

Danielle Goldfarb (Co-I) 10/01/2020-03/31/2026
1R01AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $28,351,326 Total Project
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

David Brafman (PI) 04/09/2020-03/21/2023
Glen Swette Memorial Funds
Swette Young Investigator in ALS

David Brafman (PI) 04/01/2019-03/31/2022
R21 AG063358
NIH-NIA
A Pluripotent Stem Cell-Based Model to Investigate the Mechanisms of TBI-Induced

David Brafman (PI) 10/26/2018-06/30/2021
Department of Defense, T0138
Adaptable multi-modality nanoprobes for non-invasive real-time monitoring of engineered cells and tissues

David Brafman (PI) 04/01/2018-12/31/2021
Department of Defense, T0042-C
Biomanufacturing of cells in the neuroectoderm fate space

David Coon 07/01/2020-06/30/2022
1862894-38-C-20 (Underiner) $70,000
National Endowment for the Arts (NEA)
Creative Health Collaborations Hub

David Coon (Core Leader) 08/15/2016-06/30/2021
P30 AG019610 (Reiman) $57,216
NIH | NIA
Arizona Alzheimer's Disease Center - Outreach, Recruitment, and Engagement Core

David Coon (PI) 05/15/2016-04/30/2022
R01 AG049895 $1,960,783
NIH | NIA
EPIC: A Group-based Intervention for Early-stage AD Dyads in Diverse

David Coon (PI) 09/01/2017-08/31/2021
90ALGG0019-01-00 $808,150
HHS: Administration for Community Living (ACL)
ADI-SSS Arizona's Dementia-Capable System Enhancement

David Coon (PI) 01/01/2019-03/31/2022
SPA00002017; 3032709; PO 500933462-0-SERV $181,816
Dignity Health-St. Joseph's Hospital: Barrow Neurological Institute (BNI)
Parkinson's Partners in Care: Focus Group and Pilot

David Coon (PI) 07/01/2020-06/30/2021
LTR 07/14/20 $191,904
Arizona Alzheimer's Consortium (FY21)
ADRD Family Caregiving during a Pandemic: Outcomes and Intervention

David Raichlen (PI) 09/15/2020-08/31/2021
R56 AG067200 (Alexander/Raichlen) $499,990
NIH/NIA
Physical Activity Predictors of Cognitive and Brain Health in the Risk for Alzheimer's Disease.

David Raichlen (Sub PI) 07/01/2020-06/30/2021
U19 AG057377-03S1 Supplement (Promislow) $49,905
NIH/NIA/University of Washington
Development of Cognitive and Physical Activity Biomarkers for a Companion Dog Model of Alzheimer’s Disease

David Shprecher (Co-I) 09/01/2019–04/30/2021
R34 AG 056639 (Yo-El Ju) $25,280 Total Project
NIH/NIA via Washington University St. Louis
Neuroprotective treatment trial planning in REM sleep behavior disorder

David Shprecher (Project PI) 07/01/2020-06/30/2021
Arizona Alzheimer’s Research Consortium (Reiman) $17,333 Total Project
AZ DHS CTR040636 via AARC (Shprecher)
Laying the Groundwork for Prodromal Lewy Body Dementia Research in REM Sleep Behavior Disorder

David Weidman (Co-I) 01/01/2021-08/31/2022
NIH R41/R42 TBD (Lure) $237,162 Total Project
NIH STTR via MS Technologies
Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized

David Weidman (Project PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $25,000 Total Project
AZ DHS via AARC
Native American Outreach, Recruitment, and Retention Program

David Weidman (Site Leader) 07/01/2016-06/30/2022
5 P30 AG019610 (Reiman) $12,516,208 Total Project
NIH/NIA via ASU
Arizona Alzheimer's Disease Core Center – Clinical Core

David Weidman (Site Leader) 07/01/2016-06/30/2022
5 P30 AG019610 (Reiman) $12,516,208 Total Project
NIH/NIA via ASU
Arizona Alzheimer's Disease Core Center – Outreach and Recruitment Core

David Weidman (Site PI) 02/24/2020-11/30/2022
U24 AG057437 (Aisen) $896,667 Total Project
NIH/NIA via USC (ATRI)
Alzheimer's Clinical Trial Consortium

David Weidman (Site PI) 05/01/2019-04/30/2023
R01 AG053798 (Aisen) $60,000 Total Project
NIH/NIA via USC (ATRI)
Global Alzheimer's Platform Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease

Del Eckman (PI), T. Bucky Jones (Co-PI), Johana Vallejo (Co-PI) 04/01/2018-02/28/2021
ADHS 17-00007401 $225,000
Arizona Department of Health Services
Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4 Targeted-Replacement Mice

Don Saner (Co-I) 09/30/2020-03/31/2026
R01 AG069453 (Reiman/Su/Chen/Langbaum/Caselli) $27,473,070
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Don Saner (Co-I) 04/01/2017-03/31/2023
R01 AG055444 (Reiman/Tariot/Lopera) $14,893,051 Total Project
NIH/NIA
Alzheimer's Prevention Initiative ADAD Colombia Trial

Don Saner (Co-I) 09/01/2018-11/30/2024
R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot) $32,005,950 Total Project
NIH/NIA
API / A4 Alzheimer's Prevention Trial

Don Saner (Core Co-Leader; Co-I) 07/01/2016-06/30/2021
P30 AG019610 (Reiman) $12,516,208
NIH/NIA
Arizona Alzheimer's Disease Core Center – Data Management & Statistics Core

Don Saner (Data Science Sr. Director (IT/EHR Lead)) 04/01/2018-03/31/2023
OT2 OD026549 (Kraft/Moreno/Reiman/Theodorou) $3,947,349 Total Project
NIH via University of Arizona
University of Arizona-Banner Health Precision Medicine Initiative Cohort Enrollment Center

Don Saner (Project PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $30,000 Total Project
State of Arizona DHS via AARC
Enhancements to a Centralized Data Management System for the Arizona Alzheimer's Disease Core Center (ADCC), Brain and Body Donation Program (BBDP), and Apolipoprotein E4 (APOE4) Gene Dose Program

Dona Locke (Co-I) 07/01/2020-06/30/2021
ADHS12-010553 (Caselli)
Arizona Department of Health Services
Normal and Pathological Aging (Preclinical Alzheimer's Disease

Dona Locke (Co-I) 09/30/2020-03/31/2026
R01 AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $1,634,948
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Dona Locke (PI) 09/01/2017-Present
Ralph C. Wilson Foundation Development Fund
HABIT Registry

Emily Cope (Co-I) 04/01/2018-03/31/2021
478478 / ADHS18-198857 (Duca) $17,604
University of Arizona / Arizona Biomedical Research Commission
Role of the Small Intestine in the Prebiotic Treatment/or Obesity

Emily Cope (PI) 02/01/2018-04/30/2021
U54MD012388 (Baldwin/Stearns) $59,997
SHERC Pilot grants program (PI: Cope)
NIH/NIMHD
Addressing asthma health disparities through diet-based modification of the gut-microbiome airway axis

Emily Cope (PI) 07/01/2019-06/30/2021
Cystic Fibrosis Research Inc. (Cope) $120,000
A Multi-'Omic Approach to Evaluate Concurrent Sinus and Pulmonary Disease in Cystic Fibrosis

Emily Cope (PI) 01/01/2019-12/31/2021
Flinn Foundation Research Grant (Cope/Rank) $100,000
Project #2188
Precision Treatment of Asthma Through Targeted Manipulation of the Gut Microbiome Lung Axis

Emily Cope (PI), J. Gregory Caporaso (PI) 07/01/2019-12/31/2020
ADHS 14-052688 / Grant # CTR040636 $40,000
Arizona Alzheimer's Research Center, Inc
Longitudinal analysis of the gut microbiome-brain axis in Alzheimer's Disease

Eric Reiman (Co-I) 10/01/2020-03/31/2026
1 R01 AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $27,473,070 Total Project
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Eric Reiman (Co-I) 08/01/2017-07/31/2021
U19 AG024904 (Weiner) $400,000 Total Project
NIH/NIA via Northern California Institute Res & Educ.
Alzheimer's Disease Neuroimaging Initiative

Eric Reiman (Co-I) 09/30/2016-05/31/2021
P01AG052350 (Zlokovic/Toga) $471,912 Total Project
NIH via USC
Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer's Disease

Eric Reiman (Co-I) 03/01/2020-02/28/2021
VCID-17-209279 (Zlokovic) $159,401 Total Project
Alzheimer's Association via USC
Vascular Contributions to Dementia and Amyloid and Tau Lesions in APOE4 Carriers (VCID)

Eric Reiman (Co-I) 07/01/2014-06/30/2021
U01 AG016976 (Kukull) $159,900 Total Project
NIH/NIA via University of Washington
National Alzheimer's Coordinating Center

Eric Reiman (Co-I) 09/01/2017-05/31/2022
R01 AG054671 (Quiroz) $208,812 Total Project
NIH/NIA via Massachusetts General Hospital
Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease

Eric Reiman (Co-I) 03/01/2021-02/28/2026
1R01AG070883 (Bendlin/Kind) $264,852 Total Project
NIH/NIA via University of Wisconsin-Madison
The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

Eric Reiman (Co-I) 09/22/2017-04/30/2022
U54MD000507 (Manson/Buchwald) $98,067 Total Project
University of Colorado Denver/NIH/NIMHH
American Indian and Alaska Native Health Disparities

Eric Reiman (Co-I) 12/01/2016-11/30/2020
SAGA-17-415540 (Rasgon) $80,474 Total Project
Alzheimer's Association via Stanford University
Sex Specific Interactions of Modifiable and non-Modifiable Risk Factor of AD

Eric Reiman (Co-PI) 09/01/2020-08/31/2024
Gates Ventures via Banner Alzheimer's Foundation $3,085,720 Total Project
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

Eric Reiman (OSC) 09/01/2017-08/31/2022
RF1AG054617 (Pa) $22,636 Total Project
NIH via USC
Gender and APOE4 effects on brain morphometry, cognition, and clinical progression to Alzheimer's Disease

Eric Reiman (PI) 07/01/2016-06/30/2022
P30 AG019610 (Reiman) $12,516,208 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Core Center

Eric Reiman (PI) 05/01/2008-03/31/2021
5 R01 AG031581 (Reiman/Caselli) $10,115,089 Total Project
NIH/NIA
Brain Imaging, APOE, & the Preclinical Course of Alzheimer's Disease

Eric Reiman (PI) 04/01/2017-03/31/2023
R01 AG055444 (Reiman/Tariot/Lopera) $14,893,051 Total Project
NIH/NIA
Alzheimer's Prevention Initiative ADAD Colombia Trial

Eric Reiman (PI) 09/01/2018-11/30/2024
R01 AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot) $32,005,950 Total Project
NIH/NIA
API / A4 Alzheimer's Prevention Trial

Eric Reiman (PI) 12/15/2015-11/30/2022
U01 NS093334 (Stern/Cummings/Reiman/Shenton) $281,796 Total Project
NIH/NINDS via Boston University/Mayo Clinic
Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course and Risk Factors

Eric Reiman (PI) 04/01/2018-03/31/2023
OT2 OD026549 (Kraft/Moreno/Reiman/Theodorou) $2,655,634 Total Project
NIH via University of Arizona
University of Arizona-Banner Health All of Us Research Program

Eric Reiman (PI) 09/01/2007-06/30/2022
NOMIS Foundation (Reiman/Liang/Beach/Readhead/Dudley) $5,000,000 Total Project
NOMIS Foundation via Banner Alzheimer's Foundation
A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Regions, Associated Whole Genome Sequencing, Longitudinal Clinical and Neuropathological Data, and Cell-Specific Multi-Scale Networks in the Alzheimer's and Aging Brain

Eric Reiman (PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $130,000 Total Project
State of Arizona
Alzheimer's Prevention Initiative

Eric Reiman (PI) 01/01/2016-12/31/2020
Alzheimer's Association/GHR/FBRI (Reiman/Tariot/Langbaum) $10,000,000 Total Project
Alzheimer's Prevention Initiative APOE4 Trial

Fabian Fernandez (PI) 07/01/2020-12/01/2022
Velux Stiftung (Switzerland) $275,000 TC
Programming the Circadian Clock with Precision Flashes of LED Light

Garilyn Jentarra (Co-PI), Haiwei Gu (PI, ASU), Doug Jones (Co-I) 05/01/2021-03/31/2023
$462,644
R21AG072561-01 (Gu/Jentarra)
NIH/NIA/Arizona State Universtiy
Targeting whole-body fatty acid metabolism in Alzheimer's disease, with special interest in lauric acid

Garilyn Jentarra (PI), T. Bucky Jones (Co-PI), Fernando Gonzalez, (Co-PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Consortium $17,162
Identification and culture of microbes in brain tissue from Alzheimer's disease patients and controls

Garilyn Jentarra (PI), T. Bucky Jones (PI) 07/01/2019-06/30/2020
Arizona Alzheimer's Consortium $36,278
Following the Evidence: The Role of Microbes in the Development of Alzheimer's Disease

Geidy Serrano (Co-I) 07/01/2020-06/30/2022
3P30AG019610-20S1 (Reiman) $386,476 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center - Presence and Neuropathological Consequences of CNS Covid-19 in Consecutive Autopsies During the Worldwide Pandemic.

Geidy Serrano (Co-PI) 09/01/2020-08/31/2024
Gates Ventures via Banner Alzheimer's Foundation $3,085,720 Total Project
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

Geidy Serrano (PI) 10/01/2019-01/05/2022
Astrocyte Biology in PD Grant ID 17901 $148,395 Total Project
Michael J. Fox Foundation for Parkinson's Research
Characterization of isolated human astrocyte population in aging and Lewy body pathology

Geidy Serrano (PI) 12/01/2020-02/31/2021
Research Grant 667-2020-06 $90,000 Total Project
CurePSP
Single-whole-cell characterization in progressive supranuclear palsy

Geidy Serrano (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $89,074 Total Project
AZ DHS CTR040636 via AARC (Beach)
Developing a Shared Resource of CSF, Plasma, Serum, PBMC samples from Arizona's Longitudinal Brain and Body Donation and APOE4 Gene Dose Program

Geidy Serrano (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $43,333 Total Project
AZ DHS CTR040636 via AARC (Lue)
Patient-based postmortem fibroblast banking for translational research

Geidy Serrano (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $40,926 Total Project
AZ DHS CTR040636 via AARC (Atri)
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Geidy Serrano (Project PI) 07/01/2020–06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $69,333 Total Project
AZ DHS CTR040636 via AARC
A Human Brain Single-Cell Suspension Resource

Gene Alexander (Co-I) 07/01/2020-06/30/2021
U19 AG057377-03S1 Supplement (Promislow) $300,577 (UA Sub TC)
NIH/NIA/University of Washington
Development of Cognitive and Physical Activity Biomarkers for a Companion Dog Model of Alzheimer's Disease

Gene Alexander (Co-I) 10/01/2019-09/30/2021
McKnight Brain Research Foundation (Williamson) $60,000 (UA Sub TC)
Transcutaneous Vagal Nerve Stimulation and Cognitive Training to Enhance Cognitive Performance in Healthy Older Adults

Gene Alexander (Co-I; Data Management and Statistics Core) 07/01/2016-06/30/2021
P30 AG019610 (Reiman) $93,648 (UA Sub TC)
NIH/NIA
Arizona Alzheimer's Disease Core Center

Gene Alexander (Co-PI) 05/01/2018-04/30/2021
McKnight Brain Research Foundation $120,000 TC
(Alexander/Bowers/Woods)
A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults

Gene Alexander (Co-PI) 09/01/2015-12/31/2022
McKnight Brain Research Foundation $800,000 TC
(Alexander/Cohen/Levin/Wadley)
McKnight Inter-institutional Cognitive Aging Assessment Core

Gene Alexander (Co-PI) 01/01/2015-12/31/2022
McKnight Brain Research Foundation $931,760 TC
(Alexander/Cohen/Visscher/ Wright)
McKnight Inter-institutional Neuroimaging Core and Brain Aging Registry

Gene Alexander (Core Leader) 09/15/2018-06/30/2022
P30 AG019610 (Reiman) $3,701,167 Core TC
NIH/NIA
Arizona Alzheimer's Disease CoreCenter - Brain Imaging and Fluid Biomarkers (BIFB) Core

Gene Alexander (PI) 07/01/2020-06/30/2021
State of Arizona/Banner Good Samaritan Subcontract Grant $30,000 (TC)
Behavioral Biomarkers in Brain Aging and Alzheimer's Disease Risk

Gene Alexander (PI) 09/01/2020-08/31/2021
R56 AG067200 (Alexander/Raichlen) $767,484 (TC)
NIH/NIA
Physical Activity Predictors of Cognitive and Brain Health in the Risk for Alzheimer's Disease.

Gene Alexander (PI) 08/01/2019-04/30/2024
R01 AG064587 (Bowers/Alexander/Woods) $3,797,232 (TC)
NIH/NIA
Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation.

Gene Alexander (UA PI) 05/01/2020-4/30/2022
R01 AG054077-05S2 Supplement (Woods/Cohen/Marsiske) $221,577 (UA Sub TC)
NIH/NIA
Augmenting Cognitive Training in Older Adults: the ACT COVID Ancillary Study

Gene Alexander (UA PI) 09/01/2016-04/30/2022
R01 AG054077 (Woods/Cohen/Marsiske) $1,474,342 UA Sub TC
NIH/NIA/University of Florida
Augmenting Cognitive Training in Older Adults – The ACT Grant

Geoff Ahern (Co-I) 07/01/2016-06/30/2021
P30 AG019610 (Reiman) $43,084 Annual DC
NIH/NIA
Arizona Alzheimer's Disease Core Center (UA Clinical Core)

Heather Bimonte-Nelson (Co-I) 01/01/2016-05/31/2021
R01 NS097537 (Newbern) $535,936
NIH/NINDS
Functions of ERKMAPK Signaling in GABAergic Circuit Development

Heather Bimonte-Nelson (Co-I) 09/30/2017-07/31/2022
R01 DA043172 (Olive) $250,000
NIH/NIDA
Characterization and Reversal of Neurocognitive Dysfunction Produced by Long-term Synthetic Cathinone Use

Heather Bimonte-Nelson (Co-I) 07/01/2020-06/30/2021
LTR 07/14/20 (Coon) $26,307
Arizona Department of Health Services
Arizona Alzheimer's Consortium (AAC) FY21

Heather Bimonte-Nelson (Co-I) 12/21/2020-08/31/2025
R01 NS116657 (Stabenfeldt) $364,515
NIH/NINDS
Exploiting sex-dependent brain injury response for nanoparticle therapeutics

Heather Bimonte-Nelson (Core Leader) 07/1/2020-06/30/2021
P30 AG019610 (Reiman) $45,306
NIH/NIA
Arizona Alzheimer's Disease Core Center – Research Education Component

Heather Bimonte-Nelson (PI) 09/01/2018-05/31/2023
R01 AG028084 $220,000
NIH/NIA
Variations in Hormones During Menopause - Effects on Cognitive and Brain Aging

Hillary Protas (Co-I) 09/15/2017 - 06/30/2022
RF1AG054617 (Pa) $22,636 Total Project
USC/NIH
Gender and APOE4 effects on brain morphometry, cognition, and clinical progression to Alzheimer's Disease

Hillary Protas (Co-I) 07/01/2017-06/30/2022
5R01AG054671 (Quiroz) $208,812 Total Project
NIH via MGH
Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease

Hillary Protas (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS via AARC (Su)
Advanced Image and Statistical Data Analysis Techniques for Detection and Monitoring of Alzheimer's and Related Disease

Hillary Protas (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $20,000 Total Project
State of Arizona DHS Via AARC (Su)
Statistical and Neuroimaging Core Resources Serving the Consortium members for Alzheimer's disease and prevention related studies

Hillary Protas (Project Co-I) 07/1/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS Via AARC (Su)
Resource to Support Computational Data Analysis and Collaborative Research

Hillary Protas (Subrecipient Co-I) 09/30/2017-07/31/2022
U19AG024904 (Weiner) $400,000 Total Project
NIH via NCIRE
Alzheimer's Disease Neuroimaging Initiative

Ileana Ratiu (PI) 11/21/20-12/31/21
NIRG8475 $10,000
American Speech-Language-Hearing Foundation
The Impact of Auditory Distraction on Executive Function and Reading Comprehension in Individuals with and without Mild Traumatic Brain Injury: An Eye- Tracking Study

J Gregory Caporaso (Project Co-I) 7/1/2017 - 6/30/2022
U54MD012388 (Baldwin/Stearns) $435,353
NIH / NIMHD
Southwest Health Equity Research Collaborative (SHERC)
Project 1 (PI Pearson): Do Pathogen Genotypes, Carriage, and Social Network Differences Lead to Health Disparities in MRSA/MSSA Infections?

J. Gregory Caporaso (Co-I) 12/15/2019-10/31/2022
G-2019-12432 (Stachurski) $59,535
Alfred P. Sloan Foundation / The Australian National University
Document Creation and Publishing Tools for Next-Generation Scientific Textbooks

J. Gregory Caporaso (Co-I) 4/1/2020 - 3/31/2022
2017-67013-26255 / F0003750302014 (Kaplan) $40,012
National Institute of Food and Agriculture / Purdue
Optimizing Plant-Soil Feedbacks for High Intensity Crop Production Systems

J. Gregory Caporaso (PI) 4/1/2018-3/31/2021
478478 / ADHS18-198857 (Caporaso) $38,225
University of Arizona / Arizona Biomedical Research Commission
Role of the Small Intestine in the Prebiotic Treatment/or Obesity

J. Gregory Caporaso (PI) 07/15/2020-06/30/2025
U24CA248454 $752,538
NIH/NCI
Advanced Development of Informatics Technologies for Cancer Research and Management

J. Gregory Caporaso (Project PI) 9/1/2019 -8/31/2024
5U54CA143925 (Ingram) $60,000
NIH/NCI
The Partnership for Native American Cancer Prevention Project 1: Viewing Native American Cervical Cancer Disparities through the Lens of the Vaginal Microbiome

James Gregory Caporaso (PI) 5/1/2016 – 4/30/2020
1565100 $525,795
National Science Foundation (Caporaso)
Extensible, reproducible and documentation-driven microbiome data science.

Jessica Andrews-Hanna (PI) 7/1/20 – 6/30/21
AZ Dept Health Services / Arizona Alzheimer's Consortium $20,000 TC
Why is the glass half-full? Sources of the positivity effect in healthy aging and AD risk.

Jessica Andrews-Hanna (PI) 4/01/21-1/31/26
R01 MH125414-01 (Andrews-Hanna/Sbarra) $2,925,543 TC
NIMH Connected Lives - Overcoming the Self through Empathy (CLOSE): A dyadic, multi-method study

Jessica Langbaum (Co-I) 04/01/2017-03/31/2023
R01AG055444 (Reiman/Tariot/Lopera) $14,893,051 Total Project
NIH/NIA
Alzheimer’s Prevention Initiative ADAD Colombia Trial

Jessica Langbaum (Co-I) 09/30/2018-05/31/2025
1 R01 AG061848 (Aisen/Johnson/Sperling) $750,000 Total Project
NIH/NIA via University of Southern California
Combination anti-amyloid therapy for preclinical Alzheimer’s Disease

Jessica Langbaum (Co-I) 02/01/2021-01/31/2026
1 R01AG070349-01 (Edwards) $5,822,736 Total Project
NIH via University of South Florida
Cognitive Training to Reduce Incidence of Cognitive Impairment in Older Adults

Jessica Langbaum (Co-PI) 01/01/16-12/31/20
Alzheimer’s Association/GHR/FBRI (Reiman/Tariot/Langbaum) $10,000,000 Total Project
Alzheimer’s Prevention Initiative APOE4 Trial

Jessica Langbaum (PI) 09/01/2018- 11/30/2024
R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot) $32,005,950 Total Project
NIH/NIA
API A4 Alzheimer’s Prevention Trial

Jessica Langbaum (PI) 09/01/2019-06/30/2024
R01 AG063954 (Langbaum/Bleakley) $8,793,374 Total Project
NIH/NIA
Establishing the science behind Alzheimer’s recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials

Jessica Langbaum (PI) 09/15/2020-06/30/2022
3 R01 AG063954-02S1 (Langbaum/Bleakley) $387,949 Total Project
NIH/NIA
Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials

Jessica Langbaum (PI) 07/01/2020-03/31/2026
1 R01 AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $27,473,070 Total Project
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Jessica Langbaum (PI) 09/15/2019-02/28/2021
1R43AG055218-01A1 (Aggarwal/Langbaum) $27,846 Total Project
NIH/NIA via Provoc, Inc.
Improving Mobile Access for Recruiting Study Volunteers from Underrepresented Populations for Alzheimer's Disease Research and Other Studies

Jessica Langbaum (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $130,000 Total Project
State of Arizona DHS via AARC
Alzheimer's Prevention Initiative

Jessica Langbaum (Project PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $10,000 Total Project
State of Arizona DHS via AARC
Arizona Alzheimer's Registry

Jessica Powell (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $40,926 Total Project
AZ DHS CTR040636 via AARC (Atri)
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Johana Vallejo-Elias (PI) 07/01/20-06/30/21
Midwestern University Intramural Funds $4,000
The effects of APOE isoforms on Caveolae expression and Localization in the hippocampus and cerebral cortex of mice

John Fryer (Co-I) 11/1/2020-04/30/2021
R37AI071106 (Kita)
NIH/NIAID
Mechanisms of Allergen-induced Type 2 Immunity-Administrative Supplement

John Fryer (PI) 09/30/2015-08/31/2020
R01NS094137 (Fryer) $342,344
NIH/NINDS
The role of Clusterin in cerebral amyloid angiopathy

John Fryer (PI) 08/01/2019-03/31/2024
RF1AG062110 (Fryer/Liu) $4,000,570
NIH/NIA
Microglial apoE in neuroinflammation and Alzheimer's disease

John Fryer (PI) 08/15/2019-03/31/2024
RF1AG062077 (Fryer/Petrucelli) $4,037,235
NIH/NIA
Novel genetic modifiers of C9orf72 and Tau toxicity

John Fryer (PI) 08/01/2019-07/31/2021
R56AG062556 (Springer/Fryer) $782,049
NIH/NIA
Selective autophagy in Alzheimer's disease and related dementias

John Fryer (PI) 2019 – 2021
Coins for Alzheimer’s Trust
The role of microglial lipid signaling in Alzheimer’s disease pathogenesis

John Fryer (PI) 02/01/20-01/31/22
Cure Alzheimer’s Foundation curealz.org
The role of Clusterin in tau pathology

John Fryer (PI) 07/01/19-06/30/22
Mayo Clinic Alzheimer’s Disease Center pilot grant
Single-cell/nucleus transcriptional signatures underlying Alzheimer’s disease pathology

John Fryer (Project PI) 09/20/2019-06/30/2024
U54NS110435 (Ross/Fryer/Chang) $624,533
NIH/NINDS
Lewy Body Dementia CWOW, Project 1: Omics driven network analysis in LBD

John Fryer (Project PI) 09/30/2014-03/31/2025
5P01NS084974-07 (Petrucelli) $422,550
NIH/NINDS
Pathobiology of Neurodegeneration in C9ORF72 repeat expansion – Project 1

Jonathan Lifshitz (Co-I) 12/15/2017 – 11/30/2022
R01 NS100793 (Thomas) $310,034
NIH/NINDS
Electrochemical Assessment of Behaviorally Relevant Circuit Function After TBI

Jonathan Lifshitz (Co-I) 04/01/2020 – 03/31/2025
I01 BX003767 Supplement (Migrino) $100,000
VA BLR&D
Testing and Development of Monosialoganglioside-Containing Nanoliposomes to Mitigate Damage from Cerebrovascular Disease

Jonathan Lifshitz (Consultant) 09/30/2020 – 08/31/2022
R21 NS120022 (Rowe) $415,482
NIH/NINDS
Bidirectional Relationship Between Growth Hormone and Sleep Following Juvenile TBI

Jonathan Lifshitz (Co-PI) 08/01/2017 – 07/31/2021
W81XWH-17-1-0473 (Migrino/Lifshitz) $295,110
Department of Defense USAMRAA / Carl T Hayden Medical Research Foundation
Probing the Mechanistic Role of Vascular Dysfunction & Vascular Inflammation in TBI Cognitive Dysfunction

Jonathan Lifshitz (Co-PI) 4/01/2021 – 03/31/2025
VA Merit I01002691 (Migrino) $1,200,000
U.S. Dept. of Veterans Affairs
Mechanistic role of vascular dysfunction in TBI-mediated cognitive dysfunction

Jonathan Lifshitz (Mentor) 06/01/2020 – 05/31/2023
F31 NS113408 (Giordano) $118,617
NIH/NINDS
Precision Identification and Targeting of Rod Microglia in Diffuse Brain-Injured Cortex

Jonathan Lifshitz (PI) 03/15/2019 – 06/30/2023
VA Merit I01 RX002472 $278,533
U.S. Dept. of Veterans Affairs
Brain Injury Rehabilitation Modality, Regulation, & Structural Plasticity

Jonathan Lifshitz (PI) 12/01/2020 – 06/30/2023
VA Merit I01 RX002472 Supplement $526,529
U.S. Dept. of Veterans Affairs
Developing and Testing a Novel Virtual Cognitive Rehabilitation Program to Alleviate Persistent Cognitive Dysfunction Following Traumatic Brain Injury

Jonathan Lifshitz (PI) 07/01/2020 – 06/30/2021
Arizona Alzheimer's Consortium $22,500
Detecting Rod Microglia, Tracking Inflammation, and Rehabilitating Cognitive Impairment

Joseph Scheeren (Contact PI) 09/05/2014-08/31/2024
3U18FDA005320-06 S1 $1,399,179
Food and Drug Administration
CRITICAL PATH TO PUBLIC PRIVATE PARTNERSHIPS

Joyce Lee-Iannotti (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $17,333 Total Project
AZ DHS CTR040636 via AARC (Shprecher)
Laying the Groundwork for Prodromal Lewy Body Dementia Research in REM Sleep Behavior Disorder

Judith Su (PI) 05/01/19 – 04/29/22
Flinn Foundation #26223 $56,250 TC
Identifying and detecting diseases prior to physical presentation of symptoms

Judith Su (PI) 03/01/2019 – 05/29/2021
Gordon & Betty Moore Foundation $56,250 TC
Understanding Biological Systems Using Resonator-Mediated Single-Molecule Raman Detection and Spectroscopy

Judith Su (PI) 08/01/18 – 07/31/21
NSF 1842045 $100,000 TC
EAGER: High Precision Molecular Spectroscopy and Detection Using Microtoroid Optical Resonators

Judith Su (PI) 08/01/18 – 01/31/22
Defense Threat Reduction Agency $1,860,212 TC
Sensitive, Selective, and Affordable Chemical Threat Sensing Using Frequency Locked Microtoroid Optical Resonators

Judith Su (PI) 09/01/20 – 8/31/25
5R35GM137988-02 $1,822,950 TC
NIH/NIGMS
Label-free single molecule detection for basic science and translational medicine

Judith Su (Project PI) 07/01/20 – 06/30/21
State of Arizona, DHS Grant $12,000 TC
Determining levels of Alzheimer's biomarkers in postmortem cerebral spinal fluid and serum samples

Kathy O'Connor (Project Co-I) Arizona Alzheimer's Research Consortium (Reiman) AZ DHS CTR040636 via AARC (Atri) Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking	07/01/2020-06/30/2021 $40,926 Total Project
Kendall Van Keuren-Jensen (Advisor) Grant Michael J Fox Foundation for Parkinson's Research LRRK2 CSF Advisory	10/01/2020 – 09/30/2021 $7,964
Kendall Van Keuren-Jensen (Co-I) Grant 14539 (Cookson-NIH) Michael J Fox Foundation for Parkinson's Research LRRK2 Biology Consortium Program	06/08/2018 – 03/31/2021 $200,000
Kendall Van Keuren-Jensen (Co-I) FA8650-19-C-7944 (Broderick) USAF/AFMC- Office of Naval Research Peerless Operator Biologic Aptitude (Peerless)	10/01/2019 – 03/31/2021 $342,141
Kendall Van Keuren-Jensen (Co-I) R01NS091299-05S1 (Zarnescu) NIH/NINDS/University of Arizona Supplement: RNA dysregulation in neurodegeneration	06/01/2019 – 05/31/2021 $55,800
Kendall Van Keuren-Jensen (Co-I) AAC FY21 (Reiman) Arizona Department of Health Services Grant Identification of RNA modifications altered in Alzheimer's disease (AD) and Down's Syndrome (DS)	07/01/2020 - 06/30/2021 $65,000
Kendall Van Keuren-Jensen (Co-I) RP06 (Reiman) Nomis Foundation A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Regions, Associated Whole Genome Sequencing, Longitudinal Clinical and Neuropathological Data, and Cell-Specific Multi-Scale Networks in the Alzheimer's and Aging Brain	07/01/2020 – 06/30/2021 $907,405
Kendall Van Keuren-Jensen (Consortium PI) 1UG3CA241687 (Laurent) NIH/NCI/University of California, San Diego Development and application of a scalable workflow for immunomagnetic separation of exRNA carrier subclasses and molecular analysis of their cargo.	09/01/2019 – 08/30/2023 $483,598

Kendall Van Keuren-Jensen (Co-PI) 10/16/2019 – 10/15/2022
Grant 17047 (Craig) $225,000
Michael J Fox Foundation for Parkinson's Research
Identification of RNA Isoform and Splicing Based Biomarkers For Parkinson's Disease

Kendall Van Keuren-Jensen (PI) 03/01/2019 – 06/15/2021
Foundation for the National Institutes of Health $260,291
Grant VANK19AMPPD
Accelerating Medicines Partnership Parkinson's Disease (AMP PD) (Data QC and analysis for BioFIND and PDBP)

Kendall Van Keuren-Jensen (PI) 03/01/2020 – 03/31/2021
TGen (Dorrance Foundation) (Jensen/Von Hoff) $811,392
Extracellular Vesicles

Kendall Van Keuren-Jensen (PI) 06/01/2017 – 05/31/2021
Grant 977871 $288,917
Sidell-Kagan Foundation
Advancing prevention of Alzheimer's disease: Extracellular RNAs as candidates for monitoring Alzheimer's patients

Kendall Van Keuren-Jensen (PI) 07/01/2019 – 06/30/2022
W81XWH1910277 $1,116,000
Dept of the Army (USA MRC)
Genotypic and phenotypic examination of disease pathogeneis in C9orf72 FTD

Kendall Van Keuren-Jensen (PI) 01/01/2018 – 12/31/2021
TGen Foundation $150,228
Developing Molecular Signatures for ALS to Understand and Predict Disease Progression

Kendall Van Keuren-Jensen (PI) 04/12/2019 – 10/11/2021
Grant 16521 $212,501
Michael J Fox Foundation for Parkinson's Research
Extracellular vesicles from urine are enriched in brain transcripts and have potential as noninvasive biomarkers

Kendall Van Keuren-Jensen (PI) 09/01/2019 – 08/31/2023
1UG3CA241703 (Raffai/Mateescu/Van Keuren-Jensen) $684,990
NIH/NCI/Northern California Institute
P.R.I.S.M. : Purification of exRNA by Immuno-capture and Sorting using Microfluidic

Kendall Van Keuren-Jensen (PI) 09/01/2019 – 08/31/2023
1UG3TR002878 (Das/Talisman/Van Keuren-Jensen) $841,546
NIH/NCATS/Massachusetts General Hospital
Molecular dissection and imaging of extracellular vesicles to define their origin and targets

Kewei Chen (Co-I) 5/1/2014-3/31/2021
R01 AG031581 (Reiman/Caselli) $10,115,089
NIH/NIA
Brain Imaging, APOE, & the Preclinical Course of Alzheimer's Disease

Kewei Chen (Co-I) 04/01/2017-03/31/2023
R01 AG055444 (Reiman/Tariot/Lopera) $14,893,051 Total Project
NIH/NIA
Alzheimer's Prevention Initiative ADAD Colombia Trial

Kewei Chen (Co-I) 08/01/2017-07/31/2021
U19 AG024904 (Weiner) $400,000 Total Project
NIH/NIA via Northern California Institute Res & Educ.
Alzheimer's Disease Neuroimaging Initiative

Kewei Chen (Co-I) 07/01/2020-01/31/2023
R0 1AG059390 (Smith) $27,890 Total Project
NIH/NIA via Johns Hopkins University
Longitudinal Molecular Imaging of Neuropathology and Serotonin in Mild Cognitive Impairment

Kewei Chen (Co-I) 01/01/2021-12/31/2022
2R42AG053149-02 (Lure) $241,309 Total Project
NIH STTR via MS Technologies
Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

Kewei Chen (Co-I) 03/01/2021-02/28/2026
1R01AG070883 (Bendlin/Kind) $264,852 Total Project
NIH/NIA via University of Wisconsin-Madison
The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

Kewei Chen (Co-I) 07/01/2021-02/28/2023
R01 AG061122-01 (Didsbury) $14,256 Total Project
NIH/NIA via T3D Therapeutics
Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial of T3D-959 in Mild to Moderate Alzheimer's Disease Subjects

Kewei Chen (Core Co-Leader; Co-I) 07/01/2016-06/30/2022
P30 AG019610 (Reiman) $406,122 Total Project
NIH/NIA
Arizona Alzheimer's Disease Core Center – Data Management & Statistics Core

Kewei Chen (PI) 09/30/2020-03/31/2026
R01 AG069453 (Reiman/Su/Chen/Langbaum/Caselli) $27,473,070 Total Project
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Kewei Chen (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS via AARC
Advanced Image and Statistical Data Analysis Techniques for Detection and Monitoring of Alzheimer's and Related Disease

Kewei Chen (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $20,000 Total Project
State of Arizona DHS via AARC
Statistical and Neuroimaging Core Resources Serving the Consortium members for Alzheimer's disease and prevention related studies

Kewei Chen (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS via AARC
Resource to Support Computational Data Analysis and Collaborative Research

Klaus Romero (Contact PI) 09/05/2014-08/31/2024
5U18FDA005320-07 $10,435,769
Food and Drug Administration
CRITICAL PATH TO PUBLIC PRIVATE PARTNERSHIPS

Layla Al-Nakkash (Consultant) 04/1/18-03/31/21
NIH-R15 $470,124
Physical activity as a therapeutic intervention in endometriosis

Layla Al-Nakkash (Co-PI) 07/01/19-06/30/20
Midwestern University One Health Research Stimulus Award $10,000
Effects of calcitriol on leukocyte cytokine production in dogs with type 1 diabetes mellitus

Layla Al-Nakkash (PI) 01/01/19-6/30/20
Diabetes Action and Research Foundation $10,000
High fat diet-induced diabetes is abolished by combined genistein and exercise treatment: identifying the mechanisms

Layla Al-Nakkash (PI) 07/01/19-06/30/20
Arizona Alzheimer's Consortium $24,896
Diabetic obesity results in cognitive impairment: evaluation of the relationship between inflammation, and senescence in the gut-brain axis and the response to genistein and exercise treatment

Layla Al-Nakkash (PI) 07/01/19-06/30/20
Midwestern University Intramural Grant $5,000
Assessment of the effects of genistein and exercise on intestinal physiology in high fat-high sugar fed mice

Layla Al-Nakkash (PI) 01/01/21-12/31/21
Diabetes Action and Research Foundation $10,000
Ability of 12-weeks moderate exercise and/or genistein (soy) to reverse hyperglycemia, fatty liver disease and microbiome changes induced by chronic consumption of high fat high sugar diet

Layla Al-Nakkash (PI) 07/01/20-06/30/21
Arizona Alzheimer's Consortium $11,153
Reversal of diabetic obesity with dietary modifications and/or exercise results in improved cognitive ability, inflammation, senescence and thus mitigation of AD-like pathology

Lee Ryan (PI) 07/01/20 – 06/30/21
State of Arizona, DHS Grant $8,225 TC
Assessing the Impact of COVID-19 on Cognitive Functions

Lee Ryan (PI) 07/01/20 – 06/30/21
State of Arizona, DHS Grant $30,000 TC
Assessing medial temporal lobe network integrity using high resolution fMRI

Lih-Fen Lue (Co-I) 07/01/2018-06/30/2022
5P30AG019610-21 (Reiman) $1,261,052 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Neuropathology Core

Lih-Fen Lue (Project Co-I) 07/01/2020–06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $69,333 Total Project
AZ DHS CTR040636 via AARC
A Human Brain Single-Cell Suspension Resource

Lori Nisson (Project Co-) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $25,000 Total Project
AZ DHS via AARC
Native American Outreach, Recruitment, and Retention Program

Matthew Grilli 07/01/20 – 06/30/21
State of Arizona, DHS Grant $10,000 TC
Transcranial Magnetic Stimulation for Mild Cognitive Impairment

Matthew Grilli (PI) 7/1/20 – 6/30/21
AZ Dept Health Services / Arizona Alzheimer's Consortium $20,000 TC
Autobiographical memory, future thinking, and neuropsychology in Hispanics

Matthew Grilli (PI) 7/1/19 – 6/30/21
R03 AG060271 $153,500 TC
NIH/NIA
The episodic autobiographical memory hypothesis of preclinical Alzheimer's disease: Developing a new approach for early cognitive detection and measurement of Alzheimer's disease.

Matthew Grilli (PI) 9/15/20–8/30/21
R56 AG068098 (Grilli/Andrews-Hanna) $642,211 TC
NIH/NIA
Tracking autobiographical thoughts: a smartphone-based approach to the detection of cognitive and neural markers of Alzheimer's disease risk.

Matthew Grilli (Sponsor) 09/18/2020-11/17/2022
F31 AG069443 (Acevedo Molina) $45,520 (Annual DC)
NIH/ NIA
Aging and autobiographical memory in bilingual and monolingual Hispanics

Matthew Huentelman (Co-I) 07/01/2016-06/30/2021
P30 AG019610 (Reiman) $127,442 Total Project
NIH/NIA
Arizona Alzheimer's Disease Core Center

Matthew Huentelman (Co-I) 06/01/2020 - 06/30/2021
3P30 AG019610-20S1 (Reiman) $86,199 Total Project
NIH/NIA
Arizona Alzheimer's Disease Core Center- (COVID-19 Supplement)

Matthew Huentelman (Co-I) 09/21/2016 - 08/31/2021
UG30D023313 (Deoni) $604,625 Total Project
NIH
The Developing Brain: Influences and Outcomes

Matthew Huentelman (Co-I) 05/15/2017 - 04/30/2022
R01 AG054180 (Kaczorowski) $100,700 Total Project
NIH
Systems Genetics of Cognitive Aging and Alzheimer's Disease

Matthew Huentelman (Co-I) 09/01/2019 - 08/31/2023
W81XWH1910534 (Schwedt) $1,247,594 Total Project
DOD
A mulitidisciplinary translational approach to investigate the mechanisms, predictors and prevention of persistent post traumatic headache

Matthew Huentelman (Co-I) 09/01/2023 - 08/31/2024
2R01MH097803-06A1 (Gallitano) $255,767 Total Project
NIH
Environmental Regulation of Cortical Gene Expression and Circuit Function

Matthew Huentelman (Co-I) 05/01/2020 – 04/30/2025
R01 AG067781 (Rogalski) $397,866 Total Project
NIH
Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease

Matthew Huentelman (Co-I) 09/01/2019-08/31/2021
R56AG045571 (Rogalski) $104,500 Total Project
NIH (Northwestern University)
Exceptional Cognitive Aging: Neuropsychologic, Anatomic and Pathologic

Matthew Huentelman (Co-I) 09/01/2017 – 11/20/2021
Grant#20170715 (Padilla) $71,370 Total Project
Aging Minds Foundation
Early Onset Alzheimer's Disease Genomic Study

Matthew Huentelman (Co-I) 10/01/2019-05/31/2021
DARPA (Broderick) $46,103 Total Project
HR001119S0021-MBA-FP-002 (BTO)
Peerless Operator Biologic Aptitude (Peerless)

Matthew Huentelman (Co-Mentor) 04/06/2020 - 03/31/2022
1K99HD099307 (Lewis) $0 Total Project
NIH
Host DNA methylation as a mechanism of microbiome influence on internalizing behavior

Matthew Huentelman (Co-PI) 08/07/2019 – 08/06/2021
SOW 33 PO# 67513702 (Vargas) $71,255 Total Project
Mayo Clinic, Arizona
Characterizing Chemo-Radiotherapy Treatment–related cardiac changes

Matthew Huentelman (Co-PI) 05/23/2019-05/21/2021
RP 29 AVM (Zabramski) $47,646 Total Project
St. Joseph's Hospital and Medical Center
Genetics of Arteriovenous Malformations

Matthew Huentelman (PI) 03/01/2020-06/30/2021
TGen Foundation $1,925,000
Gene Surgery

Matthew Huentelman (TGen PI) 07/01/2020 - 06/30/2021
CTR04636-AAC-DHS $43,333 Total Project
AAC - State of Arizona, DHS (Reiman)
Common genetic polymorphisms associated with exceptional verbal memory performance in aging.

May Khanna 07/01/20 – 06/30/21
State of Arizona, DHS Grant $20,000 TC
Developing an Alzheimer Drosophila model co expressing TDP-43 and Tau

Meredith Wicklund (PI) 07/01/2020-06/30/2021
AARC $39,717
Collection of biofluids and generation of cell lines from AD and FTD patients

Meredith Wicklund (PI) 07/01/20-06/30/2021
AARC $37,389
Hispanic Enrollment in Alzheimer's Research Trials (the HEART Program at BNI)

Michael Malek-Ahmadi (Co-I) 09/15/2007-06/30/2022
1RF1AG057547-01 (Kantarci/Gleason) $466,457 Total Project
NIA/NIA via Mayo Clinic
Prevention of Alzheimer's disease in women: risks and benefits of hormone therapy

Michael Malek-Ahmadi (Core Leader; Co-I) 04/01/2020-03/31/2025
P01AG014449 (Mufson) $793,090 Total Project
NIH/NIA via Dignity Health
Neurobiology of Mild Cognitive Impairment in the Elderly

Michael Malek-Ahmadi (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS via AARC (Su)
Advanced Image and Statistical Data Analysis Techniques for Detection and Monitoring of Alzheimer's and Related Disease

Michael Malek-Ahmadi (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $20,000 Total Project
State of Arizona DHS via AARC (Su)
Statistical and Neuroimaging Core Resources Serving the Consortium members for Alzheimer's disease and prevention related studies

Michael Malek-Ahmadi (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS via AARC (Su)
Resource to Support Computational Data Analysis and Collaborative Research

Minsub Shim (PI) 12/01/19-11/30/22
R15CA246429 $450,000
NIH/NCI
Cyclooxygenase-2 signaling in cell senescence and its role in chemotherapy-induced long-term adverse sequelae

Minsub Shim (PI), Layla Al-Nakkash (Co-PI), Tom Broderick (Co-PI) Arizona Alzheimer's Consortium 07/01/19-06/30/20
$28,702
Exercise-mediated mitigation of cellular senescence as a peripheral control mechanism for Alzheimer's disease risk

Mitra Esfandiarei (PI) 01/15/19-12/31/21
R15HL145646 $441,049
NIH/NHLBI
Targeting endothelial function in a genetic mouse model of aortic aneurysm: implications for prevention and therapy

Mitra Esfandiarei (PI) 10/1/18-9/30/23
MOP-111266 $750,000
Canadian Institutes of Health Research (CIHR)
The role of endothelial function in the pathogenesis and management of Marfan syndrome-associated aortic disease

Nadine Bakkar (PI) 07/1/2020-06/30/2021
AARC $70,560
Comparative transcriptomics of the blood-CSF barrier in frontotemporal dementia (FTD), Alzheimer's disease and Amyotrophic lateral sclerosis (ALS)-FTD

Nafisa Jadavji (PI) 01/01/20-12/31/21
20AIREA35050015 $152,735
American Heart Association Research Enhancement Award (AIREA)
Identification of developmental factors involved in ischemic stroke outcomes in adulthood and old age

Nafisa Jadavji (PI) 07/1/20-06/30/21
Arizona Alzheimer's Consortium $8,510
Identification of developmental factors involved in ischemic stroke outcomes in adulthood and old age

Paul Coleman (PI) 8/1/14 – 5/31/21
R01 AG049464 (Alexander/Barnes/Coleman) $2,435,845 (TC)
Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain

Pierre Tariot (Co-I) 09/01/2019-06/30/2024
R01 AG063954 (Langbaum/Bleakley) $8,793,374 Total Project
NIH/NIA
Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials

Pierre Tariot (PI) 04/01/2017-03/31/2023
1R01AG055444 (Reiman/Tariot/Lopera) $14,893,051 Total Project
NIH/NIA
Alzheimer's Prevention Initiative ADAD Colombia Trial

Pierre Tariot (PI) 09/01/2018-11/30/2024
R01 AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/Tariot) $32,005,950 Total Project
NIH/NIA
API / A4 Alzheimer's Prevention Trial

Richard Caselli (Consortium PI) 07/01/16-06/30/21
P30 AG019610 (Reiman) $18,962
NIH/National Institute on Aging
Arizona Alzheimer's Disease Core Center - Data Core

Richard Caselli (Consortium PI) 07/01/16-06/30/21
P30 AG019610 (Reiman) $18,962
NIH/National Institute on Aging
Arizona Alzheimer's Disease Core Center - Administrative Core

Richard Caselli (Consortium PI) 08/01/2020-07/30/2022
R21AG065942-01 (Wang) $23,081
NIH/NINDS/Arizona State University
Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transportation

Richard Caselli (Consortium PI) 09/01/2016-06/30/2022
R01 AG054048-05 (Sierks) $168,429
NIH/Arizona State University
Protein Variants as Blood-based Biomarkers for Diagnosing and Staging AD

Richard Caselli (PI) 07/01/2020-03/31/2026
R01AG069453 (Reiman/Caselli/Su/Chen/Langbaum) $1,634,948
NIH/NIA
APOE in the Predisposition To, Protection From, and Prevention of Alzheimer's Disease

Richard Caselli (PI) 07/01/20-06/30/21
ADHS12-010553 (Caselli)
Arizona Department of Health Services
Normal and Pathological Aging (Preclinical Alzheimer's Disease)

Richard Caselli (PI/Core Leader) 07/01/16-06/30/21
P30 AG019610 (Reiman) $191,728
NIH/National Institute on Aging
Arizona Alzheimer's Disease Core Center - Clinical Core

Rita Sattler (Co PI) 09/01/20 – 08/31/22
R21 NS115514-01A1 (Zarnescu) $150,000
NIH NINDS
Mechanisms underlying the protective role of glycolysis

Rita Sattler (Mentor) 07/01/20 – 06/30/21
Postdoctoral Fellowship (Gittings) $85,000
Barrow Neurological Foundation

Rita Sattler (PI) 03/01/21 – 02/28/23
Department of Defense $300,000
Targeting Synapse Loss in ALS/FTD using spine regenerating compound

Rita Sattler (PI) 07/01/19-06/30/22
Department of Defense $500,000
Genotypic and Phenotypic Examination of Disease Pathogenesis in C9orf72 FTD

Rita Sattler (PI) 08/01/20 – 07/31/21
Robert Packard Center for ALS Research $50,000
Role of microglia in C9orf72 ALS/FTD

Rita Sattler (PI) 12/01/20 – 11/20/21
Moffat Family $65,000
The role of TDP-43 proteinopathy in Lewy Body Dementia

Rita Sattler (PI) 07/2020 – 06/2022
Valley Research Partnership $49,640
Interplay between C9orf72 ALS and neurotropic viruses: Impact on viral and ALS disease pathogenesis

Rita Sattler (PI) 07/01/20 – 06/30/21
Arizona Alzheimer’s Research Consortium $54,850
Synapse loss in frontotemporal dementia (FTD): Validation by immunohistochemistry in FTD/ALS patient post-mortem tissues and PET imaging in a FTD mouse model

Rita Sattler (PI) 11/01/19 – 08/31/21
R01 Supplement award (NCE) $377,974
NIH NINDS
RNA Dysregulation in neurodegeneration

Rita Sattler (PI) 01/01/20 – 12/31/21
Fein Foundation $1,000,000
Studies of disease mechanisms and biomarker development for FTD

Rita Sattler (PI) 07/01/18 – 05/31/21
Department of Defense $250,000
Small molecules targeting TDP43-RNA interaction in ALS

Robert Wilson (PI) 04/2018 – 09/2020
McKnight Brain Research Foundation $110,000 TC
Vulnerability of Older Adults to Financial Deception Schemes

Robert Wilson (PI) 1/1/19-8/30/24
R01 AG061888 $1,765,250 TC
NIH/NIA
Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults

Roberta Brinton (Co-I) 5/2020 – 4/2024
U01 AG063768 (Rodgers) $1,533,089 annual TC
NIH/NIA
IND Enabling Studies for RASRx 1902, a Novel Mas Receptor Agonist, for Treatment of Cognitive Impairment in Patients at Risk for Alzheimer's Disease

Roberta Brinton (PI) 07/01/2019-06/30/2024
R25 NS107185 (Rodgers/Boyd/Brinton) $240,032
NIH/NINDS
Undergraduate Readying for Burgeoning Research for American Indian Neuroscientists

Roberta Brinton (PI) 08/15/2019-04/30/2025
R01 AG063826 (Brinton/Rodgers/Schneider) $7,524,944
NIH/NIA
Allopregnanolone as Regenerative Therapeutic for Alzheimer’s: Phase II Clinical Trial

Roberta Brinton (PI) 06/15/2014-06/30/2021
U01 AG047222 $325,823
NIH/NIA
Allopregnanolone a Regenerative Therapy for Alzheimer’s: FDA-Required Toxicology

Roberta Brinton (PI) 08/01/2018-06/30/2023
R01 AG059093 (Kaddurah-Daouk/Brinton/Chang/Kastenmuller) $152,046
NIH/NIA/Duke University
Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment

Roberta Brinton (PI) 08/15/2006-05/31/2026
R01 AG026572 $3,439,358
NIH/NIA
Perimenopause in Brain Aging and Alzheimer's Disease

Roberta Brinton (PI) 03/15/2017-02/28/2022
R01 AG053589 $205,000
NIH/NIA
Aging & Estrogenic Control of the Bioenergetic System in Brain

Roberta Brinton (PI) 9/2018 – 8/2023
T32 AG061897 $300,250 annual TC
NIH/NIA
Translational Research in AD and related Dementias (TRADD)

Roberta Brinton (PI) 09/01/2018-05/31/2023
R01 AG057931 (Brinton/Chang/Mosconi) $1,285,307
NIH/NIA
Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype

Roberta Brinton (PI) 04/01/2019-03/31/2022
18PTC-R-590498 $636,363
Alzheimer's Association (ALZ ASSC)
Advancing Allopregnanolone as a Regenerative Therapeutic for Alzheimer's

Roberta Brinton (PI) 12/18/2020-07/31/2021
R43 AG063674 (Ossanna/Brinton/Crockett) $105,479
NIH/NIA/Proneurogen, Inc.
Novel Formulations of Allopregnanolone To Treat Alzheimer's Disease

Sarah Stabenfeldt (PI) 01/01/2021-11/30/2025
R01 NS116657 (Stabenfeldt/Sirianni)
HHS-NIH-NINDS (R01)
Exploiting sex-dependent brain injury response for nanoparticle therapeutics

Sarah Stabenfeldt (PI) 04/01/15-03/31/21
1454282
NSF-CBET
CAREER: Elucidation and modulation of chemotactic signaling after brain injury

Sarah Stabenfeldt (PI) 04/01/19-03/31/21
R21 AG063358 (Brafman/Stabenfeldt)
HHS-NIH-NIA
A Pluripotent Stem Cell-Based Model to Investigate the Mechanisms of TBI-Induced AD

Sarah Stabenfeldt (PI) 04/01/18-03/31/21
ADHS18-198843
AZ Dept of Health Services
Regenerative rehabilitation for traumatic brain injury

Sarah Stabenfeldt (PI) 06/01/18-05/31/21
R21 NS107985 (Stabenfeldt/Sirianni)
HHS-NIH-NINDS
Nanotherapeutics to alleviate neuroinflammation after TBI

Sarah Stabenfeldt (Sub PI) 07/01/19-06/30/21
Arizona Alzheimer's Consortium (Coon)
Injury-induced neuroinflammation as a contributor to Alzheimer's Disease

Stephen Rapcsak (Co-I) 7/1/16 - 6/30/21
P30 AG019610 (Rieman) $921,067 (TC)
NIH/NIA
Arizona Alzheimer's Disease Core Center (UA Clinical Core)

Stephen Rapcsak (Co-I) 07/01/2018-03/31/2023
R01NS102220 (Chen) $346,550
NIH/NINDS
Development of High-Speed and Quantitative Neuro MRI Technologies for Challenging Patient Populations

Stephen Rapcsak (Co-I) 05/01/20-04/30/25
R01AG062543-01A1 (Chou) $3,629,385
NIH/NIA
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation

Stephen Rapcsak (PI) 03/01/2017-02/28/2021
Horizon 20/20 (Rapcsak) $350,000
European Union/Horizon
Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioral Neurology

Sydney Schaefer 12/2018-11/2021
F31 AG062057 (Lingo VanGilder) $125,485
NIH/NIA
Using diffusion tensor imaging to identify the structural neural correlates of visuospatial and motor skill learning processes

Sydney Schaefer 6/1/2020 - 5/31/2022
AGR 5/21/20 (Wang) $2,000
North American Society for the Psychology of Sport and Physical Activity (NASPSPA)
Modifying Motor Skill Learning via Neuromodulation of Frontoparietal Networks

Sydney Schaefer 9/1/2020 - 9/1/2021
104-2020 (Wang) $2,000
Arizona State University Foundation (ASUF)
Frontoparietal coherence as EEG-neurofeedback training target for enhancing motor learning

Sydney Schaefer (PI) 01/2021-12/2021
Global Sport Institute Seed Grant, Arizona State University $20,000
Gender differences in expectancy effects of transcranial direct current stimulation on motor performance

Sydney Schaefer (PI) 09/2018-05/2021
R03 AG056822 $156,729
NIH/NIA
Using standardized visuospatial tests to predict motor training responsiveness in older adults

Sydney Schaefer (Sub PI) 7/1/2020 - 6/30/2021
LTR 07/14/20 (Coon) $16,000
Arizona Alzheimer's Consortium
Arizona Alzheimer's Consortium (AAC) FY21

Ted Trouard (Co-I) 8/01/19 – 4/30/24
R01 AG064587 (Bowers/Alexander/Woods) $499,966
NIH/NIA/University of Florida
Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation.

Ted Trouard (Co-I) 9/1/16 – 4/30/22
R01 AG054077 (Woods/Cohen/Marsiske) $184,020
NIH/NIA
Augmenting Cognitive Training in Older Adults

Ted Trouard (Co-I) 9/15/18-6/30/22
P30 AG019610 (PI: Reiman; Core Leader: Alexander) $928,035
NIH/NIA
Arizona Alzheimer’s Disease Core Center - Brain Imaging and Fluid Biomarkers Core

Ted Trouard (Co-I) 1/1/15-12/31/22
McKnight Brain Res. Foundation (Alexander, Cohen, Visscher, Wright) $310,587
McKnight Inter-institutional Neuroimaging Core and Brain Aging Registry

Ted Trouard (Co-I) 7/1/18-3/31/23
R01-NS102220 (Chen) $428,723
NIH/NINDS
Development of High-Speed and Quantitative Neuro MRI Technologies for Challenging Patient Populations

Ted Trouard (Institutional PI) 4/1/20-3/31/21
1R43 AG067894-01 (Unger) $315,455
NIH/NIA
Targeted ultrasound contrast agents for the disruption of Alzheimer's plaques.

Ted Trouard (PI) 07/01/20-06/30/21
State of Arizona, DHS Grant $30,000 TC
Novel Imaging and Therapy in Rodent Models of Aging and Alzheimer's Disease

Ted Trouard (PI) 04/01/17 – 03/31/22
ADHS16-00005489 (Trouard)
Arizona Biomedical Research Commission

Thomas Beach (Co-I) 12/01/2018-11/30/2021
RF1AG029479 (Mukherjee) $40,633 Total Project
NIH R01 via University of CA-Irvine
PET Imaging Agents for a4b2 Nicotinic Receptors

Thomas Beach (Co-I) 09/17/2020-08/31/2021
1R56AG066782 – 01 (Fu) $43,544 Total Project
NIH R01 Resubmission via Ohio State University
The role of ectodermal-neural cortex 1 in selective vulnerability in aging and Alzheimer's disease

Thomas Beach (Co-I) 09/01/2020-08/31/2021
R56NS117465 (Volpicelli-Daley) $43,171 Total Project
NIH via University of Alabama – Birmingham
Alpha-synluclein aggregate induced synapse loss is a pathological event contributing to Lewy body dementias

Thomas Beach (Co-I) 09/15/2020-08/31/2021
1R01AG062479-01 (Kosik) $122,600 Total Project
NIH R01 via University of California – Santa Barbara
The complex interaction between Alzheimer's drivers and aging

Thomas Beach (Co-I) 10/01/2020-09/30/2021
ASAP-000301 $38,827 Total Project
ASAP MJFF via BWH (Scherzer)
Parkinson5D: deconstructing proximal disease mechanisms across cells, space, and progression

Thomas Beach (Co-I) 06/01/2021-05/31/2022
7R01AG068331 – 02 (Ebbert) $39,622 Total Project
NIH via Mayo Clinic – Jacksonville
Using long-range technologies as a multi-omic approach to understand Alzheimer's disease in brain tissue

Thomas Beach (Co-I) 10/15/2019-10/14/2020
17636 (Crary) $22,202 Total Project
MJFF via Mount Sinai
Screening & quantification of peripheral α-synuclein pathology using artificial intelligence

Thomas Beach (Co-I) 02/15/2020-01/31/2021
1U19AG065156-01 (MacCos) $50,229 Total Project
NIH via University of Washington
Next Generation Translational Proteomics for Alzheimer's and Related Dementias

Thomas Beach (Co-I) 06/01/2020 – 05/31/2021
5U01NS112010-02 (Zou) $35,576 Total Project
NIH via Case University
Assessing skin biomarkers for preclinical diagnosis of PD and non-PD Parkinsonism

Thomas Beach (Co-I) 08/01/2017 – 06/30/2021
NOMIS Foundation via Banner Alzheimer's Foundation $395,695 Total Project
A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Regions, Associated Whole Genome Sequencing, Longitudinal Clinical and Neuropathological Data, and Cell-Specific Multi-Scale Networks in the Alzheimer's and Aging Brain

Thomas Beach (Consultant) 10/08/2019-04/30/2022
5R33HL137081-05 (Kepler) $59,068 Total Project
NIH R33 via Boston University
The B cell repertoire as a window into the nature and impact of the lung virome

Thomas Beach (Consultant) 05/17/2021-05/16/2023
2I01BX003767-05 (Migrino) $30,000 Total Project
Phoenix VA Health Care System
Discovering novel mechanisms for aging-related dementia: probing medin and abeta vasculopathy

Thomas Beach (Consultant) 04/01/2017-03/31/2021
Carl T. Hayden Medical Research Foundation (Migrino) $30,000 Total Project
Discovering novel mechanisms for aging-related dementia: probing medin and abeta vasculopathy

Thomas Beach (Co-PI) 09/01/2020-08/31/2024
Gates Ventures via Banner Alzheimer's Foundation $3,085,720 Total Project
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

Thomas Beach (Core Leader; BSHRI PI) 07/01/2016-06/30/2022
5P30AG019610-21 (Reiman) $1,261,052 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Neuropathology Core

Thomas Beach (PI) 06/23/2016-04/01/2022
MJFF-020674 (Beach) $532,948 Total Project
MJFF
Systemic Synuclein Sampling Study

Thomas Beach (PI, Neuropathology Core) 07/01/2020-06/30/2022
3P30AG019610-20S1 (Reiman) $386,476 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center - Presence and Neuropathological Consequences of CNS Covid-19 in Consecutive Autopsies During the Worldwide Pandemic

Thomas Beach (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $43,333 Total Project
AZ DHS CTR040636 via AARC (Lue)
Patient-based postmortem fibroblast banking for translational research

Thomas Beach (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $40,926 Total Project
AZ DHS CTR040636 via AARC (Atri)
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Thomas Beach (Project Co-I) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $17,333 Total Project
AZ DHS CTR040636 via AARC (Shprecher)
Laying the Groundwork for Prodromal Lewy Body Dementia Research in REM Sleep Behavior Disorder

Thomas Beach (Project Co-PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $69,333 Total Project
AZ DHS CTR040636 via AARC (Serrano)
A Human Brain Single-Cell Suspension Resource

Thomas Beach (Project PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $89,074 Total Project
AZ DHS CTR040636 via AARC (Beach)
Developing a Shared Resource of CSF, Plasma, Serum, PBMC samples from Arizona's Longitudinal Brain and Body Donation and APOE4 Gene Dose Program

Thomas Beach (Site Leader) 09/01/2015-08/31/2020
Avid Radiopharmaceuticals $1,856,602 Total Project
Dr. Beach is Leader of the Central Neuropathology Site for this imaging-to-autopsy Phase III clinical trial of a tau PET imaging agent for diagnostic usage

Thomas Broderick (Co-I) 04/15/21-04/14/23
Phoenix VA Healthcare System $28,760
Protocol assessment for aerobic exercise training of rats

Vanthida Huang (PI) 06/01/20-06/30/21
Shionogi & Co, Ltd $6,000
Shionogi BMD US Surveillence Program

Vanthida Huang (PI) 12/01/20-11/30/21
Allergan, LLC $164,208 (value of)
In vitro Activity of Ceftaroline Alone and in Combination with Daptomycin at High and Low Doses Against Methicillin-resistant Staphylococcus aureus in an in vitro Pharmacodynamic Model

Vanthida Huang (PI) 07/01/20-06/30/21
Midwestern University Intramural Funds $8,000
In vitro Activity of Ceftaroline Alone and in Combination with Daptomycin at High and Low Doses Against Methicillin-resistant Staphylococcus aureus in an in vitro Pharamcodyanmic Model

Wei Zhou (PI) 07/01/20-06/30/21
State of Arizona, DHS Grant $20,000 TC
Cognitive Effects of Carotid Disease and Carotid Intervention

Yalin Wang (PI) 8/1/2020-7/31/2022
R21AG065942 $444,976
HHS: National Institute of Health (NIH)
Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transport

Yalin Wang (PI) 6/1/2016-5/31/2021
RF1AG051710 (Ye/Thompson/Wang) $792,315
NIH/University of Michigan
Multi-Source Sparse Learning to Identify MCI and Predict Decline

Yalin Wang (PI) 9/21/2019-6/30/2021
000012699-A $66,513
Children’s Hospital Los Angeles
Predicting the Early Childhood Outcomes of Preterm Brain Shape Abnormalities

Yalin Wang (PI) 9/22/2017 – 6/30/2021
000013013-A $156,995
Children's Hospital Los Angeles
Influence of APOE4 Genotype on Neonatal Cortical Morphology

Yalin Wang (Project PI) 7/1/2020-6/30/2021
Arizona Alzheimer's Consortium (Coon) $20,000
State of Arizona
FY21 Arizona Alzheimer's Disease Consortium

Yalin Wang (Sub PI) 9/22/2017 – 6/30/2021
R01EB025032 (Lepore) $430,915
NIH/Children's Hospital Los Angeles
Predicting the early childhood outcomes of preterm brain shape abnormalities

Yi Su (Co-I) 04/01/2019-3/31/2021
R01 AG031581 (Reiman/Caselli) $10,115,089 Total Project
NIH/NIA
Brain Imaging, APOE, & the Preclinical Course of Alzheimer's Disease

Yi Su (Co-I) 7/01/2019-6/30/2021
BNI Grant ID BAI33132 (Stokes) $37,813 Total Project
Dignity Health
Multi-Scale MRI Assessment of Neurovascular Factors Associated with AD

Yi Su (Co-I) 07/01/2018-06/30/2022
P30 AG019610 (Reiman) $406,122 Total Project
NIH/NIA
Arizona Alzheimer's Disease Core Center – Data Management & Statistics Core

Yi Su (Co-I) 07/01/2018-06/30/2022
P30 AG019610 (Reiman) $8,948,605 Total Project
NIH/NIA
Arizona Alzheimer's Disease Core Center – Brain Imaging & Fluid Biomarker Core

Yi Su (Co-I) 04/15/2018-03/31/2023
R01 AG055444 (Reiman/Tariot/Lopera) $14,893,051 Total Project
NIH/NIA
Alzheimer's Prevention Initiative ADAD Colombia Trial

Yi Su (Co-I) 09/01/2018-11/30/2024
R01 AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/Tariot) $32,005,950 Total Project
NIH/NIA
API / A4 Alzheimer's Prevention Trial

Yi Su (Co-I) 05/01/2019-04/30/2022
U54 MD000507 (Manson/Buchwald) $178,067 Total Project
NIH/NIMHH via University of Colorado Denver
American Indian and Alaska Native Health Disparities

Yi Su (Co-I) 09/30/2017-7/31/2022
U19 AG024904 (Weiner) $400,000 Total Project
NIH/NIA via Northern California Institute Res & Educ.
Alzheimer's Disease Neuroimaging Initiative

Yi Su (Co-I) 07/01/2019-12/31/2021
ASU Grant ID PG08347 $137,334 Total Project
Arizona State University
A novel motor task as a non-invasive, rapid, low cost biomarker to predict early cognitive declines associated with preclinical Alzheimer's disease.

Yi Su (Co-I) 01/01/2021-12/31/2022
2R42AG053149 (Lure) $241,309 Total Project
NIH STTR via MS Technologies
Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

Yi Su (Co-I) 08/01/2020-05/31/2022
1R21AG065942 (Wang) $17,230 Total Project
NIH/NIA via Arizona State University
Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transportation

Yi Su (Co-I) 12/01/2020-11/30/2022
5U01NS093334 (Stern) $112,381 Total Project
NIH/NIA via Boston University
Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors

Yi Su (Co-I) 03/01/2021-02/28/2022
1R01AG061122-01 (Didsbury) $14,256 Total Project
NIH/NIA via T3D Therapeutics
Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial of T3D-959 in Mild to Moderate Alzheimer's Disease Subjects

Yi Su (PI) 09/30/2020-03/31/2026
1 R01 AG069453-01 (Reiman) $27,473,070 Total Project
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Yi Su (PI) 10/01/2017-9/30/2021
AARG17532945 (Su) $150,000 Total Project
Alzheimer's Association
Amyloid PET as a biomarker for white matter integrity in Alzheimer disease

Yi Su (PI) 7/1/2017-6/30/2021
BrightFocus ADR A2017272S (Su) $300,000 Total Project
BrightFocus Foundation
Blood Brain Barrier and Metabolism in Aging and Alzheimer Disease

Yi Su (Project PI) 07/01/2020-6/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS via AARC
Advanced Imaging and Machine Learning in Alzheimer's Research

Yi Su (Project PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $20,000 Total Project
State of Arizona DHS via AARC
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

Yi Su (Project PI) 07/01/2020-06/30/2021
Arizona Alzheimer's Research Consortium (Reiman) $45,000 Total Project
State of Arizona DHS via AARC
Resource to Support Computational Data Analysis and Collaborative Research

Ying-hui Chou 07/01/20 – 06/30/21
State of Arizona, DHS Grant $10,000 TC
Transcranial Magnetic Stimulation for Mild Cognitive Impairment

Ying-hui Chou (Co-I) 9/2020 – 8/2022
U01 EB029834 (Witte) $6,880 (Chou)
NIH/NIBIB
4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents

Ying-hui Chou (Co-I) 9/2019 – 8/2021
Department of Defense (US Army Med Res Acquisition Activity) $30,699 (Chou)
(Kilgore)
Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep

Ying-hui Chou (PI) 5/2020 – 4/2025
R01 AG062543 $735,125 annual TC
NIH/NIA
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation

Pending Grants

Alireza Atri (Co-I) 04/01/2022-03/31/2027
1R01AG077165-01 Beach) $3,929,131 Total Project
NIH
Neuropathological Consequences and Viral Brain Persistence after SARS-CoV-2 Infection in Consecutive Autopsies from a Longitudinal Clinicopathological Study of Aging and Neurodegenerative Disorders.

Alireza Atri (Co-I) 04/01/2022-03/31/2027
R01 TBD (Pascoal) $1,846,490 Total Project
NIH via University of Pittsburgh
Plasma prospectively predicting PET positivity (P5 Study)

Alireza Atri (Core Co-Leader; Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,300,085 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Clinical Core

Alireza Atri (Core Co-Leader; Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,984,211 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Biomarker Core

Alireza Atri (Site PI) 12/01/2021-11/30/2026
R01 TBD (Boxer) $639,360 Total Project
NIH/NIA via University of California, San Francisco
Biomarker Evaluation in Young Onset Dementia from Diverse Populations (BEYONDD)

Andrew Hooyman (PI) 07/2021-06/2024
F32 AG071110-01A1 $211,182
NIH/NIA
Using an Online Video Game to Predict Functional and Cognitive Decline within the MindCrowd Electronic Cohort

Ashley Stokes (Co-I) 07/01/2021-06/30/2026
R01AG070987 (Weinkauf) $554,631
NIH/NIA
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk

Ashley Stokes (PI) 12/01/2021-11/30/2026
R01NS124575 $250,000
NIH/NINDS
Multi-scale functional connectivity in preclinical models of Parkinson's disease

Ashley Stokes (PI) 09/01/2021-08/31/2023
R21NS125535 $136,113
NIH/NINDS
Investigating the role of cerebral perfusion in demyelination and repair in multiple sclerosis with MRI

Ben Readhead 7/1/2021-6/30/2026
1P30AG072980-01 (Reiman) $3,165,929
HHS: National Institutes of Health (NIH)
Arizona Alzheimer's Disease Research Center (ADRC)

Ben Readhead 9/1/2021-8/31/2026
1R01NS124803-01 (Mastroeni) $525,513
HHS: National Institutes of Health (NIH)
Membrane Attack Complex and Vascular Contributions to Dementia

Ben Readhead 9/1/2021-8/31/2026
FP00028652 $7,599
Icahn School of Medicine at Mount Sinai
Spatiotemporal proteomic profiling of AD models during aging and therapeutic drug modulation

Ben Readhead (PI) 9/1/2021-8/31/2026
1R01AG076016-01 $603,770
HHS: National Institutes of Health (NIH)
Multiscale networks of the brain microbiome, adaptive immunity, and host transcriptomics in Alzheimer’s disease

Carol Barnes (PI) 7/1/21 – 6/30/26
NIH/NIA R01 AG003376 $6,141,273 TC
Neurobehavioral Relations in Senescent Hippocampus

Carol Barnes (PI) 7/1/21 – 6/30/26
NIH/NIA U19 AG065169 $60,014,605 DC
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

Christine Belden (Co-I) 07/01/2020-06/30/2025
1R01 NS118669-01 (Beach) $3,195,450 Total Project
NIH/NINDS
Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

Christine Belden (Neuropsychologist) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,300,085 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer’s Disease Research Center – Clinical Core

Danielle Goldfarb (Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,984,211 Total Project
NIH/NIA via ASU
Arizona Alzheimer's Disease Research Center – Biomarker Core

David Brafman (PI) 07/01/2021-06/30/2023
R21 AG070406
NIH-NIA
Using hiPSCs to investigate the protective mechanisms of the ApoEch mutation

David Brafman (PI) 09/01/2021 - 08/31/2023
R21AG075612
NIH-NIA
Elucidating the protective effects of the KL-VS variant using isogenic hiPSCs

David Brafman (PI) 09/01/2021 - 08/31/2023
R21AI166422
NIH-NIA
Using isogenic hiPSCs to study the relationships between APOE isoforms, SARS-CoV-2 infection, endosomal dysfunction, and neural cell responses

David Brafman (PI) 09/01/2021 - 08/31/2026
R01AG075786
NIH-NIA
Investigating APOE2 modulation of amyloid precursor protein processing and AB uptake

David Brafman (PI) 7/1/2021-6/30/2023
FP00024963_Res1 University of Arizona $5,452
Daily Stressor, health, and emotion regulation among Hispanic and non-Hispanic white dementia caregivers

David Coon 7/1/2021-6/30/2026
2 R01 AG043392-07 (Yu) $635,640
NIH | NIA
Precision Medicine in Alzheimer's Disease: A SMART Trial of Adaptive Exercises and a Biomarker Signature to Maximize Aerobic-Fitness and Cognitive Responses to Aerobic Exercise

David Coon 7/1/2021-6/30/2024
FP00027457 Televeda Services LLC | NIH (Maxfield) $97,668
Development and assessment of user-friendly virtual activities promoting older adults' engagement to reduce risk for AD/ADRD and social isolation

David Coon 8/1/2021-7/31/2022
FP00028308 National Science Foundation (Zhao) $96,413
SCC-PG: Getting the Edge on Data-Driven Self-Managed Care: A focus on Older Veterans in Arizona

David Coon (Core Leader) 7/1/2021-6/30/2026
1 P30 AG072980-01 (Reiman) $3,165,929
NIH | NIA
Arizona Alzheimer's Disease Research Center (ADRC)
Outreach, Recruitment and Engagement Core (ORE Core)

David Coon (PI) 7/1/2021-6/30/2026
FP00018621_Res1 University of Arizona $313,060
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

David Shprecher (Co-I) 07/01/2021–06/30/2025
1R01 NS118669-01 (Beach) $3,195,450 Total Project
NIH/NINDS
Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

David Weidman (Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,300,085 Total Project
NIH/NIA
Arizona Alzheimer’s Disease Research Center – Clinical Core

Don Saner (Co-I) 09/01/2021-03/31/2022
R01 AG055444 (Reiman/Tariot/Lopera) $302,205 Total Project
NIH/NIA
Alzheimer’s Prevention Initiative ADAD Colombia Trial – Administrative Supplement

Don Saner (Core Co-Leader) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $1,312,710 Total Project
NIH/NIA
Arizona Alzheimer’s Disease Research Center – Data Management & Statistics Core

Dona Locke (Co-I) 07/01/21-06/30/26
P01 (Reiman/Caselli) $1,092,795
NIH/NIA
Arizona Alzheimer’s Disease Research Center

Douglas Jennewein (PI) 9/1/2021-8/31/2023
Mayo Clinic Rochester $4,392,780
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

Emily Cope (PI), J. Gregory Caporaso (PI) 07/01/2021-06/30/2023
PAR-19-071 $412,414
Toward a mechanistic link between Alzheimer's Disease and the gut microbiome using quantitative Stable Isotope Probing.

Eric Reiman (Co-I) 07/01/2021-6/30/2026
U01 AG016976 Competitive Renewal (Kukull) $200,000 Total Project
NIH/NIA via University of Washington
National Alzheimer's Coordinating Center

Eric Reiman (Co-I) 05/01/2021-04/30/2025
NIH OTA via UA (Nikolich) $77,511 Total Project
UNITED AGAINST COVID – Arizona Post-Covid Cohort Consortium (AZPCCC)

Eric Reiman (Co-I) 09/01/2021-08/31/2026
P01 AG052350 (Zlokovic/Toga) $1,015,500 Total Project
NIH/NIA via USC
Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer's disease

Eric Reiman (Co-I) 04/01/2022-03/31/2027
1R01AG073424-01A1 (Su) $3,873,822 Total Project
NIH/NIA
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

Eric Reiman (OSC) 07/01/2021-06/30/2026
R01AG070987 (Weinkauf) $0 Total Project
NIH
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk

Eric Reiman (PI) 07/01/2021-06/30/2026
1P30AG072980-01 $15,727,555 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center

Geidy Serrano (Co-I) 07/01/2020-06/30/2025
1R01 NS118669-01 (Beach) $3,195,450 Total Project
NIH/NINDS
Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

Geidy Serrano (Co-I) 04/01/2021–03/31/2026
1R01AG072643 – 01 (PI: Barnes) $40,875 Total Project
NIH R01 via University of Arizona
NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease

Geidy Serrano (Co-I) 04/01/2022-03/31/2027
1R01AG077165-01 (Beach) $3,929,131 Total Project
NIH
Neuropathological Consequences and Viral Brain Persistence after SARS-CoV-2 Infection in Consecutive Autopsies from a Longitudinal Clinicopathological Study of Aging and Neurodegenerative Disorders.

Geidy Serrano (Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,984,211 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Biomarker Core

Geidy Serrano (Core Co-Leader; Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $1,636,000 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Neuropathology Core

Gene Alexander (Co-I) 7/1/21-6/30/26
NIA R01 AG070987 (Weinkauf) $4,910,992 TC
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk

Gene Alexander (Core Leader, Biomarker Core) 7/1/21-6/30/26
NIA PAG 072980A (Reiman) $4,984,210 (Biomarker TC)
Arizona Alzheimer's Disease Research Center

Gene Alexander (PI) 9/01/21-8/31/26
NIA R01 AG072445 (Alexander/Raichlen/Klimentidis) $3,422,710 (TC)
Inactivity, Sedentary Behavior, and the Risk for Alzheimer's Disease in Middle Aged to Older Adults

Heather Bimonte-Nelson (Co-I) 04/01/2022-03/30/2027
FP26320 (Gipson-Reichardt) $166,194
University of Kentucky (NIH/NIDA)
Nicotine Reward Circuitry: Impact of Ovarian Hormones and Contraceptive Estrogen

Heather Bimonte-Nelson (Co-I) 04/01/2022-03/31/2024
FP29306 (Gipson-Reichardt) $32,299
NIH
Contributions of Progestins Independently and Interactively with Contraceptive Estrogen to Nicotine Use and Glutamate Plasticity

Heather Bimonte-Nelson (Co-I) 05/01/2022-04/30/2026
2138385 (Conrad) $1,051,522
NSF
Collaborative Research: Steroid Mechanisms on Prefrontal Cortex and Hippocampal Behaviors

Heather Bimonte-Nelson (Core Co-Leader) 07/01/2-21-06/30/2026
P30 AG019610 (Reiman) $15,727,544 Total Project
NIH/NIA
Arizona Alzheimer's Disease Research Center – Research Education Component

Hillary Protas (Co-I) 12/01/2021-11/01/2026
RFA-MH-21-105 $254,134 Total Project
NIA/NIH via Johns Hopkins
Molecular Imaging of Neuropathology and Serotonin in the Menopause Transition

Hillary Protas (Co-I) 04/01/2022-03/31/2027
R01AG073424 (Su) $3,873,822 Total Project
NIH/NIA
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

Ileana Ratiu (PI) 07/01/21-06/30/24
NIH R15 $428,076
The Impact of Mild Traumatic Brain Injuries and Naturalistic Auditory Distraction on Reading: An Eye-Tracking Investigation

Jeremy Pruzin (Co-I) 04/01/2026-03/31/2027
R01 TBD (Yu) $281,491 Total Project
NIH via ASU
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

Jessica Andrews-Hanna (Collaborator) Submitted Spring 2021
Social Sciences Humanties Research Council (Kam) $73,434 CAD TC
How does mind wandering impact affective well-being? A study on adults across the age spectrum with varying features of attention-deficit/hyperactivity disorder

Jessica Langbaum (Co-I) 04/01/2022-03/31/2027
R01 TBD (Pascoal) $1,846,490 Total Project
NIH via University of Pittsburgh
Plasma prospectively predicting PET positivity (P5 Study)

Jessica Langbaum (Core Co-Leader; Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 $1,836,125 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Administrative Core

Jessica Langbaum (Core Co-Leader; Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 $381,080 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Outreach and Recruitment Core

John Fryer (Co-I) 07/01/21 – 06/30/2026
1R01NS122174
R01 (Aaron Johnson PI, Mayo Clinic Rochester)
NIH/NINDS

Jonathan Lifshitz (PI) 11/01/2020 – 10/31/2025
IK6 RX003678 $798,361
U.S. Dept. of Veterans Affairs
RR&D Research Career Scientist Award Application

Jonathan Lifshitz (PI) 04/01/2021 – 03/31/2026
R01 NS122025 (Lifshitz/Kodibagkar/Stabenfeldt) $3,432,218
National Institutes of Health
Towards High Resolution Imaging of Brain Hypoxia Post Traumatic Brain Injury

Jonathan Lifshitz (PI) 04/01/2021 – 03/30/2023
R21 DA053682 (Lifshitz/Law) $422,125
National Institutes of Health
Deciphering the Impact of Cannabis Sativa Active Compounds on Neurobehavior Across Development of the Juvenile Rat

Jonathan Lifshitz (PI) 04/01/2021 – 03/31/2023
I21 RX003741 $230,000
Veterans Administration
Cognitive Rehabilitation Biomarker Discovery

Jonathan Lifshitz (PI) 07/01/2021 – 06/30/2026
R01 NS118853 (Lifshitz/Stabenfeldt) $4,001,211
National Institutes of Health
Precision Targeting of the Rod Microglia Variant in Neurological Disease

Jonathan Lifshitz (PI) 07/01/2021 – 06/30/2025
R01 NS120380 (Lifshitz/Subbian) $2,996,910
National Institutes of Health
Analytical Modeling of Acquired Neurological Injury with Rich Experimental Data Sets

Jonathan Lifshitz (Steering Committee/Core Deputy Director) 10/01/2021 – 09/30/2026
$3,733,351
Department of Veterans Affairs (Whaley-Connell)
Truman VA TBI Resource Center (TVA TBIRC)

Jose Hernandez (Co-PI) 07/01/21-06/30/23
Arizona Biomedical Research Center (ABRC) $446,495
Elucidating the role of *Rhipicephalus sanguineus* (the Brown dog tick) as a vector for Rocky Mountain Spotted Fever (RMSF) transmission in Arizona

Judith Su (Co-I) 12/1/21 – 11/30/26
NIH $703,635 TC
Prediction and experimental validation of the 3D Structure, Ligand Binding, G-Protein signaling, and beta-arrestin signaling of Human Bitter Taste Receptors

Judith Su (Co-I) 09/01/21 – 08/31/26
NIH $1,523,925 TC
Multi-Scale Sensing Platform for AI-Empowered Early Detection of Pathogenic Microbes

Judith Su (PI) 09/01/21 – 08/31/26
NIH $692,562 TC
Discovery of novel COVID-19 therapeutics using virtual screening followed with direct binding and cell assays

Kendall Van Keuren-Jensen (Co-I) 07/01/2020 – 06/30/2022
WS00479364 (Broderick) $681,216
Office of Naval Research
FY 20 Congressional Proposal: Evaluating the Benefits of Intranasal Oxytocin Administration on Human Performance and Metabolism under Extreme Conditions

Kendall Van Keuren-Jensen (Co-I) 04/01/2020 – 03/31/2022
R21NS116385-01 (Medina) $73,173
NIH
Novel knock-in mouse models of ALS and myopathy-linked Matrin 3 mutations

Kendall Van Keuren-Jensen (Co-I) 08/01/2020 – 07/31/2022
Grant (Bowser) $42,235
Muscular Dystrophy Association
Novel Mouse Models of ALS and Myopathy-linked Matrin 3 Mutations

Kendall Van Keuren-Jensen (Co-I) 06/01/2021 – 05/31/2025
FY20-PRMRP-IIA (Thlacker-Mercer) $87,830
DOD
Impact of Serine and Glycine on Age-Related Skeletal Muscle Deterioration

Kendall Van Keuren-Jensen (Co-I) 04/01/2021 – 03/31/2026
R01 NIH (Sattler) $712,500
Mechanisms of A-I RNA editing-dependent mislocalization of TDP-43

Kendall Van Keuren-Jensen (Co-I) NIH R01 (Bowser) Transforming ALS therapeutics via precision engineering of AAV specific for glial subtypes	07/01/2021 – 06/30/2026 $974,813
Kendall Van Keuren-Jensen (Co-I) NIH P50 (Ehringer) Translational Center on the Genetics of Nicotine Dependence	07/01/2021 – 06/30/2026 $841,267
Kendall Van Keuren-Jensen (Co-I) NIH R01 Defining a phenotypic switch in microglia that protects against neurodegeneration in C9orf72 FTD/ALS	09/01/2021 – 08/31/2026 $125,000
Kendall Van Keuren-Jensen (PI) NIH R01 (Sattler) Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD	04/01/2021 – 03/31/2026 $1,615,000
Kendall Van Keuren-Jensen (PI) NIH U01 A rigorous approach to assess biomarkers in small biopsies and plasma borne extracellular vesicles	04/01/2021 – 03/31/2026 $142,500
Kendall Van Keuren-Jensen (PI) NIH R01 (Sattler) Mechanisms of TDP-43 proteinopathy in AD and related dementias	07/01/2021 – 06/30/2026 $994,617
Kewei Chen (Co-I) 1P30AG072980-01 (Reiman) NIH/NIA via Arizona State University Arizona Alzheimer's Disease Research Center – Biomarker Core	07/01/21-06/30/26 $4,984,211 Total Project
Kewei Chen (Co-I) R21 TBD (Yoo) NIH via UA Daily stressors and health among Hispanic and non-Hispanic white dementia caregivers: the role of emotion regulation	07/01/2021-06/30/2023 $13,321 Total Project
Kewei Chen (Co-I) R01 AG055444 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative ADAD Colombia Trial – Administrative Supplement	09/01/2021-03/31/2022 $302,205 Total Project

Kewei Chen (Co-I) 04/01/2026-03/31/2027
R01 TBD (Yu) $281,491 Total Project
NIH via ASU
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

Kewei Chen (Co-I) 04/01/2022-03/31/2027
1R01AG073424-01A1 (Su) $3,873,822 Total Project
NIH/NIA
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

Kewei Chen (Core Leader; Co-I) 07/01/21-06/30/26
1P30AG072980-01 (Reiman) $1,312,710 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Data Management & Statistics Core

Kewei Chen (PI) 09/01/2021-08/31/2026
R01 TBD $1,040,000
NIH via ASU (Wang/Chen)
Integrating Deep Learning and Bayesian Networks for Improved MRI Utility in Predicting Beta-Amyloid and Tau Burden in Place of Expensive PET Techniques

Layla Al-Nakkash (PI) 12/01/21-11/30/24
NIH R15 $435,300
Role of genistein to influence growth and intestinal function in cystic fibrosis mice

Lee Ryan (Co-I) 04/12/21 – 04/11/25
NIH/NIA (Deoni) $2,093,591 TC
Life-course examination of genetics and neural development (LEGEND) following COVID-19 Infection

Lee Ryan (PI) 04/01/21 – 03/31/22
NIH/NIA (Ha/Ryan)
IND Enabling Studies for a Novel Mas Receptor Agonist for Treatment of Cognitive Impairment in Patients at Risk for Alzheimer's Disease Related Dementia (Admin Supplement)

Lee Ryan (PI) 07/02/21 - -06/30/24
NIH/NIA (Parthasarthy/Ryan) $1,544,276 TC
Angiotensin-(1-7): An Adjunct Protective Therapy for treating COVID-19 in Older Adults at Risk for Alzheimer's Disease Related Dementias

Lih-Fen Lue (Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $1,636,000 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Neuropathology Core

Matthew Huentelman (Co-I) 10/2020-09/2025
1R01AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $708,101 Total Project
NIH/NIA
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Matthew Huentelman (Co-I) 04/01/2021 – 03/31/2026
NIH R01 (Barnes) $1,298,796 Total Project
NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease

Matthew Huentelman (Co-I) $538,219 Total Project
R61/R33 (Deoni) 11/01/2020 – 10/31/2024
NIH
Deciphering phenotypes predictive of pediatric SARS-CoV-2 symptoms, severity, recovery and outcomes.

Matthew Huentelman (Co-I) 07/01/2021 – 06/30/2026
P30 continuation (Reiman) $84,470 Total Project
NIH
Arizona Alzheimer's Disease Core Center

Matthew Huentelman (Co-I) 07/01/2024 – 06/30/2026
NIH R01 (Madhavan) $277,925 Total Project
Stem Cell Mechanisms of Resilience in Brain Aging and Alzheimer's Disease

Matthew Huentelman (Co-I) 07/01/2021 – 06/30/2024
NIH R01 (Hays) $513,239 Total Project
Angiotensin-(1-7): An Adjunct Protective Therapy for treating COVID-19 in Older Adults at Risk for Alzheimer's Disease Related Dementias

Matthew Huentelman (Co-I) 09/01/2022 – 08/31/23
NIH R01 (Levine) $12,206
Internet-delivered management of chemotherapy-induced peripheral neuropathy (CIPN): Outcomes and Exploration of Mechanisms.

Matthew Huentelman (Co-I) 07/01/2020-06/230/2025
NIH R01/R56 (Grilli) $16,500
Tracking autobiographical thoughts: a smartphone-based approach to the detection of cognitive and neural markers of Alzheimer's disease risk

Matthew Huentelman (Co-I) NSF (Madhavan) Neural Stem Cell Mechanisms of Resilience across the lifespan	10/01/2023 – 09/30/2025 $151,108
Matthew Huentelman (Co-I) NIH R01 (Hale) Targeting Resident Cardiac Fibroblast Subpopulations for Protection Against Fibrosis	09/01/2021 – 08/31/2026 $845,457
Matthew Huentelman (Co-I) ADRC (Velazquez) Neuronal Rbbp7 as a mediator against tau pathology in Alzheimer's disease	07/01/2022-06/30/2023 $92,632
Matthew Huentelman (Co-I) NIH OTA-21-015B (Ryan) UNITED AGAINST COVID – Arizona Post-COVID Cohort Consortium (AZPCCC)	04/12/2021 – 04/11/2025 $3,592,667
Matthew Huentelman (Co-I) NIH R01 (Deoni) Assessing the Cumulative Impact of Early Life Substance and Environment Exposure on Child Neurodevelopment and Health	09/01/2021- 08/31/2026 $1,050,010
Matthew Huentelman (Co-I) G01 (Velasquez) ASU Foundation Glyphosate Exposure as a Risk Factor for Cognitive Aging and Alzheimer's Disease	10/01/2020 – 09/30/2021 $29,231
Matthew Huentelman (Multi-PI) NIH OTA-21-015B (Deoni) Life-course examination of genomics, affect, and neurocognitive changes following COVID-19 Infection: the LEGACI cohort	04/12/2021 – 04/11/2025 $23,290,717
Matthew Huentelman (Project 1 Lead, Core D Co-Lead, Core G Lead) NIH (Barnes) Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	07/01/2021 – 06/30/2026 $17,707,915
Matthew Huentelman (Project 2 and Core G Lead) NIH U19 (Rogalski/Geula) Study to uncover pathways to exceptional cognitive resilience in aging (SUPERAging)	07/01/2021 – 06/30/2026 $4,468,896 Total Project
May Khanna NIH R01 GM17486 Structural Elucidation of RNA Binding to TDP-43 and Splice Variants	Submitted 3/11/21 $1,918,750 TC

May Khanna 3/31/21 – 8/31/26
NIH/NIA R01 AG071601 $1,572,039 TC
TDP-43/Tau: Disrupting a novel brain target interaction using chemical probes for Alzheimer's disease

Meredith Wicklund (Co-I) 07/01/21-06/30/26
1P30AG072980-01 (PI: Reiman) $350,000
NIH/NIA via Arizona State University
Arizona Alzheimer’s Disease Research Center – Clinical Core

Michael Malek-Ahmadi (Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $1,312,710 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer’s Disease Research Center – Data Management & Statistics Core

Michael Malek-Ahmadi (PI) 04/01/2022-03/31/2024
1R03AG077270-01 $174,308 Total Project
NIH
Cardiovascular Genotype and APOE ε4 Carrier Status Interaction Effects on Amyloid Load in Pre-Clinical Alzheimer's Disease

Mitra Esfandiarei (PI) 04/01/21-03/30/23
R21NS121498 $399,000
NIH
Cerebrovascular and neuropathophysiological vulnerability in a model of connective tissue disorders before and after traumatic brain injury

Mitra Esfandiarei (PI) 07/01/21-06/30/24
NF200076 $785,864
Department of Defense
Understanding mechanisms underlying vascular dysfunction in the mouse model of neurofibromatosis type 1: new approaches for prevention and therapy

Mitra Esfandiarei (PI) 07/01/21-06/30/24
R15 NS120153-01 $442,446
NIH/NINDS via Midwestern University
Identifying the role of maternal and postnatal dietary deficiencies on peripheral and cerebral vasculature and stroke outcome in middle and old-age offspring

Mitra Esfandiarei (PI) 01/01/21-12/31/22
Marfan Foundation $100,000
Severity of neuroinflammation and neurovascular/neurotransmission dysregulation after traumatic brain injury in a mouse model of Marfan syndrome

Nafisa Jadavji (Co-PI) 08/01/21-07/31/21
Burroughs Wellcome Fund $25,000
Developing a data-driven individualized development plan for the academic job market

Nafisa Jadavji (PI) 07/01/21-06/30/22
American Association of University Women $24,738
The impact of one-carbon metabolism supplementation on neuroplasticity using an *in vitro* model of stroke

Richard Caselli (Co-I) 09/01/2021-08/30/2026
FP00114606 $230,915
NIH / University of Southern California
Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer's Disease

Richard Caselli (Core Leader) 07/01/21-06/30/26
P01 (Reiman/Caselli) $1,092,795
NIH/NIA
Arizona Alzheimer's Disease Research Center

Richard Caselli (PI) 09/01/2021-08/30/2026
FP00115094 (Caselli/Wang) $180,600
NIH / Arizona State University
Integrating Deep Learning and Bayesian Networks for Improved MRI Utility in Predicting Beta-Amyloid and Tau Burden in Place of Expensive PET Techniques

Rita Sattler (Mentor) 07/01/21 – 06/30/23
Postdoctoral Fellowship (Gittings) $85,000
Milton Safenowitz Postdoctoral Fellowship
ALS Association

Rita Sattler (PI) 04/01/21-03/31/26
R01 NS120331 $485,419
NIH/NINDS
Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD

Sarah Stabenfeldt (Co-I) 07/1/2021-6/30/2026
R01 NIH (Brafman)
RIPK1 as a Mediator of TBI-Induced Alzheimer's Disease

Sarah Stabenfeldt (PI) 07/01/2021-06/30/2026
R01 NIH (Lifshitz/Stabenfeldt)
Novel tools to probe the rod microglia variant in neurological disease

Sarah Stabenfeldt (PI) 7/1/2021-6/30/2023
R03 NIH (Stabenfeldt/Bowse)
Linking TBI secondary injuries to FTLD- and ALS-like neurodegeneration

Sarah Stabenfeldt (PI) 10/01/2021-09/30/2026
R01 NIH (Kodibagkar/Stabenfeldt)
Towards high resolution imaging of brain hypoxia post traumatic brain injury

Sydney Schaefer (Multi-PI) 7/1/2021 - 6/30/2026
R01 AG073630 (Schaefer/Peterson) $2,398,175
NIH/NIA
Using cognition to predict individual differences in motor learning for older adults with and without Parkinson's disease

Sydney Schaefer (PI) 07/2021-06/2022
R03 AG070658-01A1 $335,868
NIH/NIA
Validation of an unsupervised in-home motor assessment using the MindCrowd electronic cohort

Sydney Schaefer (PI) 4/1/2021 - 3/31/2026
R01 AG063890-01A1 $2,462,375
NIH/NIA
A novel motor task as a low-cost adjunct biomarker for preclinical Alzheimer’s disease

Teresa Wu (PI) 7/1/2021-6/30/2026
Iowa State University $1,694,749
Artificial intelligence innovation, modeling, and sensors to optimize aging (AIIMS)

Thomas Beach 10/01/2021-09/30/2022
U01 via Yale (Zhang) $246,952 Total Project
NIH
Single Cell Transcriptomic and Genomic Dissection of Parkinson's Disease

Thomas Beach 09/01/2021-08/31/2026
R01 via ASU (Sierks) $126,514 Total Project
NIH
The roles of individual brain cell protein variant and DNA signatures in Alzheimer's Disease

Thomas Beach 09/01/2021-08/31/2026
R01 via ASU (LaBaer) $335,126 Total Project
NIH
Multiscale networks of the brain virome, adaptive immunity, and host transcriptomics in Alzheimer's disease

Thomas Beach 07/01/2021-06/30/2026
1 P01 AG073082-01 (Corces) $200,576 Total Project
NIH P01 via UCSF Gladstone
Costs Decoding the Multifactorial Etiology of Neural Network Dysfunction in Alzheimer's Disease

Thomas Beach 07/01/2021– 06/30/2025
1R01 NS118669-01 (Beach) $3,195,450 Total Project
NIH/NINDS
Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

Thomas Beach 09/01/2021-08/31/2026
R01 via MGH (Kitchen) $99,427 Total Project
NIH
The role of isoform regulation and localization in cognitive resilience to Alzheimer's disease

Thomas Beach (Co-I) 07/01/2021-06/30/2026
R01 AG074221 (Sundermann) $128,786 Total Project
NIH/NIA
Sex differences in the clinical expression of Alzheimer's disease neuropathology and their underlying biological mechanisms

Thomas Beach (Co-I) 12/01/2021-11/30/2026
1 R01 NS122226-01A1 (PI: Bishop) $54,597 Total Project
NIH
Interrogating maladaptive serotonin raphe-striatal plasticity in L-DOPA-induced dyskinesia

Thomas Beach (Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,984,211 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Biomarker Core

Thomas Beach (Core Leader; Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $1,636,000 Total Project
NIH/NIA via Arizona State University
Arizona Alzheimer's Disease Research Center – Neuropathology Core

Thomas Beach (PI) 07/01/2021-06/30/2022
U01 via Stanford (Montine) $242,323 Total Project
NIH
Multi-omic sequencing of Parkinson's disease brain for biomarker discovery and therapeutic development

Thomas Beach (PI) 04/01/2022-03/31/2027
1R01AG077165-01 (Beach) $3,929,131 Total Project
NIH
Neuropathological Consequences and Viral Brain Persistence after SARS-CoV-2 Infection in Consecutive Autopsies from a Longitudinal Clinicopathological Study of Aging and Neurodegenerative Disorders.

Valentin Dinu (PI) 12/1/2021-11/30/2026
Iowa State University $1,694,749
Artificial intelligence innovation, modeling, and sensors to optimize aging (AIIMS)

Vanthida Huang (PI) 06/01/21-06/30/22
American Foundation for Pharmaceutical Education $5,000
Evaluation of the *in vitro* activity of eravacycline alone and in combination against *Acinetobacter baumannii* clinical isolates

Yalin Wang (PI) 7/1/2021-6/30/2026
HHS: National Institutes of Health (NIH) $1,947,064
Hierarchical Bayesian Analysis of Retinotopic Maps of the Human Visual Cortex with Conformal Geometry

Yalin Wang (PI) 9/1/2021-8/31/2026
HHS: National Institutes of Health (NIH) $3,202,396
Integrating Deep Learning and Bayesian Networks for Improved MRI Utility in Predicting Beta-Amyloid and Tau Burden in Place of Expensive PET Techniques

Yalin Wang (PI) 9/1/2021-8/31/2026
National Science Foundation (NSF) $350,000
CRCNS Research Proposal: Collaborative Research: Multivariate morphometry analysis for improved sMRI utility in predicting beta-amyloid and tau burden in place of invasive PET

Yalin Wang (PI) 7/1/2021-6/30/2026
Children's Hospital Los Angeles $233,081
Early joint cranial and brain development from fetal and pediatric imaging

Yalin Wang (PI) 9/1/2021-8/31/2026
University of California: San Diego $578,811
Cerebellar morphometry in the blind via tensor-valued and random field statistics

Yi Su (Co-I) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $1,312,710 Total Project
NIH/NIA via ASU
Arizona Alzheimer’s Disease Research Center – Data Management & Statistics Core

Yi Su (Co-I) 09/01/2021-08/31/2026
R01 TBD $1,040,000
NIH via ASU (Wang/Chen)
Integrating Deep Learning and Bayesian Networks for Improved MRI Utility in Predicting Beta-Amyloid and Tau Burden in Place of Expensive PET Techniques

Yi Su (Co-I) 04/01/2022-03/31/2027
R01 TBD $281,491
NIH via ASU
Precision Medicine in Alzheimer's Disease: A SMART Trial of Adaptive Exercises and their Mechanisms of Action Using AT(N) Biomarkers to Optimize Aerobic Fitness

Yi Su (Co-I) 09/01/2021-03/31/2022
R01 AG055444 (Reiman/Tariot/Lopera) $302,205 Total Project
NIH/NIA
Alzheimer's Prevention Initiative ADAD Colombia Trial – Administrative Supplement

Yi Su (Core Co-Leader) 07/01/2021-06/30/2026
1P30AG072980-01 (Reiman) $4,984,211 Total Project
NIH/NIA via ASU
Arizona Alzheimer's Disease Research Center – Biomarker Core

Yi Su (PI) 04/01/2022-03/31/2027
1R01AG073424-01A1 (Su) $3,873,822 Total Project
NIH/NIA
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques