



ANNUAL REPORT

July 1, 2018 to June 30, 2019

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Introduction to the Annual Report

Background

The Arizona Alzheimer's Consortium is the nation's leading model of statewide collaboration in Alzheimer's disease (AD) research. It includes more than 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, and from three 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, 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 are 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. It capitalizes on complementary resources and expertise from different disciplines and organizations to address scientific problems in the most impactful way. Its researchers receive critical support from the state of Arizona (through the Arizona Department of Health Services [ADHS]), the participating organizations, a competitive Arizona AD Core Center (ADCC) grant from the National Institute on Aging (NIA), and numerous other grants and contracts.

Eric M. Reiman, MD, is the Director of the Consortium and the NIA-sponsored ADCC, Richard Caselli, MD, is the ADCC's Associate Director, and Carol Barnes, PhD, chairs the Consortium's 26-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 ADCC grant, and 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 the Consortium and ADCC, and provide formal feedback and recommendations to the researchers, NIA, and state.

The Arizona Alzheimer's Consortium capitalizes on the state's strengths in brain imaging, genomics, the computational, mathematical and statistical analysis of complex data sets, the basic, cognitive and behavioral neurosciences, clinical and experimental therapeutics, and neuropathology research. It has made pioneering contributions to the scientific understanding, 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, it has provided data, biological samples and interested research participants for researchers inside the state and around the world, and it has

introduced promising new care models for patients and family caregivers. It continues to attract new researchers and clinicians, and to support other biomedical research developments in the state. Indeed, it has helped to make 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 framework 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. As one of our advisors observed, Arizona has become known around the world for its courage, groundbreaking organizational and scientific paradigms, and ability to make things happen in the fight against AD.

The Arizona ADCC has received continuous competitive NIA grant funding since 2001. The ADCC’s Administrative, Clinical, Data Management and Statistics, Neuropathology, and Outreach and Recruitment Cores, a Research Education Component (REC), and a competitive Pilot Project Program have supported researchers and projects inside and outside of the state. In July 2016, the ADCC received its fourth consecutive five-year renewal grant, after being noted for its exceptional track record, productivity and impact, its outstanding scientific contributions, regional, national, and international initiatives, and impact, its effective leadership and collaborative model, impressive commitments from the state and each of our participating organizations, and its leadership roles in the fight against AD. In July 2018, the ADCC received a competitive supplement to establish a critically needed Brain Imaging and Fluid Biomarker Core.

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 more than 5,000 publications, 1,000 research grants and contracts, and roughly \$2 billion in new investments.

Consortium researchers have made pioneering contributions to the study of AD, related disorders, and the aging mind and brain:

1. They have helped to clarify genetic and non-genetic risk factors and disease mechanisms, offered targets at which to aim new AD treatments, provided new insights about the pathological changes associated with AD and related disorders, and introduced promising ways to treat and prevent AD.
2. During the past year, our researchers and their colleagues have made significant contributions to the potential roles of microbial (and related neuroinflammatory contributions) and APOE (the major genetic risk factor) to the development and potential treatment and prevention of AD.
3. They have provided invaluable public resources of longitudinal, neuropathological, and gene expression data for the field; they have begun to provide a new resource of DNA and RNA sequencing data from different brain cell types and regions in brain donors with and without AD; and they have used these and other resources to implicate disease networks, risk factors, and potential drivers at which to aim new AD treatments.
4. 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, [4](https://c-</div><div data-bbox=)

path.org/programs/cpad/); and on-line memory tests and other information that has been generated in >110,000 participants in a program called MindCrowd (www.mindcrowd.org).

5. 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, and 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 provided the foundation needed to launch a new era in AD prevention research.

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

7. They have played leadership roles in brain imaging and other research studies to detect, track and study AD and related disorders starting many years before the onset of symptoms, assess genetic and non-genetic risk factors, and introduce image analysis methods to address these goals with improved power. They have played leadership roles in the effort to validate amyloid and 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 put promising cerebrospinal fluid (CSF) assays, blood tests, and mobile technologies to the test as soon as possible. For instance, they and their collaborators recently used PET to demonstrate traumatic encephalopathy (CTE) and the absence of AD in living former professional football players.

8. They continue to provide a world-leading scientific resource of longitudinal and neuropathological data, brain and body tissues for the study of AD, Parkinson's disease, and related disorders in their Brain and Body Donation Program—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. With major NIA, philanthropic donations and industry support, they established the Alzheimer's Prevention Initiative (API) to launch a new era in AD prevention research, establish the shared sense of urgency, scientific means, accelerated approval pathway, enrollment resources, public-private partnerships, and vetting mechanisms needed to rapidly test promising prevention therapies in unimpaired persons at genetic or biomarker risk. API includes a Colombian prevention trial of an anti-amyloid treatment in the world's ADAD kindred, an international prevention trial of two other anti-amyloid treatments in persons at highest genetic risk for AD in older persons, and a new NIA grant to support a proposed prevention trial of an amyloid plaque-busting treatment. These trials are intended to provide better tests of the amyloid hypothesis (the leading AD theory at this time) than failed trials of anti-amyloid treatments that have been reported in the later clinical stage of the disease, including in persons at genetic risk who have not yet demonstrated biomarker evidence of amyloid plaque burden, and groundbreaking clinical trial data and sample sharing agreements. They also provide the best fighting chance to find and support the approval of an effective prevention drug by 2025.

10. API also includes exceptionally large registries and related programs to support enrollment in AD prevention trials and related studies. It includes a Colombian API Registry with nearly 6,000 mutation carriers and non-carriers from the world's largest ADAD kindred, the North American Alzheimer's Prevention Registry with >350,000 members (www.endALZnow.org), GeneMatch (a national resource of more than >85,000 members who permitted us to characterize their APOE genotypes 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, other shared resources and collaborations to assist in this effort. Furthermore, they continue to conduct state-supported collaborative research studies to advance new ideas, find those that have the greatest impact, and generate the findings, publications and grants to have the maximum public impact. They continue to generate new findings, publications in the highest impact 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.

With the glaring exception of disappointing clinical trial findings (see below), the past year has been marked by great progress in the scientific fight against AD here in Arizona and around the world. We have contributed to the neuropathological validation of a tau (neurofibrillary tangle) PET method in persons with AD and used it to detect modest but scientifically meaningful evidence of CTE in living NFL players. We and our colleagues have contributed to the discovery of promising CSF and blood-based biomarkers; we have advanced the effort to provide a common resource of fluid samples to put to the test the promising amyloid blood tests and other fluid biomarkers recently developed by other groups as soon as possible; and we have used plasma neurofilament light measurements to detect and track neurodegeneration starting several years before the clinical onset of AD in an unusually large number of ADAD mutation carriers and non-carriers. We have generated new information about the mechanism and impact of APOE variants on the vulnerability or resistance to AD, leveraged invaluable cohorts that we helped established several years ago to do so, including new targets at which to aim APOE-modifying therapies. We demonstrated the value of applying big-data analyses to the genome-wide analysis of inherited and expressed genes in brain donors with and without AD; we galvanized interest in the evaluation of infectious contributions to the predisposition to AD; and we continue to advance a push-pull relationship between big-data analyses of omics data from human research participants and experimental data from cellular and animal models to discovery of AD mechanisms, risk factors, and new treatments. We continue to secure major grants, contracts, and philanthropic investments, recruit new researchers at most of our organizations, develop new clinical programs, and seek to address the needs of our under-represented and under-served Latino and Native American communities. We have continued to advance current and new AD prevention trials, including what may be the best tests of the amyloid hypothesis and the best chance to find an effective prevention therapy by 2025.

Challenges, Opportunities, and New Initiatives

Despite global progress in AD research, the past year has been marked by disappointing findings from several trials of anti-amyloid treatments, primarily in clinically affected patients. Nearly 100% of AD clinical trials have failed since 2002, causing stakeholders to ask what comes next. Here, we briefly summarize some of the challenges, opportunities and ongoing or planned initiatives we have in mind to address them:

Putting the amyloid hypothesis to the best possible test and providing the best chance to find and support the approval of a prevention therapy by 2025: We previously argued that while confirmation of an amyloid-modifying treatment's clinical benefit in impaired patients would be a game-changer, supporting amyloid's role in the development, treatment, and potential prevention of AD, we also noted that negative findings would not exclude the possibility that the right anti-amyloid treatment might have a beneficial effect prior to clinical onset in cognitively unimpaired persons at genetic or biomarker risk and, in particular, prior to biomarker evidence of amyloid plaque deposition in cognitively unimpaired persons at genetic risk (Reiman, Nature 2017). API has several ongoing and proposed studies of anti-amyloid therapies, three of which are noted here: 1) The API ADAD trial is evaluating the oligomeric amyloid antibody drug crenezumab in unimpaired therapy (in Colombian ADAD mutation carriers, more than half of whom do not yet have a positive amyloid PET scan. This trial will provide a better test of this putative anti-oligomeric amyloid-modifying treatment than the recently declared futile trial of this drug in clinically affected patients. 2) API Generation Study 1 is evaluating the relatively selective BACE1 inhibitor umibecestat in cognitively unimpaired APOE4 homozygotes (i.e., persons at the highest genetic risk for sporadic AD), more than a third of whom are estimated to not yet have a positive amyloid PET scan. If this BACE inhibitor continues to be distinguished from other BACE inhibitors by the absence of early non-progressive cognitive worsening, it will provide a better test of the amyloid hypothesis than the failed BACE-inhibitor trials in clinically affected patients—and with an orally administered drug that reduces the productivity of different amyloid species.3) In September 2018, API and A4 received a large NIA grant to support the evaluation of the amyloid plaque-clearing antibody aducanumab in unimpaired amyloid positive older adults. We proposed to initiate the trial prior to the completion of the Phase 3 trials of aducanumab, such that positive findings would have permitted us to support the qualification of the trials' theragnostic biomarkers endpoints as surrogate endpoints and seek approval of the prevention therapy by 2023—and that negative findings would cause us to continue to evaluate the trial using clinical endpoints, such that there was a chance to support their approval of this treatment by 2025. Given aducanumab's recently reported futility findings in clinically affected patients, we will work with Biogen to consider the safety, tolerability, and possible evaluation of this drug in our originally planned prevention trial, consider alternative plaque-busting treatments as well, and consider refinements in the study design to give this treatment the best possible test. 4) We continue to communicate with our colleagues from the Dominantly Inherited Alzheimer's Network about their options for their proposed "primary prevention study of an anti-amyloid treatment in young adult ADAD mutation carriers." If it turns out all of these interventions fail to demonstrate a clinical benefit, that would provide invaluable information for the field. If any of the treatments work, it would provide the best chance to find and support the approval of a prevention therapy by 2025.

Diversifying the portfolio of promising AD treatments. Whether or not the amyloid hypothesis is refuted, there is an urgent need to diversify the portfolio of promising treatments. We believe there are new opportunities to do just that, even though it is likely to take additional years to demonstrate their clinical benefit. We will be taking a multi-faceted approach to address this urgent need: 1) As briefly noted in last year's report, we are using high-quality brain tissue from our Brain and Body Donation Program to develop a public resource of RNA and DNA sequencing data from different brain cell types and regions in 100 AD cases and controls, and we are actively

involved in the development and analysis of complementary omics data in the Accelerated Medicines Partnership for AD (AMP-AD). We have recruited leaders in the big-data analysis of these omics data sets, such that we can discover multi-scale networks, drivers of these networks, and repurposed or new drugs for this fundamentally human disease, and put them to the test in relevant cellular, animal, and other experimental models. Conversely, we can use the human data sets to clarify the extent to which novel findings from the experimental models are relevant to the human disease. This push-pull relationship between experimental and human data, along with close collaborations with other groups, will be a defining feature of two of our developing translational research programs. 2) As summarized in two AAIC abstracts (and unpublished manuscripts), we have new data to suggest that the right APOE-modifying treatments could have a more profound impact than previously believed, and that its impact is not simply related to the abundance of amyloid plaques. We have initiated several collaborations to put these ideas to the test—and we predict that APOE-modifying will become an increasing focus of attention in the next few years. 3) Meantime, Arizona researchers continue to explore other approaches to the treatment and prevention of AD in translational, and to a lesser extent, early phase studies including those that target metabolic, mitochondrial, hormonal, tau, neuroinflammatory, and/or hormonal processes. We have commitments to support the recruitment of researchers at several Arizona institutions. 4) There will also be opportunities to extend API's prevention trials to emerging anti-tau therapies and combination therapies.

Appealing to our industry partners to remain engaged in the fight against AD and related diseases. Now more than ever, public-private partnerships and NIA funding are needed to give makers of promising treatments the courage and conviction to stay the course despite so many disappointments in clinical trials and do so in innovative yet rigorous ways. We are well positioned to advance that effort in both the drug discovery and drug development effort.

Brain Aging Research. Arizona researchers continue to play a leadership role in the study of the normal aging brain and the continued promotion of healthy aging. This effort is reflected by the UA's McKnight Research Program, a wide range of studies in unimpaired older and younger adults, non-human primates, laboratory rodents, and other models, studies of aging in the MindCrowd Program, promising drug development efforts, and a recently submitted U19 grant to support further advancement of these and other ambitious efforts.

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 and biological fluid samples to characterize amyloid, tau, neurodegenerative and cerebrovascular disease burden, and when available other neurodegenerative (e.g., synuclein and TDP-43) pathologies. Unfortunately, brain imaging biomarkers are too expensive to use on all of our participants, lumbar punctures for existing and emerging CSF assays are relatively invasive and somewhat limited in availability, and promising blood tests remain to be further clarified. We have invested in several initiatives to address this challenge: 1) We are implementing efforts to significantly reduce the cost per radiotracer dose of our amyloid and tau radioligands by arranging for multiple scans from a single dose, having two identical PET/CT scanners available for research studies at the same time. 2) We secured competitive revisions for our ADCC Brain Imaging and Fluid Biomarker Core and APOE Cohort Study, and recently generated "A/T(N)" findings from a large number of APOE4 homozygotes, heterozygotes, and non-carriers in collaboration with Mayo Clinic Rochester, and we are investing significant state and institutional resources to support the acquisition of brain imaging and fluid biomarkers in as many Brain and Body Donation participants as possible. 3) We have begun to acquire an ample supply of blood samples in our longitudinal cohorts, helped our NCRAD colleagues secure an administrative supplement to acquire an ample supply of blood samples from 3,000 AD Center participants, and are working with NCRAD and other co-PIs to

submit a proposed AD Center Fluid Biomarker Initiative to provide a rapidly accessible, less depletable resource of blood (and to a lesser extent CSF) samples to further develop, test, and compare promising fluid biomarkers, and aim to support the approval of an amyloid blood test within the next 3-4 years. 4) We have introduced the possibility of an amyloid blood test screening program for our next prevention trial in collaboration with makers of a promising scalable assay. 5) We continue to make significant investments in the development of our ADCC, APOE, and API data management programs to provide a shared resource of data, images, samples, and analyses for researchers inside and outside of Arizona. 5) We are contributing to the development of observational and clinical trial data sharing programs through the Collaboration for Alzheimer's Prevention (CAP) and the recent NIH AD Summit.

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 ADCC Clinical Core and other research programs. 1) We have begun to capitalize on interactions with the Strong Heart Stroke Study and University of Washington AD Center Native American Satellite Core, contribute to the acquisition of genetic and MRI data, analysis of brain imaging, other biomarker and cognitive data, and mentorship of young investigators. 2) We are working with (and play a leadership role in) the UA-Banner All of Us Research Program, which has already enrolled >26,000 persons, including >8,400 and 1,400 Hispanic and Native American participants, respectively. 3) We plan to develop and maintain an active cohort of at least 100 Native American and 100 Hispanic research participants in our clinical core by July 2020.

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, other outreach, educational and research internship programs for students from a wide range of ages and backgrounds, and support for their participation in our Consortium's Annual Conferences and recent research retreat. We will further develop these research education and training programs over the next year.

Looking Ahead

During the next few years, we and our colleagues will continue to develop several new scientific and clinical initiatives. We continue to lead and expand our AD prevention trial programs. We continue to develop public resources of data and biological samples to advance the study of AD, and support the development of promising CSF and blood biomarkers of AD and related disorders. We and our colleagues continue to advance the study of CTE in former football players and develop a shared resource of electronic health record data and biological samples from 100,000 persons in the All of Us Research Program, including a large proportion of persons from Hispanic, Native American and other under-represented groups. We continue to find new ways to advance the understanding and promotion of healthy brain aging, develop new models of dementia care, provide a foundation to discover a more diversified portfolio of promising treatments, and provide the best fighting chance to find and support the approval of a prevention therapy by 2025. We are extremely grateful to the state of Arizona, NIA, our participating organizations, colleagues, collaborators, advisors, research participants, and other supporters. We are proud of our progress and excited about our plans. Together, we are determined to make a transformational difference in the fight against AD.

Arizona Alzheimer's Consortium
21st Annual Conference – Thursday May 16, 2019
Banner Health (Host Institution)
Tempe Center for the Arts
700 W. Rio Salado Parkway
Tempe, AZ 85281

POSTER PRESENTATION SET-UP / CONTINENTAL BREAKFAST	8:15 – 9:30AM
WELCOME & INTRODUCTION Eric M. Reiman, MD CEO, Banner Research (this year's organizational host) Director, Arizona Alzheimer's Consortium	9:30 – 9:55AM
LEON THAL MEMORIAL LECTURE <i>"Lessons from the Oldest Old: The 90+ Study"</i> Claudia Kawas, MD Al and Trish Nichols Chair in Clinical Neuroscience Professor of Neurobiology & Behavior and Neurology University of California, Irvine	9:55 – 11:15AM
ORAL RESEARCH PRESENTATIONS – SESSION I	11:15 – 12:30AM
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 Eric M. Reiman, MD	4:15 – 4:30PM

Arizona Alzheimer's Consortium

Oral Research Presentations

SESSION I Moderator: Carol Barnes, PhD

- 11:15 – 11:30AM **Measuring physical activity in older adults: Associations with brain atrophy and white matter hyperintensities.** Gene Alexander. University of Arizona; University of Alabama at Birmingham; University of Miami Miller School of Medicine; University of Florida; Arizona Alzheimer's Consortium.
- 11:30 – 11:45AM **Hysterectomy with ovarian conservation uniquely impacts cognition and serum hormone profiles in a rat model.** Stephanie Koebele. Arizona State University; Senestech, Inc.; Arizona Alzheimer's Consortium.
- 11:45 – 12:00PM **Aged-related impairments in spatial reference frame updating.** Adam W. Lester. University of Arizona; Arizona Alzheimer's Consortium.
- 12:00 – 12:15PM **Human cells core for translational research at Banner Sun Health Research Institute.** Lih-Fen Lue. Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.
- 12:15 – 12:30PM **Correlation of presynaptic and postsynaptic proteins with pathology in Alzheimer's disease.** Geidy Serrano. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Arizona Alzheimer's Consortium

Oral Research Presentations

SESSION II Moderator: Zaven Khachaturian, PhD

- 3:00 – 3:15PM **Neurofibrillary tangle evolution in the frontal cortex of demented and non-demented subjects with Down syndrome.** Sylvia Perez. Barrow Neurological Institute; Arizona State University; University of California, Irvine Medical Center; Arizona Alzheimer's Consortium.
- 3:15 – 3:30PM **The use of human patient-derived induced pluripotent stem cells (iPSCs) to study mechanisms of disease pathogenesis in neurodegenerative diseases.** Rita Sattler. Barrow Neurological Institute; Arizona Alzheimer's Consortium.
- 3:30 – 3:45PM **ABCC1 mutation is associated with altered APP processing in a familial case of late-onset Alzheimer's disease.** Wayne M. Jepsen. Translational Genomics Research Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
- 3:45 – 4:00PM **Amyloid PET, tau PET, and MRI measurements in cognitively unimpaired persons with two, one, & no copies of the APOE4 allele.** Valentina Ghisays. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Mayo Clinic Arizona; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.
- 4:00 – 4:15PM **Relationships between baseline brain imaging biomarker measurements and age in the API Autosomal Dominant Alzheimer's Disease Colombia Trial.** Yi Su. Banner Alzheimer's Institute; Grupo de Neurociencias de Antioquia of Universidad de Antioquia; Genentech Inc.; Roche Products Ltd; University of California; Hospital Pablo Tobon Uribe; Harvard Medical School and Massachusetts General Hospital; Arizona Alzheimer's Consortium.

Arizona Alzheimer's Consortium

Poster Presentations

1. **Evaluation of a visual read method for flortaucipir PET scans.** Arora A, Pontecorvo M, Mintun M, Fleisher A, Devous M, Lu M, Galante N, Stevenson P, Flitter M, Beach T, Montine T, Serrano G, Sue L, Intorcica A, Curtis C, Salloway S, Thein S, Wellman C, Perrin A, Lowe V, Grossman M, Irwin D, Ikonovic M, Seeley W, Rabinovici G, Masdeu J. Avid Radiopharmaceuticals; Banner Sun Health Research Institute; Mayo Clinic Rochester; Hospital of the University of Pennsylvania; University of Pittsburgh; University of California, San Francisco; Houston Methodist Neurological Institute; Stanford University; Compass Research; Banner Alzheimer's Institute; Butler Hospital; Pacific Research Network, Inc; Hospice of the Western Reserve; Arizona Alzheimer's Consortium.
2. **Single cell and single nuclei RNAseq of fresh frozen Alzheimer's brain.** Antone JV, Enriquez D, Elyaderani A, Geiger P, Adkins JR, Serrano G, Beach TG, Readhead B, Mastroeni D, Dudley J, Reiman EM, Liang WS. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona State University; Icahn School of Medicine at Mt. Sinai; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
3. **Apolipoprotein E homozygosity associations with neurodegenerative disease clinical and neuropathological characteristics.** Beach TG, Adler CH, Serrano GE, Sue LI, Shill HA, Belden CM, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta SH, Burks T, Zamrini E, Shprecher DR, Spann B, Tariot PN, Davis KJ, Long KE, Nicholson LR, Intorcica A, Glass M, Walker J, Oliver J, Arce R, Sauhagen A, Sabbagh MN, Lue L-F, Walker DG, Reiman EM. Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; University of Arizona; Banner Alzheimer's Institute; Cleveland Clinic Lou Ruvo Center for Brain Health; Shiga University of Medical Science; Arizona Alzheimer's Consortium.
4. **Hyposmia is much more severe in neuropathologically confirmed dementia with Lewy Bodies as compared with Alzheimer's disease dementia.** Beach TG, Adler CH, Serrano GE, Sue LI, Zhang N, Driver-Dunckley E, Mehta SH, Shprecher DR, Zamrini E, Sabbagh MN, Shill HA, Belden CM, Davis KJ, Long KE, Nicholson LR, Intorcica AJ, Glass MJ, Walker JE, Callan M, Oliver JC, Arce R, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Spann BM, Tariot PN, Reiman EM, Gerkin RC. Banner Sun Health Research Institute; Mayo Clinic Arizona; Cleveland Clinic Lou Ruvo Center for Brain Health; Barrow Neurological Institute; University of Arizona; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.
5. **Assessment of multi-parametric diffusion-weighted MRI metrics in Alzheimer's disease.** Bergamino M, Nespodzany A, Baxter LC, Burke A, Caselli RJ, Sabbagh MN, Walsh RR, Stokes AM. Barrow Neurological Institute; Mayo Clinic Arizona; Cleveland Clinic Lou Ruvo Center for Brain Health; Arizona Alzheimer's Consortium.
6. **Specificity of activity-regulated transcript localization in somatic and dendritic neuronal compartments.** Bleul C, Chawla MK, De Both MD, Barnes CA, Huentelman MJ. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

7. **Facilitating user accessibility to regulatory-endorsed drug development tools for Alzheimer disease (AD).** Burton JK, Conrado DJ, Kern VD, Arnerić SP, Romero K, on behalf of the Critical Path for Alzheimer's Disease (CPAD) Consortium. Critical Path Institute; Arizona Alzheimer's Consortium.
8. **Mechanisms of Neurodegeneration in Alzheimer's disease.** Caccamo A, Piras I, Huentelman MJ, Readhead B, Belfiore R, Winslow W, Vartak R, Oddo S. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
9. **Age-dependent correlation between spatial and working memory does not extend to object recognition.** Carey NJ, Zempare MA, Nguyen CJ, Bohne KM, Chawla MK, Sinari S, Huentelman MJ, Billheimer D, Barnes CA. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
10. **Applying a novel integrated persistent feature to understand topographical network connectivity in older adults with autism spectrum disorder.** Catchings MT, Wang Y, Kuang L, Braden BB. Arizona State University; Arizona Alzheimer's Consortium.
11. **Predictive network analysis identifies microglial-specific key drivers for phagosome and A β -clearance in Alzheimer's disease.** Chang R. University of Arizona; Arizona Alzheimer's Consortium.
12. **Predicting likelihood of progression from MCI to probable Alzheimer's dementia with clinical ratings, brain imaging measurements and age using machine learning techniques.** Chen Y, Pan R, Luo J, Lee W, Chen K, Devadas V, Bauer III R, Reiman EM, Su Y. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
13. **Using the yeast two-hybrid system to study proteins interacting with presenilin-1.** Chow AY, Artigas JA, Bae NS, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.
14. **Lateral but not medial entorhinal cortex population representations become more sparse with age.** Comrie AE, Lister JP, Chawla MK, Barnes CA. University of Arizona; University of California, San Francisco; University of California, Los Angeles; Arizona Alzheimer's Consortium.
15. **Lessons from a community-level, music-based intervention for people with ADRD.** Coon DW, McCarthy M, Cortes M, Carll P, Jaszewski A, Gomez Morales A, Rio R, Belgrave M, Todd M, Bontrager V, Burluson M. Arizona State University; The Phoenix Symphony; Arizona Alzheimer's Consortium.
16. **Finding the needle in a haystack – Identification of circular RNAs using RNA sequencing.** Cuyugan L, Sekar S, Geiger P, Serrano G, Beach TG, Liang WS. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
17. **Strategic memory Alzheimers rehabilitation training (SMART): Cognitive protection and intervention for amnesic-type mild cognitive impairment (MCI).** DenBoer JW, Siegel E. SMART Brain Aging, Inc.; Midwestern University; Arizona Alzheimer's Consortium.

18. **Strategic memory Alzheimers rehabilitation training (SMART) memory program for amnesic mild cognitive impairment (aMCI): Reporting the results of a randomized clinical trial.** DenBoer J. SMART Brain Aging, Inc; Arizona Alzheimer's Consortium.
19. **Temporary improvement for MCI/VCI via systematic novel cognitive exercise: the SMART program.** DenBoer JW, Kline J. SMART Brain Aging, Inc.; University of Arizona; Arizona Alzheimer's Consortium.
20. **AmpliSeq transcriptome analysis of laser captured neurons from Alzheimer brain: comparison of single cell versus neuron pools.** Deng W, Xing C, David R, Mastroeni D, Ning M, Lo EH, Coleman P. Massachusetts General Hospital, Harvard Medical School; University of Texas Southwestern Medical Center; Thermo-Fisher Scientific; Arizona State University; Arizona Alzheimer's Consortium.
21. **Surface-based hippocampal morphometry analysis for studying effects of APOE-e4 allele load in cognitively unimpaired subjects.** Dong Q, Zhang W, Wu J, Li B, Schron EH, McMahon T, Shi J, Gutman BA, Chen K, Baxter LC, Thompson PM, Reiman EM, Caselli RJ, Wang Y. Arizona State University; Wellesley College; Illinois Institute of Technology; Banner Alzheimer's Institute; Barrow Neurological Institute; University of Southern California; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
22. **Effects of plasma insulin levels on cerebral metabolic rate of glucose and gray matter volume in cognitively unimpaired APOE3/APOE4 carriers.** Edlund AK, Lee W, Chen K, Su Y, Reiman EM, Caselli RJ, Nielsen HM. Stockholm University; Banner Alzheimer's Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
23. **Aspirin ameliorates the long-term adverse effects of doxorubicin through suppression of cellular senescence.** Feng M, Kim J, Field K, Reid C, Chatzistamou I, Shim M. University of South Carolina; University of North Carolina at Chapel Hill; Midwestern University; Arizona Alzheimer's Consortium.
24. **Amyloid beta-induced alterations in basal forebrain cholinergic intrinsic excitability are mediated by $\alpha 7$ and $\alpha 7\beta 2$ -containing nicotinic acetylcholine receptors (nAChRs).** George AA, Bimonte-Nelson HA, Lukas RJ, Whiteaker P. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.
25. **Amyloid PET, tau PET, and MRI measurements in cognitively unimpaired persons with two, one, & no copies of the APOE4 allele.** Ghisays V, Goradia DD, Protas H, Bauer R, Devadas V, Tariot PN, Lowe VJ, Knopman D, Petersen RC, Jack CR, Caselli RJ, Su Y, Chen K, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Mayo Clinic Arizona; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.
26. **Depression in aging and its association to age-related neurodegenerative pathology.** Glass M, Intorcchia A, Walker J, Arce R, Oliver J, Nelson C, Papa J, Arce A, Vargas D, Sue L, Beach TG, Serrano G. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
27. **Comparison of cross-sectional and longitudinal Freesurfer pipeline for estimation of florbetapir PET SUVR measurements.** Goradia DD, VanGilder PS, Thiyyagura P,

Devadas V, Chen Y, Luo J, Reiman EM, Su Y. Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

28. **GeneMatch: A novel recruitment registry of APOE characterized adults to accelerate recruitment and enrollment into Alzheimer's prevention studies.** Gordon D, Graf H, Walsh T, High N, Reiman EM, Tariot PN, Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
29. **Thalamocortical white-matter integrity and the relationship between auditory function and cognitive decline in aged macaque monkeys.** Gray DT, Burke SN, Engle JR, Umapathy L, Trouard TP, Barnes CA. University of Arizona; University of Florida; University of California, Davis; Arizona Alzheimer's Consortium.
30. **Evidence for neuroprotective effects of an over-the-counter curcumin supplement against Rotenone induced neurotoxicity.** Hall DA, Estrella MV, Thomason SC, Schilperoort LR, Anderson ML. Grand Canyon University.
31. **Cognitive improvements in patients with mild cognitive impairment and Alzheimer's disease through a personalized Mito food plan diet and cell repair therapy.** Hank NC, Pereira J, McCravey B, Christians L, Hoggan C, Dechoux F. Perseverance Research Center, LLC; Cerulean Advanced Wellness and Fitness.
32. **Facebook as a resource for Hispanic/Latino recruitment: A pilot program of the Alzheimer's Prevention Registry.** High NM, DeMarco KL, Parkhurst DK, Herbert EE, Ward AK, Reiman EM, Langbaum J. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
33. **Beneficial effects of resveratrol and exercise training on cardiac and aortic function and structure in the 3xTg mouse model of Alzheimer's disease.** Hoxha B, Esfandiarei M, Talley NA, Anderson MA, Alkhouli MF, Squire MA, Eckman DM, Jeganathan RB, Lopaschuk GL, Broderick TL. Midwestern University; Auburn University; Mazankowski Alberta Heart Institute, University of Alberta; Arizona Alzheimer's Consortium.
34. **Bacterial lipopolysaccharide (LPS) and lipoteichoic acid (LTA) detected in the serum and brain tissue of AD patients and controls.** Jentarra G, Chu P, Elliott N, Jones TB, Kaufman J, Vallejo-Elias J, Jones D, Gonzalez F, Tullot T, Potter P. Midwestern University; Arizona Alzheimer's Consortium.
35. **Targeting necroptosis for AD therapeutics.** Khanna M, Sanchez-Lares J, Oddo S. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.
36. **Convolutional neural networks for fast and accurate 3D reconstruction of histological sections.** Kyle CT, Stokes J, Meltzer J, Permenter MR, Vogt JA, Ekstrom A, Barnes CA. University of Arizona; University of California, Davis; Arizona Alzheimer's Consortium.
37. **A concise and persistent feature to study brain resting-state network dynamics: Findings from the Alzheimer's Disease Neuroimaging Initiative.** Kuang L, Dong Q, Han X, Chen K, Caselli RJ, Reiman EM, Wang Y, Alzheimer's Disease Neuroimaging

Initiative. Arizona State University; North University of China; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

38. **Aged-related impairments in spatial reference frame updating.** Lester AW, Blum CJ, Kapellusch AJ, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
39. **Protecting DNA is a family affair: Telomere length and cognition in affected individuals, unaffected siblings, and parents.** Lewis CR, Taquinod F, Cohen J, Walker N, Agrawal K, Jepsen WM, Huentelman MJ, Smith CJ, Ringenbach S, Braden BB. Translational Genomics Research Institute; Southwest Autism Research and Resource Center; Arizona State University; Arizona Alzheimer's Consortium.
40. **Addressing the gap of imaging accessibility in early detection of AD by a novel transfer learning model: A longitudinal study.** Liu X, Li J, Chen K, Wu T, Lure F, Su Y, Weidman D, Wang P. Arizona State University; Banner Alzheimer's Institute; MS Technologies; Shanghai Tongji Hospital; Arizona Alzheimer's Consortium.
41. **Human in vitro co-culture system of C9orf72-FTD/ALS patient-derived iPSC neurons and microglial cells to study mechanisms of synaptopathy.** Lorenzini I, Levy J, Burciu C, Bhatia D, Rabichow B, Almeida S, Gao FB, Van Keuren-Jensen K, Sattler R. Barrow Neurological Institute; University of Massachusetts Medical School; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
42. **Amyloid beta and total tau levels in postmortem cerebrospinal fluid samples from neuropathologically-confirmed patients: A study of immunomagnetic reduction technology.** Lue LF, Chen W, Guerra A, Kuo W, Yang SY, Beach TG. Banner Sun Health Research Institute; Arizona State University, MagQu Corp, LLC; MagQu Corp, Ltd; Arizona Alzheimer's Consortium.
43. **Human cells core for translational research at Banner Sun Health Research Institute.** Lue LF, Serrano GE, Walker JE, Nunez T, Walker DG, Brafman D, Reiman EM, Beach TG. Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.
44. **HDAC2 nuclear protein reduction within cholinergic basal forebrain neurons is associated with NFT formation during the progression of Alzheimer's disease.** Mahady L, Nadeem M, He B, Perez SE, Mufson EJ. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.
45. **APOE-dependent verbal learning effects in cognitively unimpaired older adults.** Malek-Ahmadi M, Su Y, Devadas V, Henslin B, Locke DEC, Woodruff BK, Dueck AC, Caselli RJ, Reiman EM. Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
46. **Impact of cerebral ischemia scores, fibrillar amyloid- β burden and age on white matter hyperintensity volumes in cognitively unimpaired older adult APOE4 carriers and non-carriers.** Malek-Ahmadi M, Luo J, Methuku V, Devadas V, Goradia D, Su Y, Reiman EM. Alzheimer's Disease Neuroimaging Initiative, Banner Alzheimer's Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium

47. **Relationships between longitudinal rates of learning and memory decline and different forms of cerebrovascular pathology in cognitively unimpaired brain donors.** Malek-Ahmadi M, Belden CM, Powell JJ, Zamrini E, Adler CA, Sabbagh MN, Shill HA, Jacobson SA, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta SH, Shprecher DR, Spann BM, Tariot PN, Davis KJ, Long KE, Nicholson LR, Intorcchia A, Glass MJ, Walker JE, Callan M, Curry J, Cutler B, Oliver J, Arce R, Walker DG, Lue L, Serrano GE, Sue LI, Reiman EM, Beach TG. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Northwestern University; Mayo Clinic Arizona; Cleveland Clinic Lou Ruvo Center for Brain Health; Barrow Neurological Institute; University of Arizona; Molecular Neuroscience Research Center, Shiga University of Medical Science; Arizona Alzheimer's Consortium.
48. **EGR3 is required for activity dependent Bdnf factor exon IV and VI induction in the mouse hippocampus.** Marballi KK, Meyers KT, Zhao X, Campbell JM, Gallitano AL. University of Arizona; Arizona State University; Neural Stem Cell Institute; Arizona Alzheimer's Consortium.
49. **PIN1 is an indicator of age associated risk of mild cognitive impairment and subsequent Alzheimer's disease.** Mastroeni D, Velazquez R, Shireby G, Lu A, Delvaux E, Nolz J, Liang W, Lunnon K, Horvath S, Coleman P. Arizona State University; University of Exeter; University of California, Los Angeles; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
50. **Using distinct strains of the neurotropic parasite toxoplasma gondii as a tool to probe protection against amyloid beta deposition.** McGovern KE, Cabral CM, Koshy AA. University of Arizona; Arizona Alzheimer's Consortium.
51. **Frontal cortex CHI3L1 and CHI3L2 alterations during progression of Alzheimer disease.** Moreno-Rodriguez M, Nadeem M, Perez SE, Mufson EJ. Barrow Neurological Institute; Arizona Alzheimer's Consortium.
52. **Neurofibrillary tangle evolution in the frontal cortex of demented and non-demented subjects with Down syndrome.** Perez SE, Miguel JC, Nadeem M, Sabbagh MN, Lott IT, Doran E, Mufson E. Barrow Neurological Institute; University of California, Irvine Medical Center; Arizona Alzheimer's Consortium.
53. **RNA profiling on cerebellum white matter reveals a potential role of APP and endothelial genes in Cerebellar Multiple System Atrophy.** Piras IS, Bleul C, Schrauwen I, Talboom J, DeBoth MD, Naymik MA, Hallyday G, Holton J, Serrano G, Sue L, Beach TG, Huentelman MJ. Translational Genomics Research Institute; The University of Sydney School of Medicine; Queen Square Brain Bank for Neurological Disorders; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
54. **Covarying spatial patterns of tau deposition and gray matter atrophy unearthed by the informed multimodal partial least squares (MMPLS) in autosomal dominant Alzheimer's disease: Findings from the COLBOS Project.** Protas H, Pardilla-Delgado E, Lopera F, Johnson K, Sperling RA, Artola A, Baena A, Bocanegra Y, Gatchel J, Guzman-Velez E, Fuller J, Goradia D, Thiyyagura P, VanGilder PS, Luo J, Ghisays V, Lee W, Malek-Ahmadi M, Chen Y, Devadas V, Chen K, Reiman EM, Su Y, Quiroz YT. Banner Alzheimer's Institute; Massachusetts General Hospital, Harvard Medical School; Universidad de Antioquia; Arizona Alzheimer's Consortium.

55. **Individual-based network analysis: A novel approach to investigate the pathological spread of PHF tau using graph theory in clinical and preclinical stages of Alzheimer's disease.** Protas HD, Goradia DD, Ghisays V, Luo JL, VanGilder P, Thiyyagura P, Malek- Ahmadi M, Lee W, Chen Y, Devadas V, Bauer III R, Landau SM, Weiner M, Jagust WJ, Chen K, Su Y, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona State University; University of California, San Francisco; University of California, Berkeley; Arizona Alzheimer's Consortium.
56. **APOE isoforms differentiate neuronal- and astrocytic mitochondrial bioenergetic capacity and fuel dependency.** Qi GY, Mi YS, Chen SH, Brinton RD, Yin F. University of Arizona; Arizona Alzheimer's Consortium.
57. **Relation of physical activity to regional maps of cortical gray matter volume in the healthy oldest old: Findings from the McKnight Brain Aging Registry.** Raichlen DA, Bharadwaj PK, Franchetti MK, Sims S, Rezaei RF, Merritt S, Jessup CJ, Porges ES, Geldmacher D, Hishaw GA, Alperin N, Trouard TP, Wadley VG, Levin BE, Woods AJ, Rundek T, Visscher K, Cohen RA, Alexander GE. University of Arizona; University of Alabama at Birmingham; University of Miami Miller School of Medicine; University of Florida; Arizona Alzheimer's Consortium.
58. **Traumatic brain injury and Alzheimer's disease associated changes in sleep behavior occurs through comparable inflammatory mechanisms.** Saber M, Hur Y, Rowe R, Lifshitz J. Barrow Neurological Institute; University of Arizona College of Medicine–Phoenix; Phoenix Veterans Affairs Health Care System; Arizona Alzheimer's Consortium.
59. **Targeting RIPK3-MLKL protein-protein interactions in necroptosis.** Sanchez J, Gokhale V, Oddo S, Khanna M. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.
60. **Gender differences in Alzheimer's disease: Brain atrophy, synaptic loss, histopathology burden and cognition.** Serrano G, Walker J, Oliver J, Nelson C, Glass M, Arce R, Intorcica A, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
61. **Single-cell analysis in human brain neurodegenerative disease.** Serrano G, Intorcica A, Walker J, Cutler B, Glass M, Arce R, Piras I, Talboom J, Oliver J, Sue L, Lue L, Huentelman MJ, Beach TG. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
62. **Cardiac sympathetic denervation and synucleinopathy in Alzheimer disease and Lewy-type-synucleinopathies.** Shprecher DR, Callan M, Cutler B, Serrano G, Adler CH, Shill HA, Caviness JN, Sabbagh MN, Belden CM, Driver-Dunckley E, Mehta SH, Sue LI, Davis KJ, Zamrini E, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
63. **Pilot study comparing home sleep profiler to in-laboratory polysomnogram for REM sleep behavior disorder diagnosis.** Shprecher D, Levendowski D, Guevarra C, Lazarz G, Lee-Iannotti J. Banner Sun Health Research Institute; University of Arizona; Advanced Brain Monitoring; Arizona Alzheimer's Consortium.

64. **Neuroanatomical changes of the olfactory bulb of subjects with Parkinson's disease.** Sinakevitch I, Serrano G, Beach TG, Adler CH, Smith BH. Arizona State University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
65. **Amelioration of neurodegenerative changes in mice undergoing transverse aortic constriction by mas agonists.** Soto M, Jadhav S, Butler R, Gaffney K, Rodgers K. University of Arizona; Arizona Alzheimer's Consortium.
66. **Influence of genistein diet and exercise on weight loss and markers of Alzheimer's disease in high fat-high sucrose-fed mice.** St Aubin C, Fisher A, Oddo S, Caccamo A, Al-Nakkash L. Midwestern University; Arizona State University; Arizona Alzheimer's Consortium.
67. **Relationships between baseline brain imaging biomarker measurements and age in the API Autosomal Dominant Alzheimer's Disease Colombia Trial.** Su Y, Romenets SR, Tariot PN, Sink KM, Clayton D, Hu N, Guthrie H, Smith J, Cho W, Langbaum JB, Thomas RG, Giraldo-Chica M, Tobon C, Acosta-Baena N, Navarro A, Piedrahita F, Alvarez S, Chen K, Goradia D, Thiyyagura P, VanGilder PS, Luo J, Ghisays V, Lee W, Malek-Ahmadi MH, Protas HD, Chen Y, Ho C, Suliman S, Quiroz YT, Paul R, Lopera F, Reiman EM, API ADAD Colombia Trial Group. Banner Alzheimer's Institute; Grupo de Neurociencias de Antioquia of Universidad de Antioquia; Genentech Inc.; Roche Products Ltd; University of California; Hospital Pablo Tobon Uribe; Harvard Medical School and Massachusetts General Hospital; Arizona Alzheimer's Consortium.
68. **Cognition is associated with several health and lifestyle factors: MindCrowd follow-up survey results.** Talboom JS, Håberg AK, De Both MD, Naymik MA, Schrauwen I, Lewis CR, Bertinelli SF, Hammersland C, Myers AJ, Hay M, Barnes CA, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Norwegian University of Science and Technology; University of Miami; University of Arizona; Arizona State University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
69. **NPTX2 knockout rats: a novel model for protection of synaptic function in aging and disease.** Terrazas A, Zampare M, Carey N, Bohne K, Do L, Trouard T, Worley PF, Pyon W, Barnes CA. University of Arizona; Johns Hopkins School of Medicine; Arizona Alzheimer's Consortium.
70. **Hippocampal mediation of subjective memory complaints differs by hypertension status in healthy older adults.** Van Etten EJ, Bharadwaj PK, Nguyen LA, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.
71. **Necroptosis contributes to tau mediated neurodegeneration.** Vartak RS, Rodin A, De Court B, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
72. **Hypothermia during isoflurane anesthesia does not aggravate memory impairments in an Alzheimer's disease-like condition induced by intrabrain streptozotocin in rats.** Vizin RCL, Harris GT, Almeida MC, Carrettiero DC, Romanovsky AA. St. Joseph's Hospital and Medical Center; Federal University of ABC; Arizona State University; Arizona Alzheimer's Consortium.

73. **Correlation of presynaptic and postsynaptic proteins with pathology in Alzheimer's disease.** Walker J, Glass M, Arce R, Oliver J, Intorcica A, Nelson C, Papa J, Arce A, Vargas D, Sue L, Beach TG, Serrano G. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
74. **A subspace decomposition-based univariate neurodegenerative biomarker system.** Wang G, Su Y, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Ludong University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
75. **Impact of reference region used to quantify amyloid burden on interpreting the relationship between amyloid burden and genetic risk factors of AD.** Wang Q, Del-Aguila JL, Cruchaga C, Reiman EM, Su Y. Arizona State University; Washington University in St. Louis; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
76. **Interpreting florbetapir-PET scan results: Assessment and analysis of discordant cases from the IDEAS study.** Weidman D, Ghisays V, Protas H, Luo J, Chen Y, Devadas V, Leger J, Sidarous G, Su Y. Banner Alzheimer's Institute; Banner University Medical Center Phoenix; Arizona Alzheimer's Consortium.
77. **Integrating genomic and imaging biomarkers for early detection of Alzheimer's disease.** Wu J, Wang P, Nyarige V, Caselli RJ, Wang Y, Wang J. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
78. **Sirtuin 3 mediates tau deacetylation.** Yin J, Li S, Nielsen M, Beach TG, Guo L, Shi J. Barrow Neurological Institute; The Second Hospital of Hebei Medical University; University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

STUDENT POSTER PRESENTATIONS

79. **Cognitively normal older adults show elevated semantic detail generation for multiple forms of autobiographical memory retrieval.** Acevedo-Molina MC, Robertson AC, Teposte M, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.
80. **Aging, exploration, and their neuropsychological correlates.** Alvarado L, Farrell Skupny A, Frisvold A, Mizell JM, Wang S, Keung W, Sundman MH, Franchetti MK, Chou Y, Alexander GE, Wilson RC. University of Arizona; Arizona Alzheimer's Consortium.
81. **PARO robot intervention perspectives with dementia patients.** Ames L, Andersson E. Midwestern University; Arizona Alzheimer's Consortium.
82. **Using multi-method approaches to characterize maladaptive repetitive thought in older adults.** Andrews E, Raffaelli Q, O'Connor M-F, Wilcox R, Mehl M, Matijevic S, Seeley S, Arballo T, Robertson A, Ryan L, Grilli M, Andrews-Hanna J. University of Arizona; Arizona Alzheimer's Consortium.
83. **Convergent biological mechanisms revealed by SNP's linked to Alzheimer's disease.** Baldwin E, Fang J, Han J, Li J, Yin F, Lussier YA, Li H. University of Arizona; Arizona Alzheimer's Consortium.

84. **Relation of white matter lesion load to cortical gray matter thickness in healthy aging.** Bharadwaj PK, Nguyen LA, Hishaw GA, Trouard TP, Moeller JR, Habeck CG, Alexander GE. University of Arizona; Columbia University; Columbia University Medical Center; Arizona Alzheimer's Consortium.
85. **Histopathological responses to candida albicans infection in 3xTG-AD mice.** Brown C, Vallejo-Elias J, Gonzalez F, Jentarra G, Potter P, Kaufman J, Tullo T, Jones D, Jones TB. Northwestern University; Arizona Alzheimer's Consortium.
86. **The Intellicage: an automated system for assessing cognition in transgenic mouse models of Alzheimer's disease.** Bustos L, Velazquez R, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
87. **Deep learning algorithms for brain image classification.** Champaneria H, Luo J, Su Y, Pan R. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
88. **Challenges of pain management for long term care residents with dementia.** Conant RA, Uriri-Glover J. Arizona State University; Arizona Alzheimer's Consortium.
89. **In vivo characterization of cardiac and aortic function & structure in the human apolipoprotein E mouse model of Alzheimer's disease.** Curry T, Dickman R, Hoxha B, Gadagkar S, Vallejo-Elias J, Jones TB, Esfandiarei M. Northwestern University; Arizona Alzheimer's Consortium.
90. **Evaluation of aortic wall contractility & structural integrity in the human apolipoprotein E mouse model of Alzheimer's disease.** Dickman R, Talley N, Hoxha B, Curry T, Alexander T, Johnson N, Gadagkar S, Vallejo-Elias J, Jones TB, Esfandiarei M. Northwestern University; Arizona Alzheimer's Consortium.
91. **Diffusion weighted MRI characterization of APOE4 effects on sex and genotype in mouse model.** Do L, Bernstein A, Mishra A, Desai M, Lindley MD, Ugonna C, Chen NK, Brinton R, Trouard TP. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.
92. **MRI assessment of sex differences in APOE4 knock-in in rodent brains.** Do L, Mishra A, Bernstein A, Lindley MD, Ugonna C, Chen NK, Brinton R, Trouard TP. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.
93. **Interactive effect of sex and BDNF Met allele on memory in older adults.** Elias M, Matijevic S, Ryan L, Huentelman MJ. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
94. **The development of a highly selective and orally bioavailable inhibitor of DYRK1A for treatment of Alzheimer's disease.** Foley C, Dunckley T, Hulme C. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.
95. **Relation between physical sport activity and white matter hyperintensity volume in older adults.** Franchetti MK, Bharadwaj PK, Nguyen LA, Klimentidis YC, Hishaw GA, Trouard TP, Raichlen DA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

96. **Elemental and configural odor discrimination in APP/PS1 mice.** Gupta TA, Sanabria F, Oddo S, Smith BH. Arizona State University; Arizona Alzheimer's Consortium.
97. **Individual cognitive stimulation therapy effect on caregivers of persons with dementia.** Hershkowitz AB, Uriri-Glover J, Buchanan BL. Arizona State University; A.T. Still University; Arizona Alzheimer's Consortium.
98. **ABCC1 mutation is associated with altered APP processing in a familial case of late-onset Alzheimer's disease.** Jepsen WM, De Both M, Piras IS, Siniard AL, Henderson-Smith A, Ramsey K, Serrano G, Caselli RJ, Beach TG, Huentelman MJ. Translational Genomics Research Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
99. **Pim1 inhibition as a novel therapeutic strategy for Alzheimer's disease.** Knowles S, Velazquez R, Caccamo A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
100. **Hysterectomy with ovarian conservation uniquely impacts cognition and serum hormone profiles in a rat model.** Koebele SV, Palmer JM, Hadder B, Melikian R, Fox C, Strouse IM, DeNardo D, George C, Daunis E, Bimonte-Nelson HA. Arizona State University; Senestech, Inc.; Arizona Alzheimer's Consortium.
101. **fMRI examination of contextual effects on pattern separation in younger and older adults.** Lawrence A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
102. **Role of white matter integrity in age-related differences in autobiographical memory.** Matijevic S, Grilli M, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
103. **The perceived benefit of nature on the well-being of skilled nursing facility residents.** O'Neil L, Sokoloski M, Andersson E. Midwestern University; Arizona Alzheimer's Consortium.
104. **Context-dependent memory in cognitively-normal older e4 carriers and non-carriers.** Palmer JM, Lawrence A, Grilli M, Talboom J, Huentelman MJ, Ryan L. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
105. **Cerebral artery reactivity in adult APOE3 and APOE4 mice.** Patel RG, Souders L, Hoxha B, Ion E, Vallejo-Elias J, Jones CB, Powell J, Virden T, Struthers J, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.
106. **An assessment of the transition to menopause in the rat in the TgF344-AD model of Alzheimer's disease.** Peña, VL, Northup-Smith S, Woner VE, Bulen HL, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.
107. **Let's talk about sex (hormones): Cognitive characterization and evaluation of gonadal hormone deprivation in a rat model of Alzheimer's disease.** Peña, VL, Bulen HL, Northup-Smith S, Barker C, Woner VE, Prakapenka AV, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

108. **Investigating genetic sex differences to explain Alzheimer's disease mechanisms.** Peters M, Natri H, Evanovich A, Wilson MA. Arizona State University; Arizona Alzheimer's Consortium.
109. **The effects of family history of Alzheimer's disease and apolipoprotein E4 status on cognitive functions.** Sangam S, Stickel A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
110. **Sex differences in cognitive and symptom profiles of older adults with autism spectrum disorder.** Stoeckmann M, Baxter LC, Smith CJ, Foldes E, Webb C, Gonzales A, Braden BB. Arizona State University; Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona Alzheimer's Consortium.
111. **Effects of expression of human APOE3 and APOE4 on elastic properties of murine aortae.** Strange T, Dickman R, Pascual A, Esfandiarei M, Jones C, Jentarra G, Vallejo-Elias J, Jones TB. Midwestern University; Arizona Alzheimer's Consortium.
112. **An evaluation of the levonorgestrel-releasing intrauterine device and its impact on cognitive function in a rat model.** Strouse IM, Prakapenka AV, Northup-Smith SN, Woner VE, Peña VL, Koebele SV, DeNardo D, Sirianni RW, Bimonte-Nelson HA. Arizona State University; Barrow Neurological Institute; University of Texas Health Science Center at Houston; Arizona Alzheimer's Consortium.
113. **Isometry invariant shape descriptors for brain surfaces: Applications to Alzheimer's disease.** Tu Y, Wen C, Wu J, Caselli RJ, Chen K, Reiman EM, Lepore N, Gu X, Wang Y. Arizona State University; Stony Brook University; Mayo Clinic Arizona; Banner Alzheimer's Institute; Children's Hospital, Los Angeles; Arizona Alzheimer's Consortium.
114. **Using diffusion tensor imaging to identify structural neural correlates of motor learning and visuospatial processes in cognitively-intact older adults.** VanGilder JL, Fitzhugh MC, Rogalsky C, Schaefer Y. Arizona State University; Arizona Alzheimer's Consortium.
115. **Out of the lab, into the real-world: Preliminary evidence that measuring autobiographical memory retrieval in a naturalistic setting replicates laboratory-based findings.** Wank AA, Moseley S, Polsinelli AJ, Glisky EL, Mehl MR, Grilli MD. University of Arizona; Minnesota Epilepsy Group; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.
116. **The cognitive effects of the highly selective progestin nesterone in a rat model of surgical menopause.** Woner VE, Koebele SV, Northup-Smith S, Willeman M, Barker C, Schatzki-Lumpkin A, Valenzuela Sanchez M, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.
117. **Ovarian hormones mediate acquisition of nicotine self-administration and accumbens glutamatergic plasticity.** Leyrer-Jackson JM, Pina J, Ulangkaya, J, Bimonte-Nelson H, Gipson CD. Arizona State University; Arizona Alzheimer's Consortium.

118. **An adaptive sampling framework for partial volume correction of β -amyloid PET.**
VanGilder P, Luo J, Goradia DD, Ghisays V, Protas H, Thiyyagura P, Malek-Ahmadi M, Lee W, Chen Y, Devadas V, Reiman EM, Su Y. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

2019 Oral Research Presentation

Abstracts

MEASURING PHYSICAL ACTIVITY IN OLDER ADULTS: ASSOCIATIONS WITH BRAIN ATROPHY AND WHITE MATTER HYPERINTENSITIES. Alexander GE, Bharadwaj PK, Franchetti MK, Nguyen LA, Sims S, Rezaei RF, Merritt S, Jessup CJ, Klimentidis YC, Porges ES, Geldmacher D, Hishaw GA, Alperin N, Trouard TP, Wadley VG, Levin BE, Woods AJ, Rundek T, Visscher K, Cohen RA, Raichlen DA. University of Arizona, University of Alabama at Birmingham, University of Miami Miller School of Medicine, University of Florida, and Arizona Alzheimer's Consortium

Background: Aging is associated with increases in cortical atrophy and white matter hyperintensity (WMH) lesion load. Physical activity (PA) may play an important role in reducing these aging effects by helping to maintain cognitive and brain health. Wrist-worn accelerometers and self-reported PA each provide ways to assess engagement in moderate to vigorous physical activity (MVPA). We sought to determine whether high levels of MVPA are associated with greater cortical gray matter volume and less WMH lesion load in cohorts of healthy older adults.

Methods: To evaluate the relation of cortical gray matter to MVPA, 40 community-dwelling, cognitively unimpaired oldest-old adults, ages 85 to 95 were included (mean±sd age = 88.6±3.2 yrs). T1-weighted 3T MRI scans were processed using FreeSurfer (v6.0). Measures of MVPA were obtained with Actigraph accelerometers worn for up to seven consecutive days. Analyses tested the relation of MVPA to gray matter volume maps, with significance thresholds maintaining an overall $p < 0.05$ false positive rate (Greve and Fischl, 2018). To investigate the effects of PA on WMH, we obtained self-reported physical sport activity from a separate cohort of 196 healthy older adults, ages 50 to 89 (mean ± SD age = 69.8 ± 10.6 yrs). Participants reporting high sport activity (n=36) were compared to those with low sport activity (n=160). Total WMH volume was computed with a multispectral, automated method using 3T MRI T1 and T2 FLAIR scans to produce probability maps using SPM12 and the lesion segmentation toolbox (LST; Schmidt et al., 2012). Total intracranial volume (TIV) was computed to adjust brain volumes for head-size.

Results: Results in our oldest old cohort showed that, after adjusting for TIV, higher levels of MVPA were significantly associated with increased volumes in the vicinity of left and right precentral cortical regions. Linear regression analysis showed that the average cortical gray matter volumes extracted from the two prefrontal regions was positively associated with cognitive function scores on the MoCA after controlling for gender, years of education, and age ($p \leq 0.03$). In testing the relation between self-report of physical sport activity and WMH, we observed a strong trend for an effect of PA ($p = 0.0503$), main effect for age group ($p = 0.005$), and an age by PA group interaction ($p = 0.005$). The total WMH volume for the high PA group was comparable between the young-old and old-old groups. The old-old with low PA had a significantly greater WMH volume than both the young-old with low PA ($p = 2.72E-10$) and the old-old with high PA ($p = 0.00038$). These latter findings remained significant after adjusting the WMH volumes for TIV.

Conclusions: These findings suggest that, among oldest old adults, engaging in more MVPA is associated with greater brain volume in regions of frontal cortex. For WMH, among the low PA groups, total WMH lesion volume was greater in the old-old than young-old. This finding suggests an age group difference that was not observed in the high PA groups, indicating diminished age effects with greater physical sport activity. Together, these results suggest that engaging in high levels of physical activity may be an important lifestyle factor that can help maintain the integrity of gray and white matter in old age, leading to successful cognitive aging.

HYSTERECTOMY WITH OVARIAN CONSERVATION UNIQUELY IMPACTS COGNITION AND SERUM HORMONE PROFILES IN A RAT MODEL. Koebele SV, Palmer JM, Hadder B, Melikian R, Fox C, Strouse IM, DeNardo D, George C, Daunis E, Bimonte-Nelson HA. Arizona State University; Senestech, Inc.; Arizona Alzheimer's Consortium.

Background: Hysterectomy (surgical removal of the uterus) is the second most common gynecological surgery following only cesarean section (CDC, 2010; Carlson et al., 1993). The majority of hysterectomies are performed in women prior to age 51 (Wright et al., 2013), which is the average age for natural menopause onset, and prior observations suggest that surgical removal of the ovaries before natural menopause onset may be detrimental to cognition. Thus, ovaries are preserved in about half of hysterectomy procedures. In the last decade, these findings have been extended, such that hysterectomy itself prior to natural menopause onset has also been implicated in an increased relative risk of developing dementia compared to women who did not undergo gynecological surgery (Rocca et al., 2007, 2012; Phung et al., 2010). The factors underlying cognitive and brain changes with variations in surgical menopause remain unclear and warrant further evaluation.

Methods: We examined spatial learning and memory using a rat model of variations in surgical menopause, including a novel model of hysterectomy with ovarian conservation. Adult Fischer-344-CDF female rats underwent sham, ovariectomy, hysterectomy, or ovariectomy plus hysterectomy surgery. Six weeks after surgery, subjects were tested on the water radial-arm maze, a spatial working and reference memory task. Serum hormone profiles and ovarian follicle counts were also obtained.

Results: Results indicate that hysterectomy impaired spatial working memory performance when working memory load was taxed compared to the control group as well as to the other variations in surgical menopause. Serum ovarian hormone profiles were altered in rats with hysterectomy compared to sham-operated rats, while histological analyses of the ovarian tissue suggested that surgical intervention did not alter ovarian morphology itself, at least at the time point assessed.

Conclusions: This is the first systematic pre-clinical evaluation of the cognitive effects of hysterectomy with and without ovarian conservation. These results underscore the critical need to further study the contribution of the uterus to the female phenotype, including effects of hysterectomy with and without ovarian conservation, on the trajectory of brain and endocrine aging to decipher the impact of common variations in gynecological surgery in women. Moreover, findings demonstrate that the nonpregnant uterus is not dormant, and indicate that there is an ovarian-uterus-brain system that becomes interrupted when the reproductive tract has been disrupted, leading to alterations in brain functioning.

AGED-RELATED IMPAIRMENTS IN SPATIAL REFERENCE FRAME UPDATING. Lester AW, Blum CJ, Kapellusch AJ, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Both the hippocampus and the medial portion of the entorhinal cortex (MEC) contain functionally distinct sub-networks of spatially modulated neurons which are believed to work cooperatively to support spatial navigation. The two broad categories of spatial feedback utilized to anchor and update the spatial firing of these cells are allocentric (i.e., external) and egocentric (i.e., self-motion). As with older adults, aged rats show robust impairments on a number of different spatial navigation tasks (Lester et al., 2017). There is some evidence that these navigation impairments are accompanied by a bias away from using an allocentric navigation strategy towards relying on an egocentric strategy.

Methods: To test the degree and timing with which aged animals utilize these two forms of spatial information, a novel behavioral arena was developed in which rats are trained to traverse a circular track and to stop at a learned goal location that is fixed with respect to a panorama of visual cues projected onto the surrounding walls. By instantaneously rotating the cues we are able to put allocentric and egocentric reference frames in direct and immediate conflict and characterize how quickly and accurately aged animals utilize allocentric feedback to navigate to a new rotated goal location.

Results: Behavioral data collected from five young (9 – 15 mo) and four aged (23 - 30 mo) animals reveal that both age groups are able to update their behavior following cue rotation, although aged rats tend to perseverate to the original goal location more often. Young rats, by comparison, were more likely to stop at some intermediate location between the original and rotated goal location. These findings suggest that when spatial reference frames are put in conflict, young rats settle on a strategy that combines both sources of spatial information, while aged animals adhere more rigidly to only one spatial reference frame. We are currently collecting electrophysiology from both CA1 and MEC while animals perform the task.

Conclusions: Based on our behavioral findings, we predict that when spatial reference frames are put into conflict, the CA1 place cells in young animals will show variability in terms of which reference frame they anchor to (as in Lee et. Al., 2004). We predict that aged CA1 place cells, by comparison, will have a greater tendency to remain anchored to the already established reference frame. If the age-related behavioral changes we observe are due to intrahippocampal network impairments, spatially-modulated cells of upstream MEC should show comparable realignment in both age groups.

HUMAN CELLS CORE FOR TRANSLATIONAL RESEARCH AT BANNER SUN HEALTH RESEARCH INSTITUTE. Lue LF, Serrano GE, Walker JE, Nunez T, Walker DG, Brafman D, Reiman EM, Beach TG. Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Animal models are widely used for research in neurodegenerative diseases and have made significant contributions to the understanding of disease mechanisms and developing potential therapeutics. However, there are distinct human features that cannot be entirely recapitulated in animal models. To improve translation from animal research to effective treatment, utilization of cellular models developed from human subject tissues offer promise. At Banner Sun Health Research Institute (BSHRI), the Brain and Body Donation Program (BBDP) yearly receives and processes 50-75 autopsy cases and to provides brain tissues from rapid autopsy (postmortem delay median: 3.5 hours) for neuropathological research. This is a unique resource, as each autopsy case has longitudinal clinical and medical data available from the time of enrollment to death, and neuropathological diagnosis from autopsied tissues. Here, we describe the strategy and progress in using our experiences to establish a comprehensive aged human cell core resource at BSHRI.

Methods: Procedures have been developed for processing human scalp and brain tissues on a routine basis. Scalp tissue obtained from autopsy cases were processed < 20 hours after autopsy. Dermal tissues cut into approximately 1-mm² cubes were used for explant cultures in at 37°C in a cell culture incubator supplied with 5% CO₂ and 95% air until cell outgrowth. Confluent cell cultures from original plating are expanded for three generations before cryo-storage. For microglia, our previously published procedure is used. We plan to use magnetic beads selection methods to obtain pure microglia and astrocytes.

Results: We have implemented procedures for routine culturing of postmortem scalp explants to obtain fibroblasts and for isolating and culturing microglia from cortical tissues. Averagely, we processed 2-3 autopsy cases each month. Currently, 6 cases were used for isolation of both microglia and fibroblasts. The other cases were used either for microglia or fibroblast cultures. The clinical diagnoses of these cases were 6 normal controls, 4 Alzheimer's disease, 4 Parkinson's disease, and 2 mild cognitive impairment. All these cases have demographic information, postmortem delay intervals, detailed clinical assessment for cognitive and movement disorders along with ApoE genotypes. Identification of ApoE genotype is an important feature for all cases in this cell bank. Among 12 cases from which fibroblasts were isolated, there are 2 ApoE allele 3/4 cases, with the remainder being ApoE allele 3/3. No ApoE allele 4/4 or ApoE allele 2 carrier cases have been done yet. The total cell yields varied from case to case. We were able to bank 3-10 vials of 0.5-1.0 million fibroblasts per case. The fibroblasts from a collection of cases with known genotypes will be used for neuron production using hiPSC-technology in a collaboration with stem cell research scientists at Arizona State University. As for microglia, we are testing selection methodology using the surface markers CD11b with antibody-conjugated magnetic beads from Miltenyi Biotec and StemCell Technologies. These procedures are being optimized in our laboratory. After optimization of the microglia selection procedure, we will test a similar procedure for selecting astrocytes.

Conclusions: The initial effort for establishing Human Cells Core for Translational Research using autopsy scalp tissues and cortical tissues has made substantial progress. Characterization of the banked cells is ongoing. We anticipate that the characterized banked cells will be available as a shared resource to research scientists by the third quarter of 2019.

CORRELATION OF PRESYNAPTIC AND POSTSYNAPTIC PROTEINS WITH PATHOLOGY IN ALZHEIMER'S DISEASE. Walker J, Glass M, Arce R, Oliver J, Intorcica A, Nelson C, Papa J, Arce A, Vargas D, Sue L, Beach TG, Serrano G. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Synaptic transmission is essential for nervous system function and its dysfunction is a known major contributor to dementia. The correlation between synaptic loss and Alzheimer's disease dementia (ADD) was established in the late 1980s using electron microscopy (EM) techniques. These methods are precise but are limited by the laborious tissue processing required and by their practical restriction to extremely small tissue samples. In the 1990s, immunochemical quantification became possible and confirmed 30-50% neocortical synaptic protein losses in ADD, but there has not yet been a comprehensive profiling of different synaptic proteins in different brain regions in ADD.

Methods: In this study we quantified densities of two synaptic proteins, the presynaptic protein SNAP25 and the postsynaptic protein PSD95 using enzyme-linked immunosorbent assays (ELISA). Grey matter from cingulate, hippocampus and frontal, visual and entorhinal cortex were dissected for protein extraction from non-demented controls (ND, n=25) and ADD subjects (n=25). Cases were selected by a database search of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Case selection aimed to avoid differences in age and include different levels of ADD pathology.

Results: Our analysis demonstrates that SNAP25 and PSD95 protein expression were significantly reduced in ADD entorhinal cortex as compared to ND controls ($p < 0.0001$). No other brain region showed significant changes in both SNAP25 and PSD95. Significant reductions of presynaptic SNAP25 alone were found in frontal and visual cortex but not in hippocampus and cingulate gyrus. Paradoxically, significant reductions in postsynaptic PSD95 were present in hippocampus and cingulate gyrus but not in frontal and visual cortex.

Conclusions: Caution should be taken in interpreting changes in synaptic protein expression as synaptic loss, but to our knowledge this is the largest set of cases across multiple brain regions used to study synaptic protein expression in ADD. Our results suggest that synaptic transmission in the entorhinal cortex of ADD patients is severely affected, most probably because this brain region is one of the earliest affected areas and by the time of clinically-manifest dementia has very high densities of neurofibrillary tangles. The entorhinal area is the main interface between the hippocampus and neocortex, making this area crucial for memory formation and consolidation.

NEUROFIBRILLARY TANGLE EVOLUTION IN THE FRONTAL CORTEX OF DEMENTED AND NON-DEMENTED SUBJECTS WITH DOWN SYNDROME. Perez SE, Miguel JC, Nadeem M, Sabbagh MN, Lott IT, Doran E, Mufson E. Barrow Neurological Institute; University of California, Irvine Medical Center; Arizona Alzheimer's Consortium.

Background: Although all individuals with Down syndrome (DS) exhibit an age-related increase in A β plaque and tau neurofibrillary tangle (NFT) pathology, not every case develops dementia. We found that phosphorylated NFT pathology in the frontal cortex was greater in demented compared to non-demented DS, while A β pathology was similar in both groups, suggesting that tau pathology plays a greater role in the dementia seen in DS.

Methods: The present study examined the appearance of phosphorylation, truncation and conformational posttranslational tau epitopes in frontal cortex pyramidal layers V-VI neurons in age-matched DS without dementia (n=6) and DS with dementia (DS-D) (n=10) using immunofluorescence combined with quantitative analysis. Triple immunofluorescence was performed using antibodies against early and late tau markers: phosphorylated AT8 (1:50), early phosphorylated pre-tangle pS422 (1:50), conformational Alz50 (1:50) or truncated TauC3 (1:50) epitopes.

Results: Quantitation revealed that the number of AT8+pS422+Alz50, TauC3+pS422+Alz50, pS422+Alz50 and TauC3+pS422 positive NFTs were significantly higher in DS-D compared to DS, suggesting a differential evolution of frontal cortex NFT formation in DS-D. A within group analysis revealed that cortical AT8+pS422+Alz50 positive NFT numbers were significantly greater than pS422+Alz50 NFTs in DS with and without dementia, while AT8+pS422+Alz50 NFTs were greater than AT8+Alz50 NFTs in DS-D, but not in DS. Numbers of NFTs reactive for TauC3+pS422+Alz50 were significantly greater than those displaying pS422+Alz50 and TauC3+Alz50 in DS-D. TauC3+pS422 positive NFTs were significantly greater than pS422+Alz50 NFTs in DS-D. Conversely no differences were found between double or triple labeled NFTs containing TauC3 in DS.

Conclusions: In conclusion, the large number of pS422, Alz50, TauC3 as well as pS422+TauC3 NFTs in DS-D compared to DS, suggest that truncation at glutamic 421 (TauC3) and phosphorylation at serine 422 (pS422) are differentially altered between DS groups. In addition, the observation that NFT numbers containing Alz50+pS422 and Alz50+TauC3 are lower compared to AT8+pS422+Alz50 and TauC3+pS422+Alz50 NFTs respectively, in DS and DS-D, indicates that phosphorylation and truncation changes precede conformational tau events in DS.

THE USE OF HUMAN PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS (IPSCS) TO STUDY MECHANISMS OF DISEASE PATHOGENESIS IN NEURODEGENERATIVE DISEASES. Sattler R, PhD, Moore S, BS, Lorenzini I, PhD, Alsop E, PhD, Van Keuren-Jensen K, PhD. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

The variety of symptoms and heterogeneity of affected individuals make diseases of the central nervous system (CNS) difficult to diagnose, study, and treat. Patient-derived human induced pluripotent stem cells (iPSCs) have become a novel tool to complement the static examinations of post-mortem tissue, which make it difficult to study cellular and molecular mechanisms of degeneration or the interaction between different CNS cell types, such as neurons and glial cells. Here we present data exemplifying how patient iPSCs were applied to study mechanisms of neurodegeneration in the spectrum disease of FTD/ALS. In particular, we will discuss two disease pathways that are thought to contribute to neuronal dysfunction, and ultimately, neurodegeneration in the familial form of C9orf72 FTD/ALS using iPSC differentiated motor neurons, cortical neurons and microglial cells.

C9orf72 patient-derived human induced pluripotent stem cells (hiPSCs) were differentiated into spinal motor neurons (hiPSC-MNs), forebrain cortical neurons (hiPSC-CNs) and microglial cells (hiPSC-MGs) using modifications of previously published protocols. Human cells were used for studies on 1) deficits in RNA metabolism due to nucleocytoplasmic trafficking defects and 2) mechanisms of neuronal synaptopathy and the contribution of microglial to this disease pathogenesis.

Our studies show that nucleocytoplasmic trafficking defects lead to the mislocalization of the RNA editing enzyme ADAR2, which in turn causes widespread RNA editing aberrations, affecting numerous disease relevant genes and pathways. In addition, we show that neuronal mono-cultures derived from C9orf72 patients have significant synaptic dysfunctions as shown by changes in dendritic branching, dendritic length and synapse density. We further detected aberrant expression of synaptic proteins in conjunction with changes in neuronal excitability measured via longitudinal micro-electrode array (MEA) analyses. We also generated hiPSCs differentiated microglial cells from healthy and C9-FTD/ALS patients and examined changes in microglial gene expression and microglial-specific brain functions, such as phagocytosis. Preliminary experiments support the co-culturing of hiPSC-CNs with hiPSC-MGs, which are currently being studied for neuronal and microglial activities in different co-culture combinations.

We established disease-relevant phenotypes in hiPSC MNs, CNs and MGs as mono-cultures. The *in vitro* co-culture system of hiPSC-derived neuron-microglial cells will now be used to determine the role of microglial cells in neuronal synaptic dysfunction in C9-FTD/ALS. These human *in vitro* culture models (mono-cultures and neuronal-glial co-cultures) not only allows for the studies of C9 FTD/ALS disease pathogenesis, but any other neurodegenerative disorder, including other subtypes of FTD, Alzheimer's disease and Down's Syndrome.

ABCC1 MUTATION IS ASSOCIATED WITH ALTERED APP PROCESSING IN A FAMILIAL CASE OF LATE-ONSET ALZHEIMER'S DISEASE. Jepsen WM, De Both M, Piras IS, Siniard AL, Henderson-Smith A, Ramsey K, Serrano G, Caselli RJ, Beach TG, Huentelman MJ. Translational Genomics Research Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Genome wide association studies (GWAS) have provided valuable insight into the complexities of the common polymorphic variants associated with Alzheimer's disease (AD). However, GWAS has failed to completely describe the heritable risk for AD; therefore, approaches utilizing genome sequencing are now necessary in order to characterize the remaining rare variants and genes that may alter AD risk.

Methods: The investigated family consisted of 10 siblings, 6 of whom were diagnosed with dementia, most frequently with a behavioral variant suggestive of frontotemporal dementia (FTD). However, a recent autopsy of an affected sibling revealed a high level of AD neuropathological change with no evidence of FTD. Whole exome sequencing analysis was utilized to identify the top genetic variants associated with dementia diagnosis. The identified variant was studied in vitro to confirm modulation of hallmark AD-associated peptides and transcripts via ELISA, flow cytometry, RNA-seq, and qRT-PCR.

Results: We identified a germline mutation in the ABCC1 gene (chr16:16216007 A>G, p.Y1189C) associated with increased extracellular Abeta1-40,1-42, and Abeta/sAPPalpha peptide ratios, in vitro. Further analysis revealed that the effect is most likely due to modulation of TIMP3, a metallopeptidase inhibitor capable of altering alpha-secretase cleavage of APP. ABCC1 is also shown to influence the expression of PLXNA4, KCNIP4, and MEGF10, all of which are associated with AD pathology.

Conclusions: This serves as strong evidence for the association of ABCC1 in the pathogenesis of AD, thereby adding further human genetic support to the "amyloid hypothesis", and is – to the best of our knowledge – the first germline mutation in ABCC1 to be associated with human disease. Modulation of ABCC1 is predicted to be a novel way to therapeutically alter Abeta processing in humans via its multimodal influence on AD pathology and amyloidogenesis.

AMYLOID PET, TAU PET, AND MRI MEASUREMENTS IN COGNITIVELY UNIMPAIRED PERSONS WITH TWO, ONE, & NO COPIES OF THE APOE4 ALLELE. Ghisays V, Goradia DD, Protas H, Bauer R, Devadas V, Tariot PN, Lowe VJ, Knopman D, Petersen RC, Jack CR, Caselli RJ, Su Y, Chen K, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Mayo Clinic Arizona; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: We recently characterized relationships between tau PET measurements and apolipoprotein E4 (APOE4) gene dose in cognitively unimpaired late middle-aged and older adults and the extent to which these relationships are associated with age, amyloid- β (A β) positivity, and long-term verbal memory decline. We now extend those findings to a larger number of research participants, incorporate MRI measurements of cortical atrophy and provide new information about the AD biomarker classification of those with two, one, and no APOE4 alleles using the (A β /tau[neurodegeneration]) "AT(N)" framework.

Methods: Pittsburgh Compound-B (PiB) PET, flortaucipir PET, and T1-weighted volumetric MRI were used to assess fibrillar A β burden, paired helical tau burden, and cortical atrophy in 165 participants, ages 47-86, in the Arizona APOE Cohort Study and Mayo Clinic Study of Aging, including 26 APOE4 homozygotes, 48 heterozygotes, and 91 non-carriers matched for age, sex, and education. SPM12 and previously described regions-of-interest (ROIs) were used to characterize composite cortical-to-cerebellar PiB standard uptake value ratios (SUVRs) and entorhinal cortex, inferior temporal cortex, and composite cortical-to-cerebellar flortaucipir SUVRs; FreeSurfer and previously described cortical ROIs were used to provide a composite measure of cortical thickness. Previously described composite PiB SUVR \geq 1.42, flortaucipir SUVR \geq 1.23, and cortical thickness \leq 2.67mm thresholds were used to classify participants using the AT(N) framework.

Results: 38%, 35%, and 12% of the APOE4 homozygotes, heterozygotes, and non-carriers had a "positive" PiB PET scan. Compared to non-carriers, the homozygotes and heterozygotes had higher PiB SUVRs ($p < 0.01$). They also had higher entorhinal flortaucipir SUVRs and greater associations between composite flortaucipir SUVRs and age, findings that were solely attributable to those carriers with a positive PiB PET scan ($p < 0.05$). We will discuss these and other findings, including the percentages of each AT(N) classifications and the extent to which downstream biomarkers are influenced by A β positivity, age, and their interaction with two, one or no APOE4 alleles.

Conclusions: This study provides new information about AT(N) measurements and classifications in an unusually large number of cognitively unimpaired persons at three levels of genetic risk for late-onset AD. Tau pathology is preferentially affected in unimpaired APOE4 carriers with a positive A β PET scan.

RELATIONSHIPS BETWEEN BASELINE BRAIN IMAGING BIOMARKER MEASUREMENTS AND AGE IN THE API AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE COLOMBIA TRIAL. Su Y, Romenets SR, Tariot PN, Sink KM, Clayton D, Hu N, Guthrie H, Smith J, Cho W, Langbaum JB, Thomas RG, Giraldo-Chica M, Tobon C, Acosta-Baena N, Navarro A, Piedrahita F, Alvarez S, Chen K, Goradia D, Thiyyagura P, VanGilder PS, Luo J, Ghisays V, Lee W, Malek-Ahmadi MH, Protas HD, Chen Y, Ho C, Suliman S, Quiroz YT, Paul R, Lopera F, Reiman EM, API ADAD Colombia Trial Group. Banner Alzheimer's Institute; Grupo de Neurociencias de Antioquia of Universidad de Antioquia; Genentech Inc.; Roche Products Ltd; University of California; Hospital Pablo Tobon Uribe; Harvard Medical School and Massachusetts General Hospital; Arizona Alzheimer's Consortium.

Background: We previously used data from 54 cognitively unimpaired and impaired 20-59 year-old presenilin 1 (PSEN1) E280A mutation carriers and noncarriers from the world's largest autosomal dominant kindred (median age of 44 at mild cognitive impairment [MCI] onset) to characterize associations with age and estimated ages at onset (AAO) of brain imaging and fluid biomarker abnormalities in the mutation carrier group (Fleisher, 2015). Here, we analyzed baseline brain imaging measurements of amyloid- β ($A\beta$) plaque deposition, precuneus glucose hypometabolism, and hippocampal volume from 242 cognitively unimpaired 30-53 year-old PSEN1 E280A mutation carriers and non-carriers in the Alzheimer's Prevention Initiative (API) ADAD Colombia Trial, characterized their relationships with age, and estimated their AAO in the mutation carrier group.

Methods: Baseline florbetapir PET, fluorodeoxyglucose (FDG) PET, and volumetric MRI images from 167 mutation carriers and 75 age matched noncarriers were analyzed using previously established pipelines (Fleisher, 2015; Su 2015) to characterize 1) $A\beta$ plaque burden using mean-cortical-to-pontine florbetapir standard uptake value ratios (SUVRs), 2) cerebral glucose hypometabolism using precuneus-to-whole brain FDG SUVRs, and 3) neurodegeneration using hippocampal-to-intracranial volume ratios. Linear regression models were used to characterize biomarker associations with age in the two genetic groups. AAOs, defined as the age at which mean biomarker values diverge significantly between the mutation carrier and non-carrier groups, were estimated using both approximate t-tests and the 95% confidence interval (CI) band of age associations.

Results: AAO of mean cortical increases in florbetapir SUVR, decreases in precuneus FDG SUVR, and declines in hippocampal volume were less than 30 years, 36 (95%CI 30-40) years, and 42 (95% CI 37-48) years, respectively.

Conclusions: This study provides information about associations between baseline brain imaging measurements and age in a large number of cognitively unimpaired PSEN1 E280A mutation carriers and non-carriers from the API ADAD Colombia Trial. Findings are roughly consistent with observational studies of ADAD (Bateman, 2012; Fleisher 2015), and the extent to which they support the hypothetical ordering of biomarker changes in preclinical AD (Jack 2018) will be presented.

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 four years (2015-2018). 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 understandings and therapies 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 of Alzheimer's disease to study new treatments as well as mechanisms and trajectory of pathology (Oddo and Caccamo laboratories), in the development of novel induced pluripotent stem cell and other cellular models (Brafman laboratory), in antibody and novel compound strategies for the treatment of Alzheimer's and other neurodegenerative diseases (Khdour laboratory), in the development and use of animal models in the evaluation of sex differences and gonadal hormone contributions to the trajectory of behavioral and neuropathological change across aging (Bimonte-Nelson laboratory), in processes to pinpoint mechanisms contributing to sex differences in the development and progression of Alzheimer's disease (Wilson Sayres laboratory), in the evaluation of age-related changes in neurobehavioral underpinnings of nicotine addiction vulnerability in females, in the development and implementation of computational image analysis and biomathematical techniques to increase the power to detect and track progression from MCI to Alzheimer's disease (Wang laboratory), and in the development of multicomponent interventions for individuals living alone with MCI (Coon research 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 Center¹. The center is an extension of the partners' work with the Arizona Alzheimer's Consortium and is envisioned to become one

¹ <https://science.asu.edu/neurodegenerative-disease-research-center>

of the world's largest basic science centers for the study of Alzheimer's and other neurodegenerative diseases. The Center is expected to grow to include about 20 new laboratories and additional affiliated laboratories. It will foster push-pull relationships between big data and other analyses of post-mortem and other human data sets and experimental models and leverage an emerging collaboration among several consortium partners to provide a public resource of detailed omics data from different cell types and regions in clinically and neuropathologically characterized brain donors. The Center is intended to further clarify disease mechanisms and risk factors for AD and related disorders, provide new therapeutic targets, and support the discovery of new treatments and biomarkers.

A strength of ASU is the training, mentoring, and education of future generations of aging and neurodegenerative disease researchers and academicians, spanning high school students, to undergraduate students, to graduate students, to postdoctoral fellows. The approach to training is hands-on, multifaceted, and interdisciplinary, with the goal to engage future scientists in aging and neurodegenerative research to yield maximal impacts on research discovery and translational outcomes. The new Research Education Component, Co-Directed by Dr. Heather Bimonte-Nelson (ASU) and Dr. Yonas Geda (Mayo) reflects this strong and extensive training commitment. Notably, ASU offers graduate degrees in Statistics and Biomedical Informatics, the Behavioral Neuroscience Program² within the Department of Psychology, as well as the Interdisciplinary Graduate Program in Neuroscience³. The latter two training programs focus upon approaches that integrate multiple levels of analysis using systems and interdisciplinary approaches – cellular, behavioral, and cognitive – to address preclinical, clinical, and translational questions about brain and behavior relationships.

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
Ahamed, Anisa	--	Undergraduate Research Assistant
Ahmed, Kinza	--	Undergraduate Research Assistant
Angulo, Aylin	BS	Research Specialist
Austin Vural	--	Research Technician
Barker, Charlotte	--	Undergraduate Research Assistant
Belfiore, Ramona	PhD	International Graduate Student
Bhandarkar, Siddhi	BS	Graduate Researcher
Bimonte-Nelson, Heather	PhD	PI, Professor
Brafman, David	PhD	PI
Brookhouser, Nicholas	MS	Graduate Researcher
Bulen, Haidyn	--	Undergraduate Research Assistant
Bull, Amanda	--	Undergraduate Research Assistant
Bustos, Lynette	MS	Graduate Student
Caccomo, Antonella	PhD	Assistant Research Professor
Campos, Nicole	--	Undergraduate Student
Carbajal, Berta	--	Research Specialist
Carfagno, Vince	--	Undergraduate Research Assistant
Carll, Phil	MSW	Research Specialist
Coon, David	PhD	PI, Professor
Cordova, Lourdes	--	Survey Interviewer
Cortes, Marilysse	MSW	Program Manager
Cutts, Joshua	MS	Graduate Researcher
Decker, Annika	--	Student Worker
Ferreira, Eric	MS	Research Technician
Fux, Chaya	BS	Research Technician
Gipson-Reichardt, Cassandra	PhD	Assistant Professor
Glinka, Allison	MS	Research Specialist
Goldman, Jami	MSW	Research Specialist
Gomez Morales, Abi	MS	Ph.D. Student
Hecht, Sidney	PhD	Co-PI
Isosaki, Mikayla	--	Undergraduate Research Assistant
Johnson, Raena	--	Undergraduate Research Assistant
Khdour, Omar	PhD	PI, Research Professor
Knowles, Sara	MS	Graduate Student
Koebele, Stephanie	--	Graduate Student
Kostes, William	BS	Graduate Researcher
LaBaer, Joshua	PhD	PI, Executive Director and Professor
Ladwig, Ducileia	--	Undergraduate Research Assistant
Leyrer-Jackson, Jonna M.	PhD	Postdoctoral Fellow
Logan-Robledo, Santiago	--	Undergraduate Research Assistant
Macomber, Alyssa	--	WINURE Student
Mann, Abigail	--	High School Research Assistant

Name (last, first)	Degree	Role on project
Manzo, Alyssa	--	Undergraduate Research Assistant
Melikian, Ryan	--	Undergraduate Research Assistant
Mifflin, Marc	--	Undergraduate Student
Montague, Richard	MS	Ph.D. Student
Namba, Mark	--	Graduate Student
Neeley, Rachel	--	Undergraduate Research Assistant
Nguyen, Cuong	BS	Graduate Researcher
Northup-Smith, Steven	--	Laboratory Manager
Oddo, Salvatore	PhD	Associate Professor
Overby, Paula	--	Lab Manager
Palmer, Justin	--	Undergraduate Research Assistant
Pena, Veronica	--	Graduate Student
Peters, Mollie	BS	Research Assistant
Piña, Jose	--	Undergraduate Research Assistant
Porwal, Anika	--	High School Research Assistant
Prakapenka, Alesia	--	Graduate Student
Raman, Sreedevi	MS	Graduate Researcher
Ramsey, Jaden	--	Undergraduate Research Assistant
Rodin, Alexis	BS	Masters Student
Schatzki-Lumpkin, Alex	--	Undergraduate Research Assistant
Schrier, Ally	--	Undergraduate Research Assistant
Srinivasan, Gayathri	MS	Research Technician
Stotler, Kassey	M.Ed.	Research Specialist
Striegel, James	--	Undergraduate Research Assistant
Strouse, Isabel	--	Undergraduate Research Assistant
Surendra, Likith	--	Undergraduate Student
Tekel, Stefan	BS	Graduate Researcher
Turk Willeman, Mari	PhD	Postdoctoral Fellow
Turner, Emily	PhD	Postdoctoral Fellow
Ulangkaya, Hanaa	--	Undergraduate Research Assistant
Underwood, Avery	BS	Research Assistant
Valenzuela Sanchez, Maria	--	High School Research Assistant
Van Do, Ngoc	--	Undergraduate Research Assistant
Vartak, Rasika	PhD	Postdoctoral Fellow
Velazquez, Ramon	PhD	Postdoctoral Fellow
Vural, Austin	BS	Research Technician
Wang, Yalin	PhD	Associate Professor
Wilson Sayres, Melissa	PhD	Principal Investigator
Winslow, Wendy	BS	Laboratory Manager
Woner, Victoria	--	Graduate Student
Zheng, Lei	PhD	Associate Scientist

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 ϵ 4 carriers and non-carriers provide a core resource for interested investigators inside and outside of Arizona.

In the next few years, BAI, BSHRI, and their partners will place a growing emphasis on the acquisition of antemortem brain-imaging, CSF, and blood-based biomarkers for AD and related disorders in their longitudinal cohorts, and help to find and support the use of promising amyloid and other blood tests for AD and related disorders. These organizations, TGen, and ASU (e.g., at the ASU-Banner Neurodegenerative Disease Research Center [NDRC]) are also developing a shared resource of DNA and RNA sequencing data from different brain cell types and regions in high-quality brain samples from AD cases and controls and are using big data analytical techniques to characterize networks and drivers at which to target in the discovery of new treatments. They and their organizational partners will also be exploring targets at which to aim APOE modifying treatments. 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 international API Generation Studies 1 and 2 in persons at particularly high risk for the clinical onset of late-onset AD, a proposed API-A4 aducanumab prevention trial in cognitively unimpaired amyloid- β positive adults (for which we just received a larger NIH grant), and other trials TBD. The 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 2023.

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] and AD in patients with Down syndrome).
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 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, and advance the complementary research goals of our partners inside and outside Arizona.
7. 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.
8. To support the clinical research and Native American outreach, education and enrollment goals of the Arizona ADCC.
9. 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 (last, first)	Degree	Role on project
Reiman, Eric	MD	Executive Director, BAI Director, Arizona Alzheimer's Consortium (AAC) and NIA-supported Arizona ADCC
Tariot, Pierre	MD	Director, BAI
Amador, Ricardo	MS	ADCC Data Coordinator
Bandy, Dan	MS, CNMT	PET Technical Director and Sr. Scientist
Batchuluun, Dawn	BA	Clinical Research Coordinator
Boker, Connie	BS, MBA	Director, Imaging Center Operations
Brand, Helle	PA	Physician Assistant, Memory Disorders Center
Burke, William	MD	Director, Stead Family Memory Center
Chen, Kewei	PhD	Consultant, Computational Image Analysis Program
Copeland, Jacquelynn	PhD	Neuropsychologist
DeMarco Kathryn	BS	Manager, Clinical Research Program
Ghisays, Valentina	PhD	Post-Doctoral Fellow
Goldfarb, Danielle	MD	Physician Neurologist, Memory Center
Gopalakrishna, Ganesh	MD	Physician Dementia Specialist, Memory Center
Goradia, Dhruvan	PhD	Bioinformatics Scientist
High, Nellie	MS	Research Project Coordinator
Jaeger, Chad	BS	Research Administrator Senior Director
Jakimovich, Laura	RN	Multi-Center Clinical Trials Manager
Jansen, Willemijn	PhD	Post-Doctoral Fellow (Part-Time)
Koren, Andrei	PhD	Senior Scientist, Lab Head Radiochemistry Research
Langbaum, Jessica	PhD	Associate Director, Alzheimer's Prevention Initiative
Langlois, Carolyn	MA	Clinical Research Program Manager
Lee, Wendy	MS	Assistant Director, Computational Brain Imaging
Lomay, Nicole	BS	Native American Outreach Representative
Patel, Roma	MS	Clinical Trials Senior Manager
Malek-Ahmadi, Michael	PhD	Bioinformatics Scientist
Nisson, Lori	MSW/ LCSW	Director, Family & Community Services
Pandya, Sachin	BS	Clinical Research Coordinator
Perrin, Allison	MD	Physician Dementia Specialist
Protas, Hillary	PhD	Bioinformatics Scientist
Saner, Don	MS	Senior Director, Data Science; Director, ADCC Data Management and Statistics Program
Su, Yi	PhD	Director, Computational Brain Imaging Analysis Program; Co-Director, ADCC Data Management and Statistics Program
Tsai, Po-Heng	MD	Physician Dementia Specialist, Memory Center
Weidman, David	MD	Physician Dementia Specialist, Memory Center

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 Memory and Movement Centers, The Division of Neuropsychology, Family and Community Services, and the Neurowellness Program; **c)** More than 25 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 1,200 research participants (~650 active), including nearly 200 in their 90s and 100s, for the study of cognitive aging; as well as a newly established Brain Health Check-In Program in December 2018 that provides scheduled and walk-in brain health concern assessments; and a newly established longitudinal validation cohort study in January 2019 for AD prevention instruments; **e)** Extensive **outreach, education, training and volunteer programs** including 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 >1,930 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 BBDP 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; **c)** Recent hiring of an Institute Director, Alireza Atri, MD, PhD; **d)** Recent launch of the Brain Health Check-In community service program at the Center for Health Aging; **e)** Enhancing BSHRI's Longevity Study cohort, and harmonizing 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/translational 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 >120 international, national, regional, and community presentations per year; and **g)** Expanding the BBDP in several impactful ways, including plans to increase to 900-1,000 annually assessed prospective brain donors in the next 1-2 years; the inclusion of blood and CSF samples and imaging data in an increasing number of BBDP participants; development of a public resource of sorted cells; and development of a resource of omics data from different cell types and regions that differ in the vulnerability and resilience to elements of AD pathology (such that we, our TGen, NDRC and other consortium colleagues, and other researchers could help to clarify disease networks, treatment targets and new treatments).

BANNER SUN HEALTH RESEARCH INSTITUTE

Key Personnel

Name (last, first)	Degree	Role on project
Atri, Alireza	MD, PhD	Director, Banner Sun Health Research Institute
Auman, Briana	PysD	Neuropsychologist
Beach, Thomas	MD, PhD	BBDP & Neuropathology Core Director, Neuropathologist
Belden, Christine	PsyD	Neuropsychologist
Burks, Teresa	NP	Nurse Practitioner
Davis, Kathryn	BA, CSP, CRC	Clinical Core Coordinator, ADCC and BBDP
Dhanani, Sara	MD	Movement Disorders Neurologist
Liebsack, Carolyn	RN, BSN, CCRC	Clinical Trials Program Operations Director Center for Health Aging
Lue, Lih-Fen	PhD	Senior Scientist, Human Cells Core for Translational Research, BBDP
Moorley, Naudia	PsyD	Neuropsychologist
O'Connor, Kathy	MS	Outreach Program Manager/Longevity Program Coordinator
Powell, Jessica	PsyD	Neuropsychologist
Reade, Marina	NP, PhD	Nurse Practitioner
Schmitt, Andrea	BS, CRA	ADCC Administrative Director
Serrano, Geidy	PhD	Anatomist Supervisor, BBDP
Shprecher, David	DO	Movement Disorders Program Director, Movement Disorders Neurologist
Spann, Bryan	DO, PhD	Dementia Neurologist
Sue, Lucia	BS	Coordinator and Tissue Donation Manager, Neuropathology Core and BBDP
Zamrini, Edward	MD	Director, Memory Clinic Director; ADCC Clinical Core Site PI; Investigator, Center for Healthy Aging; Dementia Neurologist

BARROW NEUROLOGICAL INSTITUTE AT ST. JOSEPH'S MEDICAL CENTER

Institutional Abstract

The Barrow Neurological Institute focuses on human and animal research that can translate to clinical care. The BNI focus in Alzheimer's Disease and aging is in prevention, early detection and defining mechanisms of AD. Investigators at Barrow Neurological Institute engage in human subject studies including clinical trials and laboratory science research of human nervous system function in health and disease processes that can translate into improvements in clinical care. Barrow's work related to Alzheimer's disease and aging concerns new treatment intervention to combat human cognitive decline, early detection of dementing disorders, and identification or refutation hypothesized cellular and molecular mechanisms in AD.

These studies also cross over to additional work on other neurodegenerative disorders. In the past few years, neurodegenerative disease research at Barrow has expanded with the addition of both accomplished senior faculty members and more junior investigators with promise and skill and new ideas about disease mechanisms and treatment opportunities. Laboratory and clinical resources devoted to this enterprise also have increased, and further growth in this area is planned and expected.

The close relationships between clinicians and scientists mean that many cross-disciplinary studies are underway or being developed at Barrow. The Alzheimer's Disease and Memory Disorders Program has seen a 200% increase in patient clinic visits in the past year, which enhances recruitment of patients for research. Funding increases, generously matched and more by Barrow resources, allowed for expansion of pilot research project awards, including new lines of research in advanced multiparametric magnetic resonance imaging techniques in mild cognitive impairment and aging, molecular and cellular mechanisms related to amyloid plaque formation and neural degeneration, roles for inflammatory and immune responses in disease, and neural changes associated with Down's syndrome and Autism.

The Barrow Neurological Institute is focused on supporting the ADCC clinical core in recruiting minority populations into clinical trial. This includes outreach to the Native American population for enrollment into a study of advanced MRI imaging signatures focused on understanding the development of Alzheimer's Disease and related dementias. BNI also supports the clinical core in recruiting, enrolling, and retaining 100 Hispanic participants in the ADCC, with an anticipated enrollment goal for BNI of 40-50 actively enrolled Hispanic participants by 2020

Hispanics contribute to more than 38% of our total patient population. Given the culturally dense volume seeking care at BNI, we have leveraged our unique Hispanic patient population and created a dedicated a program aimed at increasing Hispanic enrollment in Alzheimer Research Trial within Arizona. This has led to the creation of the *Hispanic Enrollment in Alzheimer's Research Trials* (the HEART Program at BNI).

The HEART Program includes an outreach objective and an ADCC clinical core and/or research project recruitment and retention plan. The 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 will support the core in recruiting, enrolling, and retaining 100 Hispanic participants in the ADCC.

BARROW NEUROLOGICAL INSTITUTE AT ST. JOSEPH'S HOSPITAL AND MEDICAL CENTER

Key Personnel

Name (last, first)	Degree	Role on Project
Burke, Anna	MD	Geriatric Psychiatrist
Wicklund, Meredith	MD	Neurologist
Mufson, Elliot	PhD	Neuroscientist
George, Andrew	PhD	Neuroscientist
Perez, Sylvia E	PhD	Neuroscientist
He, Bin	MD	Neuroscientist
Coleman, Paul	PhD	Neuroscientist
Lukas, Ronald	PhD	Neuroscientist
Garcia, Angelica	BS	Study Coordinator
Batchuluun, Dawn	BA	Program Administrator
Ducruet, Andrew	MD	Neurosurgeon
Ahmad, Saif	PhD	Neuroscientist
Snell, Margeaux	MD	Study Coordinator
Hanson, Krista	PhD	Neuropsychologist
Vadovicky, Sheila	MSW	Psychometrist
Martinez, Tiffany	MA	Psychometrist
Stokes, Ashley	PhD	MR Research, Keller Center for Imaging Innovation
Bergamino, Mauricio	PhD	MR Research, Keller Center for Imaging Innovation
Niespodzany, Ashley	MS	Neurocognitive Rater
Steffe, Lori		Study Coordinator
Sattler, Rita	PhD	Neuroscientist
Van Keuren-Jensen, Kendal	PhD	Neuroscientist
Levy, Jennifer	BS	Research Technician
Lorenzini, Ileana	PhD	Post-Doctoral Fellow

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 (last, first)	Degree	Role on Project
Arnerić, Stephen	PhD	PI, Executive Director, Critical Path for Alzheimer's Disease
Burton, Jackson	PhD	Mathematician
Conrado, Daniela	PhD	
Kern, Volker	PhD	
Romero, Klaus	MD	
Stafford, Robert	--	

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). The principal institutions involved in this collaborative research effort are Mayo Clinic Arizona (primary site), Banner Alzheimer Institute, Barrow Neurological Institute, Arizona State University, 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 Dr. Rosa Rademakers at Mayo Clinic Jacksonville.

Our longitudinal study design is a unique strength with our longest participants having been followed for more than twenty 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. Presented an analysis of a computer-based cognitive task developed by Mario Parra sensitive to memory "binding" of different stimulus properties (e.g., shape and color), but we did not find this 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. Identified and characterized participants who have some behavioral features of a "broad autism phenotype" and showed how that influences subjective cognitive decline
8. Showed for the first time, actual personality changes that coincide with the transition from normal cognition to mild cognitive impairment and that in turn lay the groundwork for the behavioral disruptions that are prevalent in patients with MCI and dementia.

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

1. Correlating changes in brain function with structure, metabolism, and pathology including biomarkers in living patients
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 presymptomatic parameters for the timing of symptomatic conversion
4. Develop primary prevention strategies
5. Provide a core resource to all our collaborative partners
6. Correlating nontraditional measures of neuropsychiatric status such as intellectual achievement, sleep patterns, and personality factors with presymptomatic cerebral amyloid levels

Specific goals for this fiscal year include:

1. Coordinate the many biobanking efforts happening at multiple sites which at Mayo include members of the state funding supported Arizona APOE cohort, the federally funded Alzheimer's Disease Center Clinical Core participants, and all those clinically identified patients with young onset Alzheimer's disease.
2. Build on the results of a pilot project of whole exome sequencing in a clinical cohort of patients with biomarker supported young onset Alzheimer's disease by extending them to an autopsy confirmed cohort to test the genetic diversity hypothesis (as a risk factor for nonfamilial young onset Alzheimer's disease).
3. Publish the results of our longitudinal study examining neuropsychological, MRI-based structural, and FDG_PET physiological measures that change in advance of, and so predict the clinical diagnosis of MCI.
4. Continue our collaboration to establish lymphocyte derived iPS cells differentiated in vitro into cortical neurons to explore intraneuronal pathophysiology related to Alzheimer's disease.
5. Continue to work with Adelante Health Center to address disparities in dementia care and research opportunities in a large community-based Latino population.

This research proposal has been peer reviewed and approved by the Mayo Clinic Institutional Review Board (IRB #259-99).

MAYO CLINIC ARIZONA

Key Personnel

Name (last, first)	Degree	Role on Project
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
Hoffman-Snyder, Charlene	DNP	Nurse Practitioner
Henslin, Bruce	BA	Study Coordinator
Johnson, Travis	BA	Study Coordinator

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, Pharmacy, Veterinary Medicine, and Health Sciences, which includes 11 additional programs. We also 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. The recent opening of 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 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, and (5) 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 (GFAP δ), which also interacts with presenilin-1. Telomere shortening is a molecular cause of cellular aging, and advancing age is the greatest known risk factor for AD. This project studies the possibility that GFAP δ variants will modulate the accumulation of amyloid deposits in a cell culture model.
- 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 young and aged APOE4 mice, by measuring middle cerebral artery (MCA) function in APOE3 and APOE4 mice.

MIDWESTERN UNIVERSITY

Key Personnel

Name (last, first)	Degree	Role on Project
Jentarra, Garilyn	PhD	Principal Investigator
Jones, T.B.	PhD	Principal Investigator
Al-Nakkash, Layla	PhD	Principal Investigator
Broderick, Thomas	PhD	Principal Investigator
Potter, Pamela	PhD	Principal Investigator
Bae, Nancy	PhD	Principal Investigator
Swanson, Mark	PhD	Principal Investigator
Eckman, Delrae	PhD	Principal Investigator
Kaufman, Jason	PhD	Co-Investigator
Tullot, Tony	MD	Co-Investigator
Vallejo-Elias, Johana	PhD	Co-Investigator
Jones, Douglas	PhD	Co-Investigator
Gonzalez, Fernando	PhD	Co-Investigator
Li, Weidang	PhD	Co-Investigator
Jones, Carleton	PhD	Co-Investigator
Powell, Jessica	PsyD	Co-Investigator
Murthy, Ashlesh	PhD	Consultant
Rogers, Alexandra	BS	Research Associate
Kingston, Shanika	BS	Research Associate
Potter, Ross	PhD	Laboratory Manager
Chu, Ping	BS	Research Associate
Castro, Monica	BS	Senior Research Associate
Gallas, Genna	MS	Research Associate
Artigas, Jason	MS	Research Assistant
Hernandez, Jose	PhD	MAAC Investigator
Griffin, Michael	PhD	MAAC Investigator
Kokjohn, Tyler	PhD	MAAC Investigator
Veltri, Charles	PhD	MAAC Investigator
Ratiu, Ileana	PhD	MAAC Investigator
Christensen, Stephanie	PhD	MAAC Investigator
Revill, Ann	PhD	MAAC Investigator
Esfandiarei, Mitra	PhD	MAAC Investigator
Huang, Vanthida	PharmD	MAAC Investigator
Kozlowski, Michael	OD, PhD	MAAC Investigator
Lawson, Kathy	PhD	MAAC Investigator
Olsen, Mark	PhD	MAAC Investigator
Shim, Minsub	PhD	MAAC Investigator

Name (last, first)	Degree	Role on Project
Turner, Tamara	EdD,OTR/L	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 progression and the microbiota (the collection of microorganisms that inhabit a niche). To do this, we have established a colony of triple transgenic Alzheimer's Disease (3xTg-AD) and wild-type B6129SF2/J mice for analysis of the murine microbiome and AD-associated pathology throughout the course of AD progression.

To accomplish our research goals, we leverage our Assessment and Accreditation of Laboratory Animal Care (AAALAC)-certified animal facility, a state-of-the-art Biosafety Level (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 QIIME 2 (developed by PI Caporaso at the PMI). NAU and TGen North, located approximately one mile apart, share a sequencing core comprised of 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.

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 and development of QIIME 2 (<https://qiime2.org>; led by PI Caporaso), a microbiome bioinformatics platform. Key features of QIIME 2 focus on reproducibility and transparency of microbiome analysis. These goals are achieved through decentralized data provenance tracking wherein each step of the analysis is automatically recorded and easily obtained in the results.

The goals of our research in the Arizona Alzheimer's Consortium (AAC) are to assess changes in microbiome composition in the gut and other body sites that correlate with Alzheimer's Disease (AD) 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, and Dr. Caporaso is an expert in microbiome analysis, including recent work on using fecal microbiota transplant to improve behavioral symptoms of autism.

NORTHERN ARIZONA UNIVERSITY

Key Personnel

Name (last, first)	Degree	Role on Project
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
Dillon, Matthew	MS	Research Software Engineer
Engelthaler, Daid	PhD	Director of Programs and Operations, TGen North
Highlander, Sarah	PhD	Director of Clinical Microbiome Service Center, TGen North
Jaramillo, Sierra	BS	Graduate Student
Keefe, Chris	--	Student Research Software Engineer
Lee, Keehoon	PhD	Postdoctoral Scholar
Naimey, Turan	--	Student Research Software Engineer
Orisini, Gabrielle	--	Undergraduate Researcher

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 research with emerging molecular technologies to accelerate the development of therapeutics for human disease. Part of the unique nature of TGen is its partnering relationships with academic institutions, clinical practices and corporate entities, each aimed at accelerating the movement of discovery-based research toward clinical application.

TGen is organized into multiple research Divisions including: Cancer and Cell Biology, Molecular Medicine, Quantitative Medicine, Integrated Cancer Genomics, Neurogenomics, Applied Cancer Research and Drug Discovery, and Pathogen and Microbiome. The Neurogenomics Division 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. These clusters include geneticists, molecular and cellular biologists, brain imaging researchers, proteomics researchers 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 were 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), and in cell-free fluid biomarker identification (using extracellular vesicle molecular profiling). The Division also serves as an AD-related genomics resource for the Arizona Alzheimer's Consortium and frequently assists in generation and interpretation of genotype as well as targeted and whole-genome 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, the leverage of molecular information to identify novel drug targets, and in the deeper understanding of the genomic changes associated with disease onset and progression.

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

Key Personnel

Name (last, first)	Degree	Role on Project
Adkins, Jonathan	BS	Research Associate
Alsop, Eric	PhD	Bioinformatician
Antone, Jerry	BS	Research Associate
Bleul, Christiane	MS	Research Associate
Cuyugan, Lori	MS	Research Associate
DeBoth, Matthew	BS	Bioinformatician
Enriquez, Daniel	BS	Bioinformatician
Geiger, Philipp	MS	Research Associate
Henderson-Smith, Adrienne	BS	Research Associate
Hutchins, Elizabeth	PhD	Computational Scientist
Huentelman, Matthew	PhD	Principal Investigator
Jepsen, Wayne	BS	Graduate Student
Lechuga, Cynthia	MBA	Sr. Grants & Contract Administrator
Lewis, Candace	PhD	Postdoctoral Fellow
Liang, Winnie	PhD	Co-Investigator
Meechovet, Bessie	BS, BSN	Research Associate
Piras, Ignazio	PhD	Research Assistant Professor
Reiman, Eric	MD	Consultant
Reiman, Rebecca	BA	Research Associate
Robles, Laura	MBA	Project Accountant III
Sekar, Shobana	MS	Bioinformatician, PhD student
Sinclair, Callie	BA	Clinical Research Coordinator
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, including researchers in the fields of neuroimaging, cognitive and behavioral neuroscience, neuropsychology, psychiatry, neurology, pharmacology, 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 species with humans 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 concerning the effects of healthy and pathological aging, including 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 aging, 3) evaluating how genetic, health, and lifestyle factors brain aging and cognitive decline, 4) developing new behavioral and neuroimaging methods to improve early detection and track brain changes associated due to aging and disease, 5) identify novel therapeutic targets and develop novel pharmacological and other interventions to improve cognitive function during aging, and 6) providing information to the community to advance understanding about aging, cognitive decline, and age-related neurodegenerative disease.

Over the past year, we have begun to establish the resources required to build a database for sharing standardized measurements that will be made available to all AAC researchers. 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. It will also facilitate standardized pipelines for MRI data analysis and establish standardized protocols for collection of biomarkers from blood and CSF.

Program-related activities at the UA include several major areas of research:

Neuroimaging development and application. 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. New technologies are also being explored, including the use of MRI-guided transcranial magnetic stimulation to ameliorate memory impairment in patients with MCI, and MRI-guided focused ultrasound as a potential therapeutic method for releasing amyloid beta.

Early detection and tracking. A major theme of our research focuses 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 cognitive changes associated with hippocampal and perirhinal cortical functions, disturbances in patterns of daily thought, sleep disruptions, exercise history, 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.

Risk for AD. Multiple projects focus on identifying and understanding the factors that increase risk for age-related cognitive impairment and AD, including gender, genetic risk, maternal history, ethnicity, and health factors such as hypertension, heart disease, head injury, cardiovascular fitness, and obesity, as well as sleep disturbance and shifts in circadian rhythm.

Interventions. Research projects are studying various potential targets for intervention. These include the neuropentraxin 2 receptor, protein-protein AMP-AD interactions, inflammatory mechanisms including the MAS receptor, and T.gondii plaque clearance. 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 interventions include behavioral interventions such as exercise and cognitive engagement, technological innovations such as focused ultrasound and TMS, and pharmacological interventions such as T. gondii and neuronal pentraxin 2.

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 with a focus 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. Our researchers are actively engaged in education and outreach in the Tucson community and with a Diversity Outreach Program to enhance community outreach, education, and research participation by underserved minority groups in Arizona.

UNIVERSITY OF ARIZONA

Key Personnel

Name (last, first)	Degree	Role on Project
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
Nan-kuei Chen	PhD	Investigator, Biomedical Engineering
Chou, Ying-hui	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute Investigator, Psychology and Evelyn F. McKnight Brain Institute
Edgin, Jamie	PhD	Investigator; Psychology
Erickson, Robert	MD	Investigator, Pediatrics
Fernandez, Fabian	PhD	Investigator; Psychology, Neurology, Psychology, Evelyn F. McKnight Brain Institute
Kevin Gaffney	PhD	Investigator, Pharmacology
Glisky, Elizabeth	PhD	Investigator; 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
Klimentidis, Yann	PhD	Investigator, Epidemiology and Biostatistics
Konhilas, John	PhD	Investigator, Physiology
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
Raichlen, David	PhD	Investigator; Anthropology

Name (last, first)	Degree	Role on Project
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
Romanowski, Marek	PhD	Investigator, Biomedical Engineering
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
Sweitzer, Nancy	MD, PhD	Investigator, Sarver Heart Center
Trouard, Theodore	PhD	Investigator; Biomedical Engineering, Medical Imaging, Evelyn F. McKnight Brain Institute
Watts, George	PhD	Investigator, Genomics Shared Service, Cancer Center
Wilson, Robert	PhD	Investigator, Psychology
Yin, Fei	PhD	Investigator, Center for Innovation in Brain Science

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, and the Translational Genomics Research Institute. Through these many colleges and institutes, the UA College of Medicine – Phoenix has become an ideal location for collaborations in biomedical research and evidence-based medicine throughout the state of Arizona.

The UA College of Medicine – Phoenix mission is to inspire and train exemplary physicians, scientists, and leaders to optimize health and healthcare 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 current size, the program matriculates 80 new 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 to physicians and translational scientists to conduct these projects that cumulate in a thesis as part of the graduation requirements.

The UA College of Medicine – Phoenix is positioned to accelerate biomedical research and economic engines in Phoenix and the State, by leveraging our relationships with key clinical and community partners. 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 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).

**UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE – PHOENIX
Key Personnel**

Name (last, first)	Degree	Role on Project
Christie, Immaculate	--	Undergraduate research assistant
Giordano, Katherine R.	BS	Graduate student
Griffiths, Daniel R.	BS	Research Specialist, Senior
Hur, Yerin	BS	Technician
Law, L. Matthew	PhD	Co-investigator, Lecturer
Lifshitz, Jonathan	PhD	PI, Associate Professor, Director
Moschonas, Eleni	BS	Technician
Rojas, M. Luisa	MS	Graduate student
Rowe, Rachel K.	PhD	Collaborator
Saber, Maha	PhD	Co-investigator, Post-doctoral fellow
Tallent, Bret R.	LATG	Laboratory manager
Young, Conor	BS	Technician

Project Progress Reports

Project Progress Report
Arizona State University

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Sex matters: Evaluating sex differences in an animal model of Alzheimer's disease. Heather Bimonte-Nelson, PhD, Salvatore Oddo, PhD, Antonella Caccamo, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Project Abstract and Progress:

We aim to determine whether behavioral changes and Alzheimer's disease (AD)-like neuropathology in a transgenic rat model of AD, the TgF344-AD model, are sexually differentiated and modulated by the presence of endogenous gonadal hormones. There are over 5.3 million people in the United States affected by AD and it is the sixth most common cause of death in the nation (Alzheimer's Association, 2017). Notably, two-thirds of reported cases of AD are women. The decline in ovarian hormones at menopause has been argued to play a role in the increased prevalence of AD in women by exacerbating brain changes and cognitive decline. Accordingly, previous research in the 3xTg-AD mouse model has shown that gonadal hormone loss via surgical removal of the ovaries (via Ovx) can exacerbate AD neuropathology, and that this can be attenuated by the addition of 17-beta-estradiol (Carroll et al., 2007). It is possible that circulating gonadal hormone loss can exacerbate AD neuropathology and subsequent behavioral changes. A novel transgenic model of AD in the rat, the TgF344-AD model, allows systematic evaluation of neuropathology and behavioral changes across the disease course; indeed, the TgF344-AD model co-expresses the human APP^{SW} and PS1 Δ E9 genes (Cohen et al., 2013). Currently, there have only been a few publications using this model, with no study methodically testing sex differences and the contribution of endogenous, circulating gonadal hormones to outcomes. Data have demonstrated that TgF344-AD model rats present soluble A β and hyperphosphorylated tau at the age of 6 months (Cohen et al., 2013), and that by 9 months of age there are increases in A β plaque aggregation across the cortex and heightened levels of hyperphosphorylated tau (Joo et al., 2017). Little behavior has been done in this model, with work that has been performed showing that at 15 months of age, animals exhibit impaired spatial reference memory as well as increased locomotor and anxiety-like behavior (Cohen et al., 2013). At 16 months of age, both neurofibrillary tangles and frank neuronal loss have been detected (Cohen et al., 2013). We propose to use the TgF344-AD model to systematically evaluate a behavioral battery and AD-like pathology in males and females, with and without their respective gonadal tissues. This research will set the stage to write an extramural grant with this team of investigators to evaluate sex differences and gonadal hormone contributions to the trajectory of behavioral and pathological change across aging. To date, we have bred the animals, performed Ovx and Castration surgeries, and completed the entire behavioral testing battery. Behavioral data scoring and neuropathology evaluations are underway. We anticipate that the full data collection and analyses will be completed by the summer, and the manuscript will be submitted by the fall of 2019.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Generation and characterization of isogenic RIPK1 knockout hiPSC lines. David Brafman, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims: In this project, we will use our collective expertise in hiPSC culture, manipulation, and gene editing to accomplish the following specific aims:

Specific Aim 1: Generation of isogenic RIPK1 knockout hiPSC lines using a CRISPR/Cas9 approach. Based on our previous experience of developing technologies and strategies to modify specific loci in hiPSCs, we have developed a highly efficient method involving CRISPR/Cas9 to generate isogenic hiPSC lines. In this aim, we will use these CRISPR/Cas9 gene-editing methods to knockout RIPK1 in non-demented control (NDC) and FAD (APP-Dp) hiPSC lines.

Specific Aim 2: Phenotypic analysis of 3-D co-cultures of cortical neurons and microglia generated from wild-type (WT) and RIPK1 knockout (KO) hiPSC lines. From wild-type (WT) and knockout (KO) RIPK1 hiPSC lines, we will generate 3-D co-cultures of cortical neurons and microglia. In addition, to elucidate if RIPK1 effects are mediated through neurons, microglia, or both, WT RIPK1 hiPSC-derived cortical neurons will be mixed in culture with KO RIPK1 hiPSC-derived microglia, and vice versa. Through biochemical analysis of these cultures, we will test if RIPK1 influences: (i) modulation of A β production and oligomerization, (ii) hyperphosphorylation of the tau protein, (iii) regulation of synaptic integrity, and (iv) protection against oxidative and neurotoxic stimuli.

Background and Significance: Alzheimer's disease (AD) affects over 5 million individuals in the U.S. and has a direct cost estimated in excess of \$200 billion/year. Although the cognitive decline associated with AD has been directly linked to a progressive dysfunction and loss of cortical neurons, the mechanisms that contribute to this neuronal loss have yet to be well-established. Previous work conducted in the Oddo laboratory using transgenic mouse models has implicated RIPK1-mediated necroptosis as a chief mechanism of neuronal loss in AD1. The long-term goal of this project is to complement this work through the use of human induced pluripotent stem cells (hiPSCs) to identify the (i) role of neuronal and microglia RIPK1 in AD and (ii) mechanisms of RIPK1-mediated necroptosis activation in AD. As such, in this proposal we will generate and characterize isogenic RIPK1 knockout hiPSC lines. These lines will provide a valuable tool for future studies that will more precisely dissect the underlying mechanisms by which RIPK1-induced neuronal loss contributes to AD onset and progression.

Preliminary Data and Plan: The Brafman laboratory is well-versed in the manipulation of hiPSCs and development of protocols for their directed differentiation towards neural and astroglial lineages. In addition, the Brafman laboratory has extensive experience in the generation of hiPSC lines from non-demented control and AD patients and routinely applies a variety of biochemical and cellular assays to measure AD-related phenotypes in neural cultures derived from these hiPSC lines. Briefly, we have developed several methods to generate 3-D hiPSC-based cortical cultures that better mimic the architecture of in vivo neural tissue. Gene expression and immunofluorescent analysis of 3-D cortical cultures demonstrate high expression of mature neuronal and cortical-related markers. RNA-seq analysis revealed expression of RIPK1 in these culture, making them a suitable system for probing our hypothesis. Relative to neurons generated from NDCs, the 3-D cortical culture from APP-Dp patients have significantly higher levels of A β , A β oligomers, phospho-tau (Thr231), and were more susceptible to glutamate-induced excitotoxicity. It is important to note that these phenotypes were not readily observed in 2-D

neuronal cultures further highlighting the importance of 3-D cultures to as a means to accurately model AD-related phenotypes.

Aim 1 plan: We will use CRISPR/Cas9 technology to delete the RIPK1 gene in hiPSCs, as detailed in our previous publications. Briefly, we will use single-guide RNA flanking exon 2, which contains the ATG start codon. We will sequence the genomic DNA to confirm RIPK1 exon 2 deletion. Only clonal hiPSC lines in which both alleles have been targeted will be subject to further analysis. We will analyze hiPSC lines for (i) characteristic hiPSC cell morphology; (ii) expression of pluripotency markers; (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 (<http://crispr.mit.edu>), we will sequence 20 most likely off-target sites to control for off-target mutagenesis. For each hiPSC line, we will generate at least 3 induced versions of the same gene correction to minimize the possibility that observed phenotypes are a result of off-target effects.

Aim 2 plan: We will generate co-cultures of cortical neurons and microglia using our established and previously published protocols. For generation of 3-D cortical neuron/microglia co-cultures, we will add microglial progenitors to each well of cortical neuronal cultures. We will co-culture cortical neurons with microglia for a minimum of 14 days before starting the experiments described below. To confirm that cells within the co-cultures retain their phenotype, we will evaluate a subset of the co-culture for expression of pan-neuronal (e.g., MAP2, TUBB3, RBFOX2), cortical (e.g. FOXG1, SATB2, CTIP2, EMX1, CUX1, TBR1) and microglial (e.g., IBA1, CD11c) markers. Co-cultures will be generated from various mixtures of WT and RIPK1 KO hiPSCs to assess the cell autonomy of observed phenotypes. We will then measure A β production and oligomerization, tau phosphorylation, necroptosis activation, employing protocols routinely used in the Brafman and Oddo laboratories.

Proposed One-Year and Long-Term Outcomes: The research proposed here will allow us to establish human cellular models to investigate the mechanisms by which RIPK1 leads to neuronal loss in AD. In the future, we will be able to use these models to address important research questions such as: (1) Do the phenotypes associated with RIPK1 occur in a cell-autonomous or non-autonomous manner? (2) What are relationships between genetic risk variants, AD-related phenotypes, and RIPK1 mediated-neuronal loss? (3) Are there molecular targets that can be modulated to reduce RIPK1 mediated-neuronal loss? The preliminary data and models that we will develop as part of this research will allow us to apply for more comprehensive grants to funding agencies (e.g. NIH, Alzheimer's Association, and American Federation for Aging Research) to address these questions. Publication and presentation results shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices.

Year End Progress Summary:

Aim 1: Over the past year, we have significantly enhanced our ability to precisely modify the endogenous genome in hiPSCs. Specifically, many gene modification strategies involve the introduction of site-specific, double-stranded breaks (DSB) into the genome via the RNA-guided CRISPR-Cas9 system. Following DSB, the cell can activate endogenous repair mechanisms through non-homologous end joining (NHEJ) or homology-directed repair (HDR) pathways. In the absence of a DNA repair template, NHEJ typically results in gene deletion. However, gene modification in hiPSCs via CRISPR/Cas9-induced DSB followed by dsDNA-based HDR still suffers from low efficiencies. To that end, we developed a strategy, transient reporter for editing enrichment (TREE), that allows for the highly efficient genetic modification of hiPSCs. We are currently employing these new techniques to edit the RIPK1 locus in hiPSCs to address the scientific questions outlined in this project.

Aim 2: During the last year, we have made significant progress in the generation of various neuronal and non-neuronal cell populations from hiPSCs. In particular, we have made substantial advances to generate hiPSC-derived 3-D co-cultures as well as develop biomanufacturing methods for the large-scale generation of hiPSC-derived neural cell populations. We are currently employing this ability to generate and characterize various neural cell types differentiated from AD and control hiPSCs to address the hypothesis described in this project.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Identify proteins that increase necroptosis susceptibility in a mouse model of Alzheimer's disease. Antonella Caccamo, PhD, Ignazio Piras, PhD. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Abstract: Elucidating the mechanisms underlying neuronal loss in Alzheimer's disease (AD) will be invaluable to the development of new therapeutic approaches. We reported that necroptosis is activated in AD where it may contribute to neurodegeneration. Necroptosis is a programmed form of necrosis triggered by receptor-interactive protein kinases (RIPK) 1 and 3. Upon activation, RIPK1 binds to RIPK3 to form a multiprotein complex known as a necrosome, which is sufficient and necessary for necroptosis activation. Upon necrosome formation, necroptosis is executed by the activation, phosphorylation, and oligomerization of MLKL, which leads to mitochondrial uncoupling, lipid peroxidation, and eventually cell death. Our preliminary data show that necroptosis is activated in human AD brains. In addition, we showed that old but not young APP/PS1 mice, a widely used animal model of AD, are more susceptible to necroptosis activation. In this grant application, we will use an unbiased approach to identify possible mechanisms underlying the increased susceptibility of APP/PS1 to necroptosis activation.

Progress to Date: We have generated and aged the mice needed to perform the proposed experiments. We have also generated and validated two independent AAVs, one expressing constitutively active MLKL (caMLKL) and one expressing wildtype MLKL. We will inject these viruses into the third ventricle of APP/PS1 mice (n = 14) and non-transgenic (NonTg) littermates (n = 12). Control age- and gender-matched APP/PS1 and NonTg mice (n = 14 mice/genotype) will be injected with AAVs expressing GFP. Three months after the surgeries, we will isolate the hippocampi and send them to Creative Proteomics to conduct unbiased proteomics using their well-established isobaric tags for relative and absolute quantitation (iTRAQ)-based proteomics analysis. We will validate the proteins identified by iTRAQ against publicly available gene expression databases from human AD brains. Only proteins that are differentially expressed between AD and CTL will be considered for further analyses.

We have leveraged the preliminary data obtained to submit an R01 application, which has been funded by the NIH (PI: Oddo, Co-I: Caccamo).

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Psychosocial Intervention Development for Those Living alone with Mild Cognitive Impairment. David W. Coon, PhD, Dona Locke, PhD. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims: To develop a psychosocial intervention to improve and maintain quality of life for patients who are living alone with Mild Cognitive Impairment.

Background and Significance: Approximately 15-20% of people age 65 and older have Mild Cognitive Impairment (MCI), a condition characterized by measurable changes in thinking abilities that are noticeable to both people with MCI and their family/friends. However, people with MCI can still carry out their everyday activities. A recent systematic review suggests that approximately 32% of people with MCI go on to develop Alzheimer's within 5 years (Ward, Tardiff, Dye, & Arrighi, 2013). Depression appears to be quite common among MCI patients (25% in community samples; 40% in clinical samples) (Ismail, Elbayoumi, & Fischer, 2017), and MCI patients have reported significantly lower psychological quality of life compared to their peers with normal cognitive functioning. Moreover, living alone with MCI appears to place these MCI patients at higher risk for poorer outcomes (Muangpaisan et al., 2008). To date, no evidence-based treatments have been identified that improve and maintain quality of life for people living alone with MCI. The two investigators for the proposed project run intervention programs for individuals diagnosed with MCI and/or early-stage dementia. Early-stage Partners in Care (EPIC), led by Dr. Coon as a partnership with ASU and the Alzheimer's Association, is a program focused on patients with early-stage dementia and their care partners. This group dyadic intervention includes education and skill-training workshops designed to reduced stress, enhance well-being, and help manage challenges by hearing the patient's voice in terms of care values and future care preferences. The HABIT Healthy Action to Benefit Independence and Thinking program, led by Dr. Locke at Mayo Clinic, is a cognitive rehab and brain wellness intervention for patients with MCI and a program partner. HABIT aims to support functioning, improved quality of life, and strengthen partnerships. EPIC and HABIT can be seen as companion programs as each involves different types of interventions. The HABIT program involves: (1) cognitive rehabilitation (2) support group for both patient and partner (3) wellness classes (4) cognitive exercise and (5) yoga. However, neither program is designed to support MCI patients who do not have someone to be their partner (e.g., individuals living alone with MCI with no local family members). Using our experiences with EPIC and HABIT as a frame, we want to respond to local and federal partner requests (e.g., the Alzheimer's Association, local Area Agencies on Aging, and the U.S. Administration for Community Living) to develop an intervention program for this population.

Preliminary Data: EPIC pilot results funded from a U.S. Administration Innovation grant showed significant changes in clinical symptoms (depression and other mood states), quality of life indicators (relationship functioning, self-efficacy, care preparedness), and social validity among EPIC patients and care partners when delivered by Alzheimer's Association staff under Dr. Coon's supervision (Coon et al., 2013). EPIC is the first group dyadic intervention to show positive outcomes for both early-stage individuals and care partners. Embedded into the community through the Alzheimer's Association Chapters in Arizona and Nevada, EPIC is currently being tested through an RCT funded by an NIA R01 (Coon, PI). The backbone of the HABIT program is a cognitive rehabilitation intervention, the memory support system (MSS). Master of the MSS helps improve memory ADL functioning, improves self-efficacy, reduces caregiver depression,

and helps prevent increases in partner burden compared to untreated individuals (Greenaway et al., 2012). Research evaluating the impact of the loss of one component of the HABILIT program (e.g., dyads receiving 4/5 of the components) suggests that various combinations of different components impact different outcomes (e.g., memory ADLs, quality of life, mood, self-efficacy) such that a synergy of multiple interventions may be most beneficial on a variety of patient and partner outcomes (Locke et al., 2018). When dyads who completed the HABILIT program with all 5 components were asked about the impact of HABILIT using a Likert scale format, patients agree to strongly agree that they learned tools to cope with memory loss and that HABILIT improved their ability to function despite memory loss, improved quality of life, and improved mood. Partners expressed similar satisfaction with the program for their own quality of life and mood (Locke & Chandler, 2018).

Experimental Designs and Methods: This project will be comprised of two phases to help finalize a protocol for a psychosocial intervention to help improve and maintain quality of life for people with MCI who live alone. Both Phase I and Phase II will involve a series of six focus groups (3 focus groups with people with MCI who live alone; 3 groups with providers who assist people with MCI). Focused interviews will also be available for those who are eligible but unable to attend one of the focus groups. Phase I focus groups will help to (a) determine the key needs and concerns of people with MCI who live alone; (b) introduce key components of both EPIC and HABILIT for review, comment, and potential adaptation for people with MCI who live alone; (c) gather outreach and recruitment strategies to help identify and enroll this population in a future intervention; and, (d) identify potential barriers to enrollment (e.g., inability to drive) and strategies to overcome those barriers. Prior to Phase II, qualitative analysis of focus group and focused interview transcripts will be used to help refine key components of a psychosocial intervention protocol (e.g. outreach and recruitment material, intervention components, etc.). Phase II focus groups and focused interventions will gather additional input to help to further refine (a) outreach and recruitment strategies; (b) screening and interview material; (c) intervention components and mode of delivery; and, (d) translate key needs and concerns into intervention outcomes for evaluation. Qualitative data analysis of Phase II will help to finalize the intervention protocol for pilot testing.

Proposed One-Year and Long-Term Outcomes: The proposed short-term outcomes would be the finalization of a protocol (outreach and recruitment, screening and interview, and intervention material) for a psychosocial intervention for people with MCI who live alone. In addition, the data analyses from the focus groups and focused interviews would yield both professional presentations at meetings like such as the Gerontological Society of America, the American Society on Aging, or American Psychological Association and the submission of the findings to venues such as *The Gerontologist (Practice Concepts Section)*, *the Clinical Gerontologist*, or *Dementia*. Based on the findings, the Co-PIs (Coon & Locke) would hope to submit an R21 or perhaps even a smaller R01 submission in 2019-2020, depending on the project's findings and other funding sources for a small intervention pilot.

Year-End Progress Summary: The project is on track for completion 6/30/19. Project protocol, screening tools, focus group and focused interview guides, recruitment material, and consents were developed for the current project. Informal feedback from professionals in the field combined with the experience of the investigators and their teams helped these materials. Focus groups and focused interviews with individuals living alone with MCI and professionals who assist them will be completed by year's end. Findings from these group and individual interviews will help to refine the screening tools, recruitment materials, quantitative interviews, and the overall intervention for people living alone with MCI to be implemented in a future intervention pilot.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

An evaluation of age-related changes in the neurobehavioral underpinnings of nicotine addiction vulnerability in females. Cassandra Gipson-Reichardt, PhD, Heather Bimonte-Nelson, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Project Abstract and Progress:

We aim to determine the impact of ovarian hormone cessation in young and aged rats on acquisition of nicotine self-administration and mesolimbic circuitry underlying nicotine addiction. Women are typically more vulnerable to substance use disorders (SUDs) and studies have shown that long-term smoking cessation is more difficult to achieve in women than men in clinical trials (Perkins et al., 1999, Piper et al., 2007). Currently, more than 170,000 women die of complications related to smoking in the United States annually. Clinical research studies suggest that the menstrual cycle phase in women can affect cigarette craving and propensity to relapse to smoking following abstinence (Allen et al., 2008, Carpenter et al., 2006, Franklin et al., 2008). As well, lifetime smoking is correlated with premature menopause (Bae et al., 2018), illustrating smoking as an important factor in reproductive health in aging women. Mechanistically, it has been hypothesized that estradiol (E2) receptors are located on GABAergic medium spiny neurons (MSNs) within the nucleus accumbens core (NAcore) (Mermelstein et al., 1996), a brain region well-studied for its role in addiction and relapse. NAcore MSNs are known to synapse onto ventral tegmental area (VTA) dopamine terminals, which express E2 receptors that modulate VTA neuronal physiology (Vandegrift et al., 2017). It is therefore possible that E2 receptor activation increases dopamine transmission, and this is an important mechanism that is necessary for nicotine acquisition. Little is known about how E2 receptors gate dopaminergic transmission within the mesolimbic circuitry underlying nicotine addiction, especially in an age-dependent manner. It is important to note that dopamine signaling in the NAcore is regulated by ovarian hormones in a sexually-dimorphic manner (Becker, 1990, Castner et al., 1993). Importantly, we have previously found that nicotine self-administration potentiates NAcore MSNs (measured as increases in the ratio of AMPA to NMDA current peaks (AMPA/NMDA ratio; Gipson et al., 2013a, Gipson et al., 2013b) in young adult males. We hypothesize that aging and hormone cessation decreases synaptic plasticity and dopaminergic release within the NAcore. We propose to examine the impact of ovariectomy (OVX) with or without E2 hormonal supplementation in young adult and aged female rats on nicotine acquisition and the underlying nicotine addiction neural circuitry. This research has provided preliminary data for an extramural R01 grant submission to NIDA in February 2019 with this team of investigators to evaluate the neurobiological underpinnings of age-related changes in nicotine motivation specifically in females (see pending grant details above). To date, our data show that OVX young adult female rats have slowed acquisition of nicotine self-administration (SA) compared to intact, freely cycling females, indicating that endogenous ovarian hormones are involved in nicotine's reinforcing effects. As well, we have found that OVX in young adult female rats renders NAcore MSNs in a state of potentiation (measured via AMPA/NMDA ratio) after nicotine SA, which is reversed by re-exposure to E2. Interestingly, AMPA/NMDA ratio in nicotine-naïve OVX females is significantly lower than the nicotine-SA OVX group, illustrating that this elevation in functional plasticity is nicotine-specific. Due to difficulty in obtaining 18 month old female rats from the NIH breeding colony, we have focused on completion of the young adult experiments first, and plan to begin experimentation on aged females as soon as they become available. We anticipate the full data collection and analyses to be completed by summer 2019, and the manuscript to be submitted by the fall.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Induction of Autophagy to Modulate Neurodegenerative Disease Progression. Omar Khmour, Ph.D.; Sidney Hecht, Ph.D., Salvatore Oddo, Ph.D. Arizona State University; Arizona Alzheimer's Consortium.

Project Abstract:

Our project focuses on developing novel methylene blue/methylene violet analogues as autophagic flux inducers that can reduce total tau and phospho-tau levels and associated cytotoxicity. Autophagy is a cellular process responsible for the turnover of misfolded proteins or damaged organelles, and it also recycles nutrients to maintain energy levels for cell survival. The accumulation of misfolded amyloid beta proteins ($A\beta$) and hyperphosphorylated-tau are believed to be key players in the pathogenesis of Alzheimer's disease (AD). Autophagy-lysosomal pathways (ALPs), chaperone-mediated autophagy (CMA), and the ubiquitin-proteasome system (UPS) are actively involved in the degradation of these aggregates. Dysregulation of these systems has been observed in an early stage of AD, which argues for therapeutic intervention to maintain or restore these systems. In this context, autophagy is regarded as a potential means of therapeutic intervention in treating such pathologies.

Specific Aims:

Aim 1: Evaluate our library of MB/MV analogues (Fig. 1) for induced autophagy resulting in reduced tau levels relative to those mediated by MB or rapamycin.

Aim 2: Prioritize hits based on interpretation of the dose-response curves, and analysis of the structure-activity data of our chemical library, and by the absence of unwanted side effects associated with methylene blue. We plan to identify at least three compounds having 2-5 fold better potency than MB.

Project Progress Report:

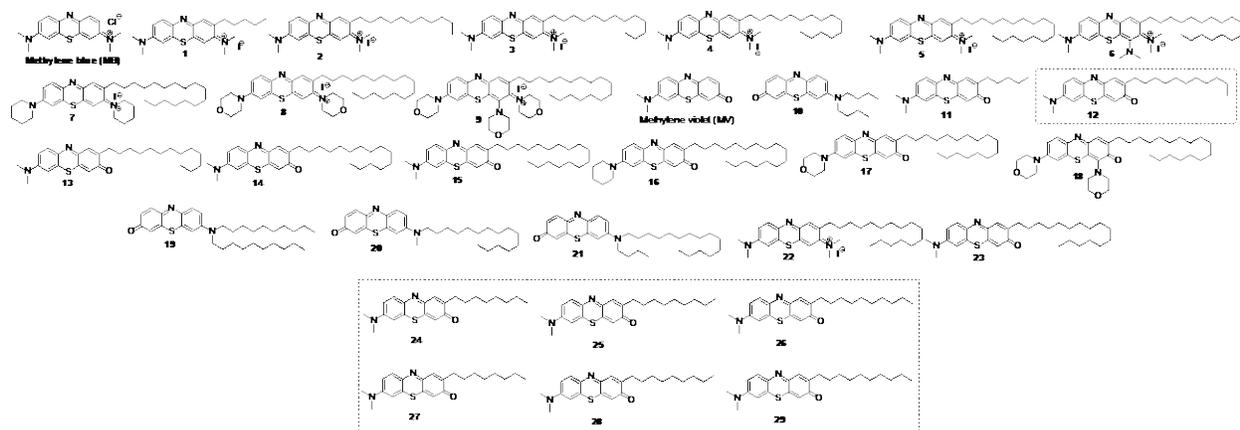


Figure 1. Methylene blue and methylene violet analogues

We and others have observed that high doses of MB are detrimental and actually increase cytotoxicity and pathology. Recently, we have developed new methylene blue and methylene violet analogues lacking cytotoxicity; these were found to be better antioxidants than the parent compounds (Fig. 1). Additionally, MV and its analogues were generally less cytotoxic in comparison to MB. Together, these and other data suggest that MB analogues may be potent modulators of protein aggregation that could influence AD onset or progression. The methylene blue/methylene blue analogues have been designed and synthesized with variations in their redox cores and their side chains (Figure 1). Although it is believed that methylene blue serves as an antioxidant, it has also been noted to foster toxicity by exhibiting prooxidant properties under certain conditions. In this regard, it seemed important to ensure that the prepared analogues were not cytotoxic. Therefore, the MB/MV analogues were evaluated for their cytotoxicity and respiratory chain effects by studying their effects on AD lymphocytes (Fig. 2). We used a nutrient-sensitized screening strategy by culturing the AD cells on galactose as the sole sugar source, forcing them to rely on mitochondrial OXPHOS to produce their ATP. Under such conditions, they become more sensitive to respiratory chain inhibitors than cells grown on glucose.

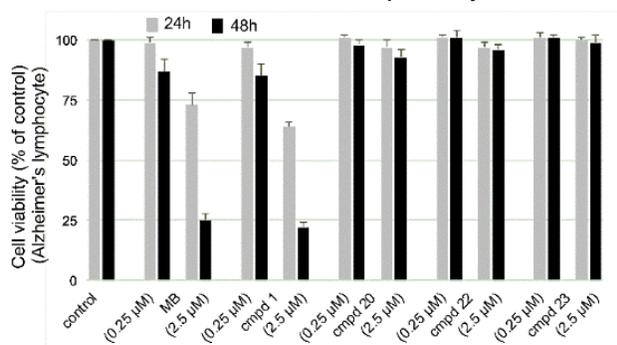


Figure 2. Methylene blue analogues were evaluated for their cytotoxicity toward cultured AD lymphocytes (familial type 3, AG06849) by incubation for 24 h or 48 h in glucose-free media (galactose) to force the cells to rely on their mitochondria to produce ATP. Flow cytometric determination of cell viability by fluorescence labeling was used employing calcein acetoxymethyl-ester.

disease, as shown in Figure 3. Compounds **2** and **23** were significantly more effective in increasing mitochondrial biogenesis than MB or compound **1** the latter of which has a short side chain (Fig. 1). On the basis of the above observations, we sought to evaluate MB/MV analogues (compounds **2**, **12**) for their ability to induce autophagy. We have demonstrated that specific compounds are autophagy-promoting compounds *in vitro* (Figs. 4 and 5). Compounds **2** and **12** are identical in structure, except that **2** is an MB analogue while **12** is an MV analogue. It is interesting that **12** was superior at inducing autophagy, and was additionally found to be considerably less cytotoxic than **2**. This underscores the ability of small structural differences to support real changes in potential therapeutic benefit. On the basis of the above observations, we sought to synthesize new compounds (**24-29**) (Fig. 1).

MB itself was quite cytotoxic when used at 2.5 μM concentration, especially after 48 hours of incubation (Fig. 2). Two of our early findings, described in part in recent studies, indicated that MB and MV were quite cytotoxic; however, derivatives of MV were less cytotoxic than MB derivatives. Moreover, the lipophilic side chains reduced the cytotoxicity of both MB and MV derivatives.

Alzheimer's disease is associated with metabolic deficits and reduced mitochondrial function. We evaluated several MB/MV analogues for their ability to normalize mitochondrial biogenesis in lymphocytes from a patient with a familial type 3 Alzheimer's

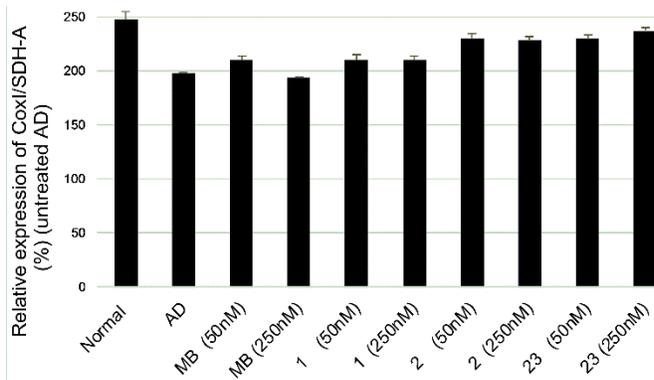


Figure 3. Effect of methylene blue on Alzheimer's disease lymphocytes (AG06849) was determined by enzyme-linked immunosorbent assay following 48 h of treatment. An in-cell ELISA kit was used to assess protein levels of succinate dehydrogenase (SDH-A), a subunit of a complex II (nDNA-encoded protein) and cytochrome C oxidase subunit 1 (COX-1), a subunit of complex IV (mtDNA-encoded). Interpretation: Higher ratios of COX-I/SDH-A (%) were correlated with increase in mitochondrial biogenesis as a consequence of mitochondrial DNA-encoded

COX-I protein synthesis being higher as compared to nuclear DNA-encoded SDH-A protein.

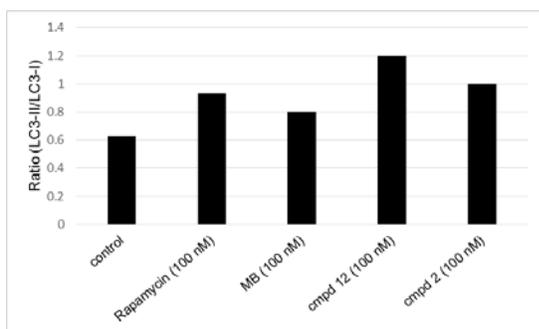


Figure 4. Demonstration that methylene blue and methylene violet analogues increased autophagy, shown increased the turnover of LC3 in HEK293 cells.

Evaluation of these new MB/MV analogue library for their induction of autophagy flux using LC3-ELISA and immunoblotting for LC3II/ LC3I ratio and other autophagy marker P62 to validate the prioritized hits from the primary assay (GFP-LC3) are in progress. Once the optimized compounds are identified

and have been shown to lack cytotoxicity and are an autophagy-promoting compounds in the primary assay, a secondary assay with a stable inducible cell line expressing aggregate-prone proteins (tau) that is process to be used for further characterization of compounds of interest. We hope to establish autophagy-promoting activity that can reduce levels of tau aggregation and associated cytotoxicity. Once the optimized compounds are identified and have been shown to carry out each of the above functions *in vitro*, we will submit applications for funding to pursue *in vivo* evaluation to establish the behavioral, cognitive, physiological, morphological, and molecular effects. PK studies will also be performed. Dr. Salvatore Oddo has agreed to collaborate with us in evaluating our compounds in an animal model of AD. We anticipate publishing at least one manuscript from this work. The results should also enable funding of the work through the Alzheimer's Drug Discovery Foundation.

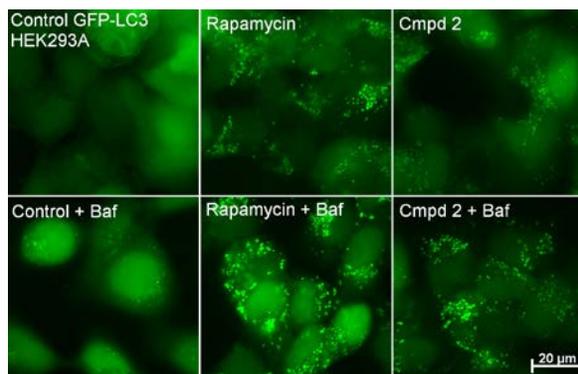


Figure 5. Stable GFP-LC3-expressing HEK293A cells were seeded in 6-well plates, allowed to adapt overnight, and maintained in control condition. Cells were then treated with 0.25 μ M rapamycin (known autophagy enhancer) or 0.25 μ M compound 2 for 16 h prior to adding bafilomycin A1 (Baf) (which is added at 100 nM in the last 4 h of the 16-h treatment period). Samples were analyzed by fluorescence microscopy (Live cell imaging). Compound 2 enhanced autophagy as shown above, by increasing GFP-LC3 puncta.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Novel mouse model to study neurodegeneration in Alzheimer's disease. Salvatore Oddo, PhD, Matt Huentelman, PhD, David Brafman, PhD. Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Abstract: Neuronal loss is a cardinal feature of AD and invariably affects multiple brain regions. Despite this indisputable evidence, the mechanisms by which neurons die are still unknown. Identifying the mechanisms leading to neuronal loss in AD is fundamental for the development of an effective therapeutic strategy to treat or slow down its progression. The long-term goal of my laboratory is to address this critical issue. Necroptosis was first identified as a result of inflammation; however, it is now clear that many micro-environmental factors can activate this pathway. Mechanistically, there are three key proteins involved in the execution of necroptosis, receptor-interacting protein kinases 1 and 3 (RIPK1 and RIPK3) and the mixed lineage kinase domain-like (MLKL) protein. A key event in the activation of necroptosis is the formation of the necrosome, a multiprotein complex comprised of RIPK1 and RIPK3. Upon necrosome formation, necroptosis is executed by various pathways, including the activation, phosphorylation, and oligomerization of MLKL; it is the activation of MLKL that leads to mitochondrial uncoupling, lipid peroxidation, and eventually cell death. In this grant application, we will test the hypothesis that **RIPK1 activity could explain a considerable portion of transcriptomic changes in AD.** To test our hypothesis, we will leverage our newly generated RIPK1 transgenic mice.

Progress to date:

Using the tetracycline-inducible system (Tet-On system), we generated six transgenic lines on a pure C57BL/6 background, in which the mouse RIPK1 gene is expressed under the control of the tetracycline-responsive element (TRE) promoter. We referred to these mice as TgRIPK1⁺⁰. The TRE promoter is active only when it binds to the reverse tetracycline transactivator (rtTA). By breeding TgRIPK1 mice with a different transgenic line in which rtTA expression is under the control of the CamKII promoter, we can restrict RIPK1 expression to neurons. In the absence of doxycycline, rtTA fails to bind to the TRE promoter and thus RIPK1 expression is inhibited. In contrast, doxycycline allows the rtTA to bind to the TRE promoter turning on RIPK1 expression.

We have identified two independent transgenic lines expressing high and moderate levels of RIPK1 in the brain. These lines will be used for future experiments and are now aging these mice to six months of age. We will then kill ten mice per genotype and use the right hemibrain to assess changes in neuronal number in the hippocampus and frontal cortex, by unbiased stereology. The left hemibrain will be used to dissect the hippocampus and the frontal cortex. This tissue will be used to perform RNAseq experiments in collaboration with Dr. Huentelman. The data obtained will be compared with the RIPK1 gene regulatory network we obtained using human AD brains.

We have leveraged the preliminary data obtained to submit an R01 application, which has been funded by the NIH.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Developing A Univariate Longitudinal Neurodegeneration Imaging Biomarker. Yalin Wang, PhD, Richard J. Caselli, PhD. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims: To develop a robust and effective univariate longitudinal neurodegeneration index and apply it to MRI brain scans of two well-characterized cohorts – the ADNI and AZ APOE cohort.

- Develop new geometry methods to compute 4D Euclidean Wasserstein distance.
- Validate univariate longitudinal brain morphometry indices by 1) progression prediction to mild cognitive impairment (MCI) and AD; 2) sample size estimation for clinical trials.

Abstract: Owing to the close relationship between neurodegeneration and cognition, atrophy measured by structural magnetic resonance imaging (sMRI) has been shown to quantitatively detect and track characteristic progressive hippocampal, regional gray matter, and whole brain atrophy in clinical and late preclinical stages of AD. Currently, a single value MRI-based atrophy measure is used as a neurodegeneration marker in the recently proposed AD descriptive “A/T/N” (amyloid, tau, neurodegeneration) system to define AD for clinical research. In clinical practice however, the “A and T” measures are rarely available. Our current project's **objective** is to build and deliver a novel and highly sensitive univariate longitudinal brain sMRI neurodegeneration index system that is clinically useful and able to expedite AD drug development by reducing clinical trial costs. **Hypothesis:** we hypothesize that this technique will better facilitate the identification of AD induced dementia and empower AD enrichment than previously shown by available competing algorithms, such as hippocampal volume, 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.

Background and Significance: AD is the most common type of dementia. Its prevalence is predicted to triple to 13.8 million by 2050. 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. With much success in brain imaging group difference study, including our own recent work, eventually a method sensitive enough to apply to individual patient's longitudinal brain scans with high diagnostic accuracy would be highly desirable for clinical use. Researchers in Arizona Alzheimer Consortium (AAC) pioneered the apolipoprotein E (APOE) e4 effect research in preclinical population. With a strong AAC support, we have successfully finished a joint R21 project (R21AG043760) which resulted in 5 joint journal papers. We made the first strides into developing shape space-based neurodegeneration indices. Together we are uniquely positioned to develop a univariate longitudinal neurodegeneration imaging index system for clinical use. The 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:

Riemannian Wasserstein distance-based brain imaging index research.

We have extensive experience in applying shape space theories to brain imaging index research.

Variational principle for optimal mass transport and Wasserstein index (WI) computation.

We discovered a variational principle for efficiently computing Euclidean OMT. The framework reduces the computational cost and enables applications to high-dimensional WI computation. **Fig. 1** shows our recent work to compute volumetric WI computation. The 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 Designs and Methods:

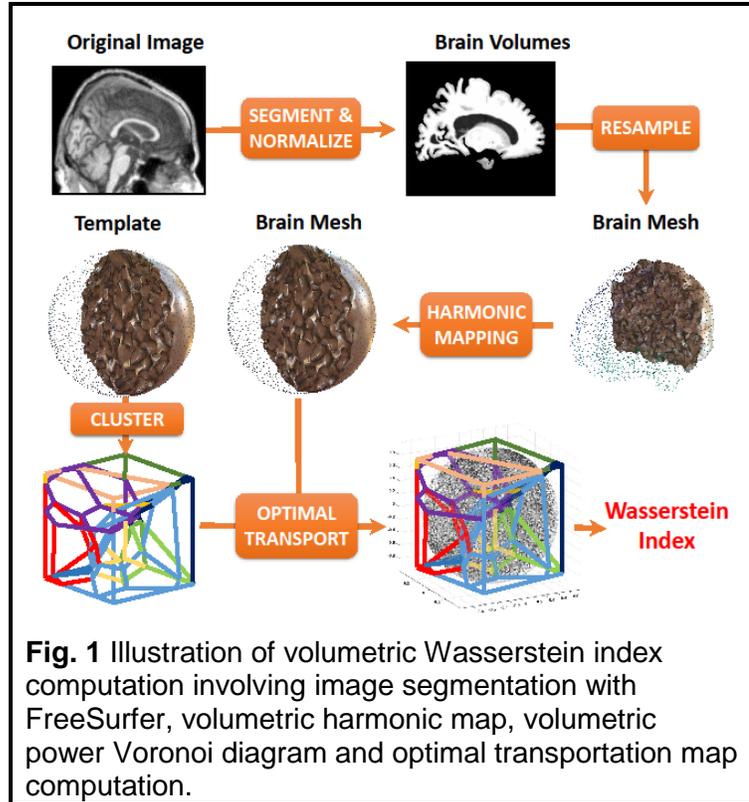
Datasets The Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset the AZ APOE cohort of presymptomatic individuals (supported by a grant in which Dr. Caselli is the PI).

4D Optimal Mass Transportation (OMT) for Univariate Longitudinal Neurodegeneration Biomarker

We propose to use a convex polyhedron to model the Euclidean geometric structure of the brain. We will first apply our prior work on volumetric harmonic map and volumetric Wasserstein distance (WD) to establish the correspondence of brain volume images on each individual time point. We will further compute 4D harmonic maps to a 4D solid sphere and use it as the canonical space. We will pursue a discrete 4D harmonic energy definition which is defined with a 4-polyhedron representation and is consistent with the conventional 4D harmonic energy. In our variational framework, we will use 4D power Voronoi diagrams to compute the gradient and the Hessian matrix. We will use an average model we use an average model from a set of normal subjects (or a fixed normal longitudinal image) as the template image, the computed 4D WD can be used as a univariate longitudinal neurodegeneration biomarker.

Applications in Preclinical AD Research To validate our system, we will apply it to study a wide variety of applications in preclinical AD research, including: (1) correlation with APOE genotype; (2) prediction on mild cognitive impairment (MCI) conversion; (3) correlation with stages of cognitive impairment or cerebrospinal fluid biomarkers; (4) correlation with other AD imaging index, e.g. HCl; et al. We expect our results will outperform other available AD severity index, and may offer potential surrogate biomarkers for use in trials of new treatment.

Proposed One-Year and Long-Term Outcomes: With our previous AAC support, we submitted an R01 on subjective cognitive impairment (SCI) research. 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 June, 2019.



AD research problems provide significant push-pull on my research: the computational theory and algorithm development is pushed by these urgent AD research problems and in turn, once it is developed, it pulls the AD research to a higher level. The PI expects to build a long-term and productive collaboration relationship between his laboratory and AAC researchers. We will keep developing novel and rigorous computational algorithms and software packages for preclinical AD diagnosis and AD prevention research.

Progress Summary: *Improved Prediction of Imminent Progression to Clinically Significant Memory Decline Using Multivariate Surface Morphometry of MRI Biomarkers and Patch-based Sparse Coding:* In collaboration with Drs. Stonnington, Reiman, Caselli, and Chen, we aimed to improve prediction accuracy using hippocampal surface multivariate morphometry statistics combined with patch-based sparse coding algorithms. From a prospective cohort study in Arizona, 18 cognitively unimpaired adults who subsequently progressed to the clinically significant memory decline within 2 years (progressors) were matched for age, sex, education, and apolipoprotein E4 allele dose to 20 adults who remained cognitively unimpaired for at least 4 years after baseline visits (nonprogressors). The same inclusion criteria and methods were then applied to the Alzheimer's disease Neuroimaging Initiative (ADNI) data set, resulting in a sample of 18 progressors and 34 nonprogressors who were older and had a greater percentage of males and non e4 carriers than the Arizona participants. We achieved promising results which indicate that sparse coding together with the surface multivariate morphometry may be applied to individual volumetric MRIs to predict imminent progression to clinically significant memory decline with great accuracy. *Univariate Imaging Biomarker on Brain resting-state functional MRI (rs-fMRI) Network Dynamics:* Collaborated with Drs. Caselli, Chen and Reiman, we proposed a threshold-free feature by integrating a prior persistent homology-based topological feature (the zeroth Betti number) and a newly defined connected component aggregation cost feature to model brain rs-fMRI networks over all possible scales. We showed that the induced topological feature (Integrated Persistent Feature) follows a monotonically decreasing convergence function and further propose to use its slope as a univariate brain network topological measure. The experimental results demonstrated that the proposed network measure shows more statistical power and stronger robustness in group difference studies in that the absolute values of the proposed measure of AD are lower than MCI and much lower than normal controls, providing empirical evidence for decreased functional integration in AD dementia and MCI. *Applying Surface-Based Hippocampal Morphometry to Study APOE-E4 Allele Dose Effects in Cognitively Unimpaired Subjects:* In collaboration with Drs. Reiman, Baxter, Caselli and Chen, we characterized the ability of our automated surface-based hippocampal morphometry algorithm to distinguish between these three levels of genetic risk for AD. We examined the APOE-e4 dose effect on cross-sectional hippocampal morphology analysis in an MRI dataset, from AZ APOE cohort, consisting of 117 cognitively unimpaired subjects aged between 50 to 85 years (mean=57.4, SD=6.3), including 36 heterozygotes (e3/e4), 37 homozygotes (e4/e4) and 44 non-carriers (e3/e3). Our experimental results demonstrated its superiority to a commonly used hippocampal volume measurement.

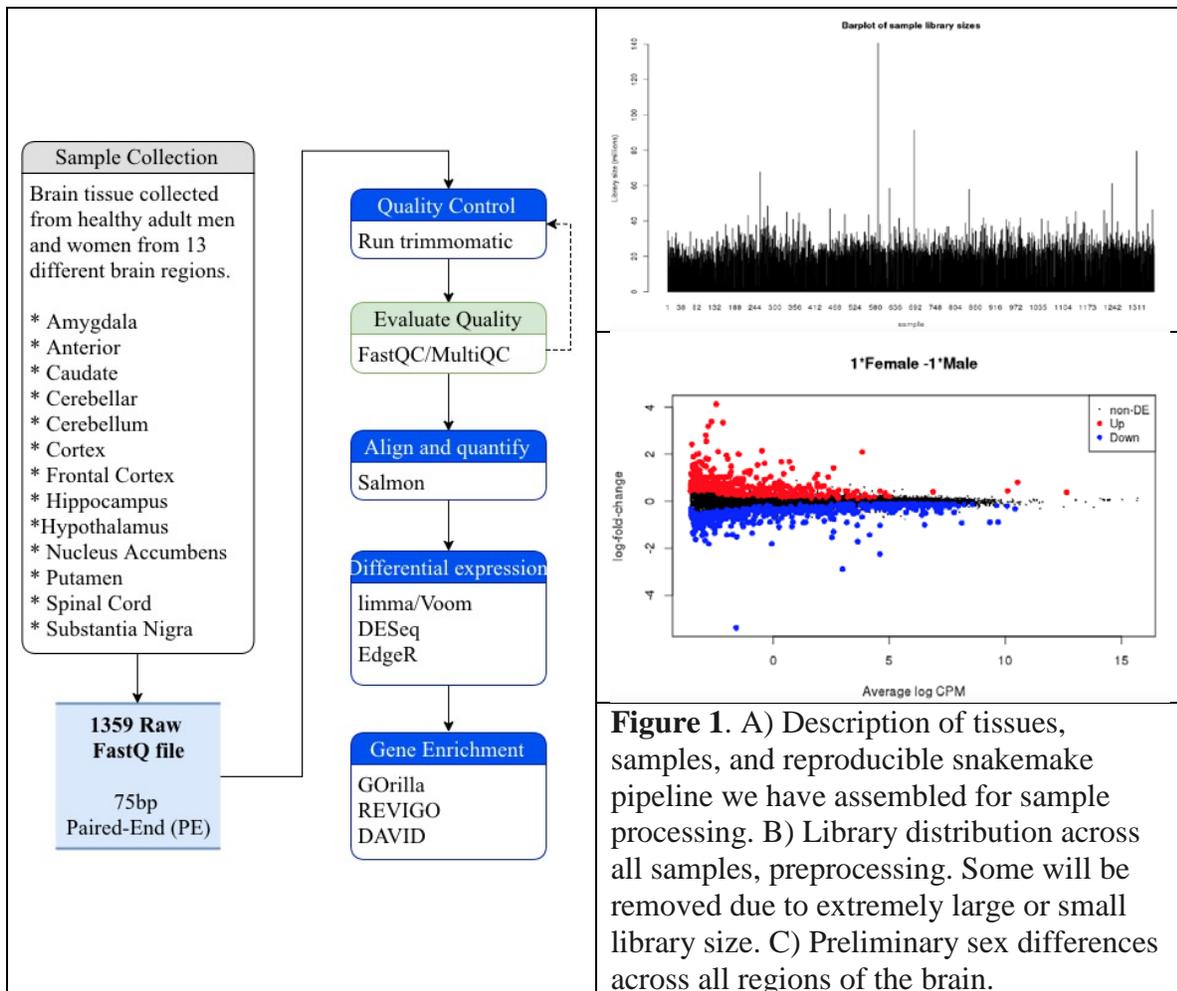
ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Investigating genetic sex differences to explain Alzheimer's disease mechanisms.
Melissa Wilson Sayres, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Project Abstract: Alzheimer's disease is a form of a dementia that causes irreversible brain tissue damage that affects an estimated 5.4 million Americans. Currently, women at the age of 65 have a 1 in 6 chance of developing Alzheimer's disease while men of the same age have a 1 in 11 chance. Evidence is emerging that the severity and progression of Alzheimer's disease is affected by the immune system. Notably, women are four times more susceptible to autoimmune diseases than men, and the X chromosome is enriched for gene expressed in the immune system. Sex differences in gene expression in the brain could be due to genetic differences (genetic females have two X chromosomes while males have one X and one Y), hormonal differences (gonadal hormones such as testosterone, progesterone and estrogen are notably different between the sexes), or a combination of the two. Genetic sex differences in gene content and expression have been shaped by millions of years of evolution. My lab has studied the evolution of these differences, and is now working to integrate this view with our understanding of human health. In particular, in this proposal we aim to study genetic and expression sex differences in healthy brains and brains from patients with Alzheimer's disease (AD) in an effort to pinpoint the mechanisms contributing to the sex differences in development and progression of AD.

Year End Progress Summary: We have developed a reproducible snakemake pipeline to process the more than 1,300 healthy brain samples from GTEx (Figure 1A). We downloaded and decrypted the nearly 3Tb of data for the brain samples from 13 different regions of the brain onto the ASU Research Computing cluster. Within that, we have developed a directory structure to implement the analysis. All parts of the pipeline have been tested on a subset of the data. We first assessed the library sizes and read lengths of all RNAseq samples. We will remove samples where the library size is more than 2 standard deviations away from the mean across all samples. This is because variance in library size can add noise to the resulting estimates of gene expression (Figure 1B). We have also conducted basic quality control steps on all samples, and removed those that have a GC content that differs from the distribution for that tissue. We found that there was one individual in particular, who always had a GC content profile, across all tissues, that differed from the others, and upon investigation identified that the samples all came from one patient, whose samples were collected more than 24 hours post-death so we, unfortunately, had to exclude those samples. Finally, we have tested the pipeline and identified nearly 1000 genes that show differential expression in males or females (Figure 1C).



Project Progress Report
Banner Alzheimer's Institute

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Alzheimer's Prevention Initiative (API). 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).
2. To conduct a preclinical AD trial/surrogate marker development program in cognitively unimpaired 60-75 year-old APOE4 homozygotes (i.e., API Generation Study 1).
3. To conduct a preclinical trial/surrogate marker development program in additional cognitively unimpaired 60-75 year-old APOE4 homozygotes and amyloid- β ($A\beta$)-positive APOE4 heterozygotes (i.e., API Generation Study 2).
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 aducanumab prevention trial).
5. To continue to support registries designed to assist with participant recruitment.

Background and Significance: The Alzheimer's Prevention Initiative (API) was established to launch a new era in AD prevention research, accelerate the evaluation of promising AD prevention therapies, and find and support the approval of effective prevention therapies in at risk persons as soon as possible. It currently includes 1) the API ADAD Colombia Trial of the primarily oligomeric $A\beta$ antibody therapy crenezumab in cognitively unimpaired PSEN1 E280A mutation carriers from the world's largest ADAD (NCT01998841), 2) API Generation Study 1 of the relatively selective BACE1 inhibitor CNP520 and the active $A\beta$ immunotherapy CAD106 in cognitively unimpaired APOE ϵ 4 homozygotes (NCT02565511); 3) API Generation Study 2 of CNP520 in APOE ϵ 4 homozygotes and $A\beta$ + heterozygotes (NCT03131453); and 4) our proposed API-A4 aducanumab prevention trial in cognitively unimpaired $A\beta$ + adults. 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 support, and help to find and support the approval of a prevention therapy as soon as possible.

Progress Summary:

1. 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 (1-3). Retention has been extremely high, and the placebo-controlled trial is intended to continue until early 2022, when the last person has been treated for 60 months. In addition to other clinical, cognitive and biomarker assessments, we plan to acquire mid-treatment and follow-up tau PET scans later this

year following final approval from the Colombian Health Authority. 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. We shared baseline information from age-matched mutation carriers and non-carriers at the 2018 Alzheimer's Association International Conference (AAIC). Approximately 50% of the enrolled carriers had a negative A β 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. Roche recently announced discontinuation of crenezumab in its Phase 3 trials of clinically affected persons based on an interim futility analysis, but also announced its intent to continue our ongoing prevention trial, which is intended to provide a better test of the amyloid hypothesis. Data from Roche's discontinued Phase 3 trials and other observational data sets may help to inform the future analysis of data from our prevention trial.

2) With primary support from an initial NIA grant, philanthropy, Novartis, and Amgen we continue to evaluate CNP520 and CAD106 in API Generation Study 1 in North America, Europe, and Australia (4). This trial includes a novel genetic testing and disclosure pre-screening component, the results from which will be informative for the field of telemedicine and precision medicine, and it has capitalized on GeneMatch and other mechanisms to identify and support enrollment of so many APOE4 homozygotes. Tau PET was recently incorporated into the trial protocol. We currently aim to complete enrollment of the BACE inhibitor arm in 2019 and continue the trial until 2024, when the last APOE4 homozygote has been treated for 60 months. Interim analyses of CAD106 are intended to clarify the treatment's immune response and A β -clearing effects. We currently plan to submit a grant application to help complete the study and share baseline and post-treatment data in accordance with CAP principles.

3) In 2017, we expanded our collaboration with Novartis and Amgen by extending the evaluation of CNP520 to additional APOE4 homozygotes, as well as in A β + APOE4 heterozygotes (NCT03131453)(4). This trial expands upon the genetic testing and disclosure program in Generation Study 1 to also include disclosure of A β PET findings. We currently aim to complete enrollment in 2019 and continue the trial until 2024, when the last participant has been treated for 60 months. Recent reports have found described associations between less selective BACE inhibitor treatment and an early, modest, and non-progressive worsening in cognitive performance. After extensive discussion with leaders from industry, academic, and other stakeholder groups, Generation Studies 1 and 2 are continuing to use the existing CNP520 doses, have asked the DSMB to closely monitor safety data, and will base future dosage decisions on the DSMB's input and recommendations.

4) In 2018, API and A4 leaders submitted a \$33M NIA grant application to help support a proposed prevention trial of the A β -plaque clearing antibody aducanumab in cognitively unimpaired A β + adults. The proposal included an option to analyze the treatment's biomarker effects, qualify relevant biomarkers, and support the accelerated approval of this prevention therapy as early as 2023 if findings from Biogen's ongoing EMERGE and ENGAGE Phase 3 trials demonstrate a clinical effect, such that one or more biomarker endpoints are associated with a clinical effect. It also included an option to continue the study using cognitive endpoints and support the possibility of approval as early as 2025 if those Phase 3 trials are negative, since the treatment might have a more profound effect before the disease is extensive. In September, we received our notification of grant award. In January 2019, Biogen announced its plan to conduct this study; and we are now working together to refine the protocol and clarify the collaborative relationship. In addition to other elements, we have begun to consider the possibility of including an A β blood test screening program to help identify and support the enrollment of suitable

participants, reduce the number of negative PET scans during the screening process, and provide a resource of blood samples and PET data to further test promising plasma A β assays. In late March, Biogen conducted a futility study in the ongoing phase III studies, declared futility (based on lack of efficacy), and is considering options for the prevention trial as noted above. While disheartening for the entire field, there is still a need to evaluate a “plaque-busting” anti-A β treatment in prevention trials (including in those with a positive A β PET scan as we had proposed and in those at genetic risk with an A β negative PET scan. This study, along with our API ADAD Colombia and Generation Study 1 studies currently have the potential to provide the best test of the amyloid hypothesis, even as the field seeks to develop a more diversified portfolio of promising treatments. We continue to work with Biogen and other industry partners, look forward to reviewing both the efficacy and important safety data as soon as possible, and will then decide the best options for our proposed prevention trial.

5) We continue to expand the Alzheimer’s Prevention Registry, a web-based registry focused on encouraging enrollment into prevention studies. The Registry has >335,000 enrollees and is actively recruiting for dozens of studies nationally and locally. In November 2015, the Registry launched its GeneMatch program which collects genetic samples from participants age 55-75 for APOE genotyping and uses the genetic results in part to help match people to research studies(5). GeneMatch is serving as one of the primary recruitment sources in the US for the API Generation Program. To date, >80,000 people have joined. Dr. Langbaum submitted a grant to the NIH in October 2018 to study the science of AD recruitment registries with the goal of increasing participant diversity and accelerating enrollment into AD trials. 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 (6), and we continue to advance the study of AD in members of this extraordinary kindred.

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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 through community outreach and other related efforts, particularly within Arizona.
2. To increase the number of study opportunities available to Alzheimer's Prevention Registry members, particularly within Arizona.
3. To compare the success rates of various approaches to promote study opportunities to Alzheimer's Prevention Registry members, tracking members' interest in each study opportunity.

Background and Significance: The suffering caused by Alzheimer's disease (AD) remains one of the greatest unmet medical needs of our times. It is currently the 6th leading cause of death in the United States (US) and the only cause of death in the top 10 that cannot now be prevented, slowed, or cured. In the US, an estimated 7.1 million have AD, projected to nearly double to 13.8 million by 2050. Interventions that delay onset even by 1 or 2 years would have a major public health impact. As a result, considerable effort, attention and funding has been placed on accelerating efforts to prevent and effectively treat the disease. These efforts include, but are not limited to the National Plan to Address Alzheimer's Disease, the European Prevention of Alzheimer's Disease (EPAD), the Global Alzheimer's Platform (GAP), and our own Alzheimer's Prevention Initiative (API), which is evaluating promising investigational preclinical AD treatments in people who, based on their age and genetic background, are at high imminent risk for progression to AD dementia. Each of these initiatives includes a call to action for more studies and expansion of recruitment mechanisms with the goal of ultimately identifying sufficient numbers of individuals to step forward and participate in AD prevention trials. 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) ("Registry") was created in 2012 to help studies meet their enrollment goals in an efficient and timely manner. Based on lessons learned from the Arizona Alzheimer's Research Registry and modeled after other web-based research registries, the Registry was purposely designed to have a low threshold of commitment at entry. At enrollment, individuals are asked to provide their email address and basic demographic information. Enrollees receive regular email communication to keep them apprised of the latest news in Alzheimer's prevention research. In addition, enrollees 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 Registry 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. 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 Registry and increase enrollment, it is imperative that we increase the number of and types of study opportunities available to Registry members and compare the effectiveness of various approaches to promote study opportunities to Registry members by tracking members' interest in each study opportunity. The results from this effort will provide invaluable information about the best way to raise awareness about study opportunities and recruit Registry members for research studies.

Year End Progress Summary: The Alzheimer's Prevention Registry is an online community of individuals ages 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 January 2019, the Registry had over 337,000 enrollees and GeneMatch enrolled over 85,000. Our manuscript describing the GeneMatch program was accepted for publication in *Alzheimer's and Dementia* (1).

Aim 1). During the funding period, considerable effort was undertaken to increase enrollment into the Alzheimer's Prevention Registry (APR) through community outreach and other related efforts. We have activated 28 GeneMatch partner sites across the United States, including 3 in Arizona, allowing sites to enroll individuals into the APR and GeneMatch and distribute recruitment materials. We have seen an increase in enrollment into the APR and GeneMatch, as well as an increase in referrals to studies at those sites. In addition, we ran a successful online advertising campaign throughout 2018 to increase enrollment into the APR and GeneMatch. This campaign will continue in 2019.

Aim 2). The APR has helped recruit for more than 82 AD-focused studies since its inception. 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. Approximately 100,000 members have opted into receive the newsletter. Over the past year, the average newsletter email open rate is 44% (compared to nonprofit healthcare industry average of 16%); average email click rate is 22% (compared to the industry average of 1.6%). We presented data at the 2018 Arizona Alzheimer's Consortium conference indicating a strong relationship between APR engagement email interaction and study invitation acceptance rates. We launched geographically targeted social media advertising to assess its impact in helping to recruit for AD-focused studies, including a Facebook campaign to increase enrollment of Hispanics into the Arizona APOE longitudinal study. The results from this campaign were submitted as an abstract to the 2019 AAIC.

Aim 3). We continue to examine success rates of various approaches to promote study opportunities to Alzheimer's Prevention Registry members, tracking members' interest in each study opportunity. We are testing targeted, study-specific email campaigns, Facebook advertising campaigns, and a new monthly email providing members with a list of all new studies added to the Registry. In GeneMatch we are examining whether the original method (Facebook, direct to website, partner site, etc.) influences participants' likelihood to accept a study invitation. Initial results were submitted as an abstract to the 2019 AAIC. In October 2018, we submitted an R01 grant application "Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials." A manuscript describing the design and rationale of GeneMatch was accepted for publication in *Alzheimer's and Dementia*. A manuscript describing the Alzheimer's Prevention Registry is being prepared for submission to a journal.

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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 (PI), Travis Johnson, Matthew Huentelman, PhD, Bruce Petersen, Thomas Beach, MD, PhD, Richard J. Caselli, MD, Eric M. Reiman, MD, and colleagues from each of the participating data acquisition and data management 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. Continue to clean and incorporate retrospective and prospective clinical, cognitive, demographic, brain imaging, other biomarker, genetic, and neuropathological data from the ADCC, BBDP and APOE4 Gene Dose Programs.
2. Continue to develop and support the productive use of a data sharing platform which external researchers can use to search the database to find cohorts of interest and then request data, images, and biological samples of interest.
3. Extend the code that generates files for upload to NACC to include consistency checks in order to reduce the number of errors received when uploading data to NACC and reduce the average time to packet finalization.
4. Create a data request intake form for researchers within the ADCC consortium which will lead them through the available variables and store the request in the centralized database.

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 Alzheimer's Disease (AD), Parkinson's Disease (PD), and related disorders, and the study of normal brain aging. These programs include common data elements, are administered through separate data management programs, and could provide even greater value under a common data management program that is optimized to fulfill the programs' common and complementary research goals. With support from the National Institute on Aging (NIA), the Arizona ADCC Clinical Core is the nation's first NIA-sponsored AD Center with multiple clinical core sites (including those at Mayo Clinic Arizona, BSHRI, UA, BNI, and BAI); it provides annual assessments in ~500 research participants with AD, related disorders, and cognitively unimpaired older adults; it includes individuals who are enrolled in BSHRI's BBDP, cognitively unimpaired individuals with two, one and no copies of the APOE4 allele, the major genetic risk factor for AD, members from Arizona's understudied Latino and American Indian communities, and other clinically affected and unaffected research participants; and it provides a shared resource of participants and data for researchers to generate new findings, publications, and grants. The BBDP includes >800 annually assessed research participants from the ADCC, the National Institute for Neurological Disorders (NINDS)-supported National Brain and Tissue Resource for PD (NBTR-PD), and other longitudinal assessments from older adults who consent to brain donation after they die, neuropathological data and exceptionally high quality brain and body tissues from >1,500 expired BBDP participants. With support from NIA, the state of Arizona and Mayo Clinic and BAI, the Arizona APOE4 Gene Dose Program provides a longitudinal cohort of research participants and data with two, one and no copies of the APOE4 gene, reflecting three levels of genetic risk for

AD, including a sub-set of subjects with extensive brain imaging and other biomarker data. This program has made pioneering contributions to the conceptualization of “preclinical AD,” established a foundation for the Alzheimer’s Prevention Initiative (API) and the accelerated evaluation of prevention therapies, and includes an invaluable resource of data and samples to help researchers detect and track the earliest biomarker and cognitive changes associated with AD, contribute to the understanding of genetic and non-genetic risk factors, develop data analysis techniques with improved power to detect and track AD and evaluate promising but unproven AD prevention therapies. Consortium researchers lead other valuable longitudinal research programs, which despite fewer common data elements, may benefit from either a shared data management program and/or mechanisms to find other relevant data in the future. In this project, we have enhanced the work done in the previous year on a centralized robust data management platform to include more real time reporting and data sources, optimize the code that extracts data for NACC submissions to include data consistency checks and create a data sharing platform.

Preliminary Data and Plan: Over the past year, with complementary AARC and ADCC support, significant progress has been made in expanding our database to support Alzheimer’s disease projects. We leveraged a general-purpose custom software application, REDCap2Relational, to bring in data from the APOE Gene Dosing Program into the central database which includes UDS, biospecimen and imaging data. We also extended our pipeline for submitting data to NACC to include the UDS data from the APOE Gene Dosing Program. One of the challenges faced with submitting data to NACC is the resolution of errors and alerts generated by NACC’s data consistency checks. This is especially difficult given that we have five sites submitting data and the existing process was largely based on email. To improve the process, we wrote a custom piece of software, Issue Tracker, where the Data Core enters all NACC generated errors and alerts and assigns them to each site for resolution. The software supports communications between sites and the data core and permits us to track metrics such as the time to resolution for each site. Feedback from the sites has been positive and the application has been adopted quickly.

Significant effort has been put into the cleaning and harmonization of the data for the APOE Gene Dosing Program and we wish to continue this to incorporate data going back to the mid 1990s. As expected with such a lengthy clinical trial numerous data collection platforms have been utilized and it is our intent to consolidate as much of this data into our centralized database as possible. Another initiative which has been started in the current funding period is a data sharing platform which will permit internal and external investigators to interrogate our data to find cohorts of interest. The data in the platform will be de-identified and include demography, UDS data, biospeciment availability, imaging availability as well as some basic imaging measurements. With the Issue Tracker in place, we can run queries to determine to most frequent errors and alerts that are generated by NACC’s data validation process. Having this information will allow us to put in “pre upload” checks that will alert the sites inconsistent / erroneous data thus speeding the process towards clean data in NACC. We anticipate this will be a time savings for both the sites and the Data Core.

As the amount and variety of data is increasing in our centralized database, we are getting an increase in requests for data. Once the data sharing platform is live we anticipate another significant increase in requests for data and therefore we wish to create a data request system. The system will intake requests from investigators with the inclusion/exclusion criteria as well as the desired data points. Additionally the system will track the fulfillment of the request as well as the final release of the data. We will also establish a standard Data Use Agreement that will at a

minimum request that we be cited in any resulting publications or grants. Having such a system in place will be valuable for progress reporting.

Proposed One-Year and Long-Term Outcomes: We anticipate that by enhancing the centralized database for Alzheimer's projects and making data available through a standardized sharing mechanism that more research projects will be feasible and result in further funding.

Year End Progress Summary: Significant progress has been made towards each specific aim. We have located all historical imaging data from the APOE study and are well under way in migrating it to our XNAT Imaging Informatics Platform. All metadata from images and biospecimen data have been populated in our APOE REDCap project. In auditing our ADCC data, we realized that there were participants who did not have APOE genotyping and/or did not have samples stored at NCRAD; as a result, we have implemented a Standard Operating Procedure to inform sites of upcoming visits for these participants so saliva can be collected for APOE genotyping and Blood collected for submission to NCRAD. We have incorporated Neuropathology data submitted into our database to facilitate antemortem and postmortem diagnostic comparisons. Our team has worked closely with the new Bioimaging and Biofluids (BI-FB) core to create a new REDCap project to manage the imaging and specimen collections. Once live, the data from the BI-FB will be incorporated into our centralized database.

We have completed the first version of our data sharing platform which permits external investigators to run queries through a web-based interface to get summary counts in both a tabular and graphical format. If they find a cohort of interest, they can then request the data including imaging and biospecimens. Additionally, we are in the process of executing legal agreements between Mayo, Banner Health, LONI and GAAIN which will permit us to deposit data from the APOE project on to GAAIN and LONI-IDA. By doing this we hope to increase the visibility of our program.

By leveraging the issue tracker tool used by sites to resolve NACC data consistency errors, we were able to identify where bottlenecks were occurring at our participating sites. We were then able to work with each site to optimize their processes to reduce the time to packet finalization. To support this effort, we have created 8 new online reports as well 7 tableau reports which are leveraged by the BAI team.

We worked closely with Kansas State University to incorporate Spanish language translations of the UDS forms into our REDCap project. Also, several new forms were released by NACC which required adding to our REDCap project as well as modifying the pipeline which generates the files for upload to NACC. A local Recruitment and Retention form has been added to REDCap as well to capture the source of referrals to the program as well as reasons participants are lost to follow-up. We have also implemented additional data consistency checks into the pipeline to catch errors prior to uploading to NACC.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Native American Outreach, Recruitment, and Retention Program. David Weidman, MD, Lori Nisson, LCSW, Richard Caselli, MD, Edward Zamrini, MD, Eric M. Reiman, MD, Pierre N. Tariot, MD, and David Coon, PhD. Banner Alzheimer's Institute; Mayo Clinic Scottsdale; Banner Sun Health Research Institute; University of Arizona; Arizona State University, and Arizona Alzheimer's Consortium.

Specific Aims:

1. To forge a close working relationship with members of our Native American Community in the awareness, care, and scientific understanding of Alzheimer's disease (AD) through educational and service-related outreach activities.
2. To support the participation of interested Native Americans in the ADCC clinical core and research studies of interest to them without detracting from our other outreach and partnership-development goals.
3. To continue to work with our Native American partners to identify and begin to prepare for one or more research studies that advance the understanding of AD and/or service to patients and families 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.

Preliminary Data and Plan: To date, 79 Native Americans have been followed through the ADCC and whose clinical findings are reported in a national database. As of January 2019, there are 54 active participants, 23 have withdrawn, and 2 died. Over the past year, over 4,200 Native Americans have participated in education and outreach efforts led by our team. We continue building working relationships with numerous Arizona tribes and have also been successful with outreach efforts from tribes outside of Arizona including Oregon, New Mexico, Wyoming, Colorado, Utah, California, North Carolina, Alaska, Hawaii, Oklahoma, Nevada and Minnesota. Our team was invited to present at the National Indian Council on Aging Biennial Conference held in September in Temecula, CA. We hosted the 14th Annual Conference on Alzheimer's disease in Native Americans in October at Fort McDowell, AZ with over 50 professional participants at our preconference intensive workshop and 220 professional and community participants at the full day conference. We were able to showcase two professionally created photos featuring Native American family caregivers and their loved ones. We utilized our recently developed, culturally sensitive Native American and Dementia Tool Kit to educate a team of 25 national Geriatrics Workforce Enhancement Program providers with a comprehensive collection of training materials to better equip them in providing education to tribal colleagues and families in effectively caring for a person with dementia.

We have initiated interactions with the Strong Heart Stroke Study (SHSS), BNI, and the University of Arizona-Banner All of Us (AoU) Program to help increase recruitment and retention of Native

Americans into our ADCC Clinical Core and to support their participation in productive and impactful research studies. BAI has helped our BNI colleagues with the acquisition of follow-up MRIs from Native American participants at BNI. It has been providing image analysis training, resources, and K01 co-mentorship of Astrid Suchy-Dacey to support the analysis of baseline MRI data. It has begun to meet with Dr. Coon, AoU, BNI, and SHSS colleagues to help recruit, retain, and promote the study of 100 active Native Americans in the ADCC Clinical Core by September 2020.

Our advisory committee has begun planning the 15th Annual Conference on AD in Native Americans in October in the Northern region of the state and we anticipate drawing more than 200 community participants. We will continue outreach efforts across Arizona and will continue to educate professional and family caregivers within our tribal communities. We have established consistent and solid working relationships with many urban and tribal communities to continue with these efforts. We will hold at least six public events to promote awareness in urban and reservation communities. Our outstanding Native American outreach staff and other colleagues will continue to establish close working relationships with stakeholders from many tribes and nations.

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 in both reservation and urban dwelling Natives.
2. Help to recruit and retain Native Americans into the ADCC Core, such that we are following >60 actively enrolled NAs at BAI and a total of >100 enrolled NAs at all of our clinical core sites, capitalizing in part on emerging relationship with our colleagues from the SHSS and AoU programs.
3. Refine methods to reach more Native Americans from youth to elders to educate using the Native American Brain Health program.
4. Increase national engagement, knowledge, and collaboration amongst clinicians and researchers treating Native Americans using data gathered through the study. Leverage available data for educational purposes at the Annual Conference on Alzheimer's disease in Native Americans.

Funds will be used in a way that complement but do not overlap with funding provided by the National Institute on Aging (NIA, which supports some of our outreach and clinical core enrollment activities), the Ottens Foundation (which provides partial support for our Annual Conference), and funds from Freeport-McMoRan Native American Partnership Fund to support development of culturally sensitive NA programs.

Year End Progress Summary:

Aim 1: During the past year, our education and outreach programs reached 1145 professionals 3129 community participants from the Native American tribal communities across Arizona. We hosted the 14th Annual Conference on AD in Native Americans in October at Fort McDowell with over 50 professional participants in our preconference intensive and 220 community participants at our full-day training. We were able to showcase two professionally created photos featuring Native American family caregivers and their loved ones. In addition, we utilized our recently developed, culturally sensitive Native American and Dementia Tool Kit to educate a team of 25 national Geriatrics Workforce Enhancement Program medical providers with a comprehensive collection of training materials to better equip them to provide education and support to tribal colleagues and families caring for persons with dementia. Our team was invited and presented our work at the National Indian Council on Aging Biennial Conference held in September in Temecula, CA.

Aim 2: Also, during the past year, we enrolled 2 new participants, completed 15 assessments, and are preparing to enroll 6 additional participants. 39 participants were lost to follow-up. To help minimize attrition, we will be working with the ADCC Education Core to find ways to optimize retention in our longitudinal research program. We have continued to reach participants at community events, and we have begun to explore new relationships with leaders from the SHSS, AoU program, and our partnering organizations to help in the recruitment, retention, and productive study of Native American research participants.

Aim 3: BAI Native American Program received funding from the Ottens Foundation, which provides partial support for our Annual Conference and funds from Freeport-McMoRan Native American Partnership Fund to support development and advancement of culturally sensitive Native American education and support programs.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Deep-Learning Image-Analysis Methods for the Detection, Tracking and Diagnosis of Alzheimer's Disease. Yi Su, PhD, Dhruvan Goradia, PhD, Kewei Chen, PhD, Yalin Wang, PhD, Zhangyang Wang, PhD, Teresa Wu, PhD, and Eric M. Reiman, MD. Banner Alzheimer's Institute (BAI); University of Arizona; Arizona State University (ASU); Translational Genomics Research Institute; Green Valley Pharmaceuticals; Texas A&M University; and the Arizona Alzheimer's Consortium.

Specific Aims:

1. To establish the collaborations needed to capitalize on this promising image-analysis in the most productive and rigorous way.
2. To develop and test deep-learning and multi-modal image-analysis methods for the early detection, tracking and differential diagnosis of Alzheimer's disease (AD).
3. To provide a shared resource for the analysis brain imaging data once these techniques are shown to be successful.

Background, Significance, Preliminary Data, and Plan: Deep learning (DL) methods have shown significant promise in the analysis of brain images, including those acquired in different clinical and pathophysiological stages of AD (see Vieira *et al.*, 2017). In the past two years, BAI's Computational Image Analysis Laboratory has established collaborations with researchers inside and outside of Arizona to further develop, test and apply deep learning image-analysis methods for the early detection, tracking, and differential diagnosis of AD. For instance, we applied an innovative patch-based deep learning method developed by Yalin Wang and his ASU colleagues to classify FDG PET images from AD dementia, mild cognitive impairment (MCI), and cognitively unimpaired control groups. (Singh *et al.*, 2017). This approach capitalized on a probabilistic principal component analysis, data pooling, and a multilayer feed-forward neural network to find the optimal classification models. More recently, we have been collaborating Zhangyang Wang from Texas A&M University to examine the feasibility of using a 3D convolutional neural network (3D-CNN) to predict a person's florbetapir ($A\beta$) PET measurements and classify a person as $A\beta$ -positive or negative on the basis of the volumetric MRI image—and to characterize a person's mean cortical florbetapir PET measurements without having to pre-define cerebral and reference regions-of-interest. Our preliminary analysis (reported in AAC 2018) found that when florbetapir PET was used as the input, the 3D-CNN model achieved a strong correlation ($r=0.97$, $p=2.2e-16$) in the estimated amyloid burden with the reference quantification method, and a sensitivity of 0.92 and specificity of 0.98 in determining amyloid positivity. When volumetric MRI was used as the input, the 3D-CNN model estimated amyloid burden was significantly correlated ($r=0.44$, $p=1.7e-07$) with the reference method, and achieved a sensitivity of 0.75 and specificity of 0.70 in determining amyloid positivity. We will further establish and capitalize on the collaborations needed to develop, test, and use deep-learning and related image-analysis tools, apply them to different kinds of PET and MRI images from well characterized research participants, and help to inform the detection, tracking, diagnosis, and prognosis of persons affected by or at risk for AD.

Proposed One-Year and Long-Term Outcomes: During the one-year funding period, we will further develop the collaborative relationships and secure the tools needed to develop, test and use the proposed deep-learning image-analysis methods.

Year End Progress Summary:

During the funding period, we have been working with the Banner Information Technology Department and Microsoft to implement the protocols and procedures needed to utilize the Microsoft Azure platform in a safe and secure way. While the Microsoft Azure platform includes the computational, technical and data storage resources that would permit us to use deep-learning and other computationally intensive image-analysis methods, it is a cloud-based third-party service that has required extensive efforts to ensure that we are able to apply it to our data with adequate safety and security. We have also been installing and learning how to use the Matlab-based toolbox “PRoNTTo”, an extension of the widely used statistical parametric mapping (SPM) toolbox, to capitalize on machine-learning image-analysis methods. Once these pipelines are established, we will begin to apply them to the analysis of AD Neuroimaging PET and MRI data. We have also explored collaborative opportunities with other vendors, such as IBM and General Electric, such that we can make informed decisions about which tools to leverage in the analysis of our data.

To date, our ability to predict florbetapir ($A\beta$) standard uptake value ratios (SUVRs) or classify participants as $A\beta$ -positive or negative has been limited. We plan to explore the value of applying our deep learning method to volumetric, resting state functional connectivity and diffusion tensor imaging MRI images, alone or in combination, in the quantification of $A\beta$ PET measurements and the classification of persons with an $A\beta$ -positive versus negative PET scan. Through our recently established collaboration with Dr. Teresa Wu at ASU, we are building a high-end deep learning workstation with multiple GPUs to facilitate further research in this direction. In a preliminary analysis using 3D-CNN and structural MR for age prediction. The initial model was trained on 255 cognitively unimpaired amyloid-negative participants and tested on 114 cognitively unimpaired participants, both from the ADNI dataset. The model achieved a mean absolute error (MAE) of 4.5 years. By comparison, Cole et al. (Neuroimage 2017) reported a MAE of 4.65 years when a large cohort of 2000 cognitively normal participants were used to build the CNN model. Further analysis is ongoing to expand the analysis to include more training data and explore the value of using the difference between predicted age and chronological age as a biomarker for predicting brain pathological burden and cognitive impairment.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Advanced Image and Statistics Analysis Techniques for the Detection, Tracking and Prevention of Alzheimer's Disease. Yi Su, PhD, Kewei Chen, PhD, Don Saner, MS, Dhruvan Goradia, PhD, Hillary Protas, PhD, Michael Malek-Ahmadi, PhD, Wendy Lee, MS, Eric M. Reiman, MD. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. To further develop, test and apply advanced image analysis techniques to help in the early detection, tracking, and differential diagnosis of Alzheimer's disease (AD), the clarification of AD risk factors, and the evaluation of AD-modifying and prevention therapies.
2. To make our data analysis algorithms available to research laboratories inside and outside Arizona.
3. To further develop our platform for sharing our brain imaging and related research data.
4. To adapt, refine, and incorporate automated image analysis pipelines developed by Dr. Su into the routine image analysis at BAI and prepare for potential deployment of this approach in future clinical trials.

Background and Significance: Over years, the Computational Image Analysis Laboratory at the Banner Alzheimer's Institute (BAI) continues to develop, test, and apply image and statistical analysis techniques aimed to improve power to detect, track, and diagnosis AD, help clarify modifiers of AD risk, and evaluate AD-modifying and prevention therapies, work closely with and assist researchers inside and outside of Arizona, and contribute to the generation of research publications, contracts and grants, and develop the data platforms needed to use and share in an appropriate, productive and user-friendly way. Several of our techniques (e.g., our non-invasive PET quantification method, our hypometabolic convergence index [HCI] and statistical region-of-interest [sROI] algorithm, composite score (such as the ones used in the API generation trial and the API-ADAD trial) and our recently developed white matter ROI method to track longitudinal amyloid- β ($A\beta$) PET measurements have had a profound impact on the field. With Dr. Su joining the team, he brings to the team several advanced image analysis techniques that allow automated, quantitative, sensitive, and robust analysis of imaging data.

Preliminary Data and Plan: This project will capitalize on FDG PET, ($A\beta$) PET, tau PET, and structural and functional MRI data from several research cohorts, including but not limited to the Arizona APOE4 cohort, AD Neuroimaging Initiative (ADNI3 started mid-2016, and now AV1451 PET data available from over 100 study participants), and Alzheimer's Prevention Initiative (API) Biomarker Study as well as some data kindly shared with us by our collaborators from Washington University and the University of Wisconsin, to further develop, and apply image-analysis algorithms with improved power to detect and track AD, clarify AD risk modifiers and evaluate AD-modifying and prevention therapies. Based on the results we obtained recently using the Braak staging and optimization procedure with scarcity constrain to establish connections among different stages, we will continue using available AV1451 PET data to further develop and improve voxel-based image analysis techniques to construct summary index, cerebral tau index (CTI), for the detection and tracking of the magnitude and spatial extent of neurofibrillary tau burden. We have used serial FDG PET images from our collaborators to validate our longitudinal HCI algorithm to track AD-related declines in FDG PET images and use other grant funds to compare it to our sROI and cross-sectional HCI methods in terms of their power to evaluate AD-modifying

and prevention therapies (collaborative works with BioClinical). We plan to extend this work to cognitively unimpaired individuals aimed to be used as a prevention trial outcome biomarker. We will continue to refine and test our cerebral and white matter ROIs to track longitudinal changes in A β PET measurements and evaluate AD-modifying treatments with greater power and with greater freedom from the potentially confounding effects of brain shrinkage and partial-volume averaging using additional data from our collaborators and start to evaluate its use (with necessary modifications) for tau-PET. We will consider the use of MMRM (Mixed Model Repeated Measurement) to further improve the power to detect the composite score based changes with and without intervention. We will continue to assist our colleagues inside and outside Arizona in the analysis of brain imaging data and the preparation of abstracts, publications, grants, and contracts. Based on the investigation on the database platform, we decided to use the REDCap last fund cycle and have implemented it for easy uses for multiple research institutes within our consortium. We will continue to our efforts to establish proper connection between REDCap and XNAT, the platform we decided to use for data storage in the cloud and for data analysis in a CFR 21 part 11 compliant manner. We will continue our efforts also for the appropriate, productive and user-friendly storage, use, and sharing of brain images and other related data and samples, including development and implementation of a graphical user interface for the use and sharing of data from the Arizona APOE cohort.

Proposed One-Year and Long-Term Outcomes: During the one-year funding period, we intend to continue improving CTI method with independent ADNI and our Arizona APOE4 cohort datasets, white matter ROI, and MMPLS methods (to account for the signal changes related to white matter integrity degradation), compare them to established methods, estimate the power of the longitudinal HCl and white matter ROI methods to evaluate AD-modifying and prevention therapies, and describe our new findings in abstracts and manuscripts. We will start implementing the mixed-model repeated measures (MMRM) analysis method for composite score changes over a 5 year or over an 8 year period in novel ways. We will also integrate the advanced imaging analysis techniques Dr. Su has developed with other tools at BAI and allow more efficient analysis of imaging data while also achieving improved sensitivity. We will continue our efforts to implement our graphical user interface and begin using it to help in the utilization and sharing of Arizona APOE cohort data. We will help our colleagues inside and outside Arizona in the analysis of brain imaging data and the preparation of abstracts, manuscripts, and grant applications.

Year End Progress Summary: During the past year, the Computational Image Analysis Laboratory continues to develop, test and apply advanced image analysis techniques to help in the early detection, tracking, and differential diagnosis of Alzheimer's disease (AD), the clarification of AD risk factors, and the evaluation of AD-modifying and prevention therapies.

A voxel-wise partial volume correction technique is currently under development that takes advantage of the anatomical information in structural MR and recovers true PET signal at high resolution. This technique penalizes local signal variation within the same tissue type while removing signal spillover from other tissue types in the surrounding area and reconstructs a high-resolution PET image using an expectation-maximization (EM) algorithm. The current implementation utilizes brain segmentation and parcellation information provided by the FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>) software and generates partial volume corrected PET data on both voxel level and surface level. Currently, validation of this technique is ongoing using longitudinal amyloid PET imaging data from ADNI. Our preliminary data demonstrate this technique can reduce the sample size needed in hypothetical clinical trials by 75% compared to PET quantification without partial volume correction and by 40% compared to PET quantification with traditional region based partial volume correction technique. This preliminary result has been submitted for consideration at the 2019 Alzheimer's Association International Conference (AAIC 2019). We are also investigating image analysis strategies

specifically designed for longitudinal data and we are examining their ability to improve sensitivity and reliability of image-derived biomarker measurements.

For tau PET imaging analysis, our group is currently developing a network analysis-based approach to investigate the spread of tau pathology in the brain. An undirected, weighted tau PET network graph derived from florataucipir PET data and its associated graph theory related measurements can discriminate between clinical groups and participants at different levels of AD risk due to APOE e4 dosage. Using a previously developed multimodel partial least squares (MMPLS) technique in our lab, we are also investigating the interaction between tau pathology and brain atrophy in an autosomal dominant AD cohort. These results were also submitted to AAIC 2019.

We continue to assist our colleagues inside and outside of Arizona in the analysis of brain imaging data and the preparation of abstracts, publications, grants, and contracts. We are currently in the process of archiving all historical imaging data from the Arizona APOE4 study using the XNAT Imaging Informatics Platform. All metadata related to imaging and biospecimen data have been populated in the REDCap system. A first version of our data sharing platform has been implemented and allows external investigators to query data available.

Since Dr. Su joined the lab, efforts have been made to establish standard operating procedures for FreeSurfer analysis of structural MR data, and to integrate a PET Unified Pipeline (PUP, <https://github.com/ysu001/PUP>) into the standard image analysis procedures in the lab. The main function of PUP is to perform automated PET image analysis utilizing a set of predetermined regions-of-interest (ROIs). PUP is designed to work with FreeSurfer defined ROIs for region-based quantification of PET data in individual space, it also performs a regional spread function (RSF) partial volume correction on PET data that has been demonstrated to improve sensitivity in detecting group difference and longitudinal changes. A streamlined procedure has been developed to perform previously established voxel-wise analysis (with statistical parametric mapping) using PUP outputs to avoid duplication of preprocessing steps while generating both FreeSurfer ROI-based quantification results as well as template-based quantification outputs. Currently, standardized FreeSurfer and PUP processing has been deployed for data from the Arizona APOE4 cohort, the API-ADAD trial baseline data, and the ADNI cohort. Standard processing results will be incorporated into our data sharing platform to allow easy sharing of such results with collaborators within and outside of the consortium.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Statistical and Neuroimaging Core Resources Serving the Consortium members for the Alzheimer's disease and prevention related studies. Yi Su, PhD, Dhruvan Goradia, PhD, Hillary Protas, PhD, Michael Malek-Ahmadi, PhD, Wendy Lee, MS, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; Barrow Neurological Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. To facilitate and prompt the use of the state-of-art methodology for optimal imaging pre-processing and voxel-based, ROI/global index-based analyses for increased statistical power, reliability and accuracy. We will offer services to our Consortium members such as image preprocessing and analyses.
2. To offer comprehensive and sound statistical and image analysis services for various data analysis needs not only limited to neuroimaging data.
3. To make our resources as part of research efforts by engaging in grant applications/ manuscript preparations especially in the aspects of statistical/image-processing and hypothesis establishment.

Background and Significance: With the support from State of Arizona, the Consortium has been making significant and growing contributions nationally for the study of Alzheimer's disease (AD), strategy for evaluating prevention, patient care and family/caregiver support. This widely recognized growth and our contributions are possible primarily due to the fact that researchers from multiple institutes work closely together. They share research ideas, provide critical feedback for others' and make themselves available to each other to carry out complementary investigations for their Consortium colleagues. With the same spirit, we, the Computational Image Analysis Laboratory at the Banner Alzheimer's Institute (BAI), have been trying our best to help and assist many researchers in the Consortium on neuroimaging pre-processing, image based statistical analyses, data mining as well as routine statistical challenges. In addition, we have been assisting a number of young investigators in starting their research careers by helping them with understanding the medical challenges, linking proper mathematical tools to scientific, medical challenges and providing careful review for grant applications and manuscript preparation. All of these are in addition to our own data analysis tasks and methodological developments. With such requests from our Consortium members coming to us often, this year again, there is a need to request additional support from the Consortium.

We are confident that our expertise in the understanding of the medical research hypothesis/challenges, the image processing and statistics and our assistance to our Consortium members will significantly contribute to the productivity and quality of the research. We have been developing a number of image processing and statistical methods/procedures ourselves and we have been adapting or using widely-used SPM, FreeSurfer, SPSS, R, SAS and MATLAB packages for years. We have been working continuously on the developments, refinements and testing of statistical procedures, image analysis and imaging processing techniques to improve power to detect and track the brain changes associated with AD and the risks to AD before its onset and to use these techniques to advance the scientific understanding, diagnosis, treatment, and prevention of AD. Among the techniques developed are methods for better characterizing functional/effective connectivity using resting-state fMRI data(Li et al., 2013; Long et al., 2007; Smith et al., 2011; Wu et al., 2007; Wu et al., 2006; Wu et al., 2009), an empirically predetermined

“statistical region-of-interest” strategy which is with improved statistical power and free of multiple regional comparisons to track AD-related brain changes and evaluate AD-modifying treatments (Chen K et al., 2004; Chen et al., 2006; Chen et al., 2007a), a multi-modal partial least square (MMPLS) technique to combine information from multiple imaging datasets (Chen et al., 2008; Chen et al., 2009), an automated iterative principal component analysis (Chen et al., 2004; Chen et al., 2007b) to characterize rates of whole brain atrophy using sequential structural MRIs from the same person, a voxel-based “hypometabolic convergence index (HCI) to characterize glucose hypometabolism in a person’s FDG PET corresponds to that in AD patients (Chen et al., 2011). For this project, we will NOT use the support from the Consortium to develop new methods or refine the existing ones (supported separately). We will take advantage of their availability together, with other widely used software packages, to assist or carry out the analyses directly for the projects when our Consortium members need our imaging processing/statistical assistance (Specific Aim 2). In addition, we will make our dedicated effort focused on Specific Aims 1 and 3. Over years collaborating with our Consortium members, we have learned from them the scientific and biomedical aspects of their research. They have also long valued our assistance in the areas of methodology development, hypothesis testing, imaging processing and statistics. Together, a number of publications have been generated with our voluntary involvement in addition to those with grant support. In discussion with a number of the Consortium members, Drs. Stonnington, Baxter, Wang, Zamrini and Beach, each expressed their strong interest and enthusiasm for us to share more of our expertise as core resources in their research. As their requests for our services have recently greatly increased we have been trying our best, using the team members’ own time, to provide comprehensive statistical/imaging analysis assistance.

Preliminary Data and Plan: *Data:* This project will involve various neuroimaging data (such as FDG, amyloid PET, functional MRI, DTI, and volumetric MRI) and other non-imaging data from various projects. *Image processing and image-based statistics:* We will share our knowledge, experiences and theoretical understanding and practical implications of various settings for a number of neuroimaging software packages. *Statistical service:* The statistical services will be either providing consultation or conducting directly analyses by our team members. *Hypotheses:* We believe that our core resource will fill the needs from many Consortium members and increase the productivity and quality of the research in the form of peer-reviewed journal papers, and grant submissions. *Core Resources as promoting comprehensive scientific collaboration:* Our involvement will be from the image preprocessing/numerical data organization and QA, imaging or other data statistical analyses, result presentations, manuscript preparation, presentation and grant writing.

Drs. Reiman and Su plan to proactively continue our on-going in-depth discussions with collaborators from the Consortium institutes. Among the projects we’ve been working on, we together with the institute PI, will identify one or two for which our core resources can be used. Each project identified during this process will be assigned with a lead person and with clear goal to accomplish (such as manuscripts to prepare, reports to file and/or grant to submit).

Proposed One-Year and Long-Term Outcomes: The scientific outcomes in the forms of presentation of findings at major meetings and their publication in high-impact peer-reviewed journals and in the form of submitting external grant applications will be our focus. Our long-term goal is to be part of the great efforts to evaluate promising symptomatic/presymptomatic AD treatments in the most rapid and rigorous way, to continue to clarify changes/mechanisms associated with the presymptomatic stages of AD, and to help in the differential diagnosis and management of AD whenever the opportunities arise.

Year End Progress Summary: In the past year, the Computational Image Analysis Laboratory (CIAL) 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. In the following paragraphs, we summarize the main collaborative research performed and the grant applications that have been submitted or are in the planning phase for which the effort for research planning, experimental design, and/or preliminary analysis was performed with the support of this grant.

Continuing our collaboration with Dr. Stonnington (Mayo), a paper was published in JAD in which we reported that regional MRI and FDG-PET measurements may be useful in predicting imminent progression to clinically significant memory decline. The CIAL team is currently helping the investigation of the role of brain derived neurotrophic factor (BDNF) genetic polymorphism and its interaction with APOE in age related brain metabolic change, amyloid accumulation and cognitive decline, and a manuscript is in preparation for this analysis. In collaboration with Dr. Weise (University of Leipzig), the CIAL team helps the investigation of the longitudinal pattern of glucose metabolism in different preclinical and clinical groups of AD and found that a decline of the glucose metabolism was more lateralized to the left hemisphere in early states of AD. This research is published in *Neuroimage: Clinical*. In collaboration with Dr. Nielsen (Stockholm University), we continued the examination of the relationship between imaging biomarkers of brain atrophy and hypometabolism with peripheral levels of insulin and apoE protein and reported preliminary findings at the 2018 ADPD conference. We also continued our collaboration with Dr. Beach at BSHRI to perform statistical analysis to investigate the impact of comorbid Lewy body disease and cerebrovascular pathology on cognitive decline due to AD. As a result of this collaboration, a manuscript is currently under review and an abstract is anticipated to be presented at 2019 AAC and AAIC conferences. In collaboration with Dr. Atri (BSHRI), we are performing statistical analysis to help understand protective and risk factors to cognitive decline in older adults. As part of this collaboration, one paper has been published in *Aging Clinical and Experimental Research*, and another manuscript is currently under preparation with part of the results presented at CTAD 2018. In addition, an abstract investigating the relationship between depression and anxiety symptoms with memory and cognitive function is anticipated to be presented at 2019 AAC and AAIC conferences.

During the past year, we worked with several investigators in planning and submitting their grant proposals and serving as part of their imaging/statistical team. Dr. Sydney Schaefer (ASU) submitted an R01 application titled "A novel motor task as a non-invasive, rapid, low cost biomarker to predict early cognitive declines associated with preclinical Alzheimer's disease", to investigate a novel motor task as an approach to identify early signs of cognitive declines. The CIAL team will perform structural MR and amyloid PET image analysis for this project. We also worked with Dr. Ashley Stokes (BNI) on her R01 application titled "Multi-Scale MRI Assessment of Neurovascular Factors Associated with AD", in which the CIAL team will help with both image and statistical analysis. An STTR application, "Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD", was also submitted with Dr. Fleming Lure (MS Technologies) and Dr. Jing Li (ASU), in which the CIAL team will help with the identification of training and validation dataset, preprocessing of imaging data, as well as interpretation of study findings. The CIAL team also participated in experimental design and grant preparation of a Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial of T3D-959 in Mild to Moderate Alzheimer's Disease Subjects in collaboration with T3D Therapeutics.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Radiochemistry PET Tracer Development. Andrei Koren, PhD, Eric M. Reiman, MD, Gene E. Alexander, PhD. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. To acquire and install the equipment, implement and optimize the radiotracer production and quality assurance procedures, and secure the IND needed to produce [18F] florbetaben (Neuraceq), an FDA-approved radiotracer used in the acquisition of fibrillar amyloid- β (A β) PET scans and [18F] PI-2620, a second generation radiotracer used in the acquisition of paired helical filament (PHF) tau PET scans.
2. To introduce the ability to produce numerous radiotracer doses from a single batch, thus dramatically reducing radiotracer cost and increase the number of participants in the Arizona Alzheimer's Consortium who have PET measurements of fibrillar A β and PHF tau burden in future years--including longitudinally assessed participants in the ADCC's Brain Imaging and Fluid Biomarker Core, additional longitudinally assessed participants in the Brain and Body Donation Program, additional longitudinally assessed participants in the APOE4 Gene Dose Program, and participants in preliminary studies seeking to generate findings in support of competitive grant applications.

Background, Significance and Research Plan: With the reconceptualization of Alzheimer's disease (AD) as a progressive sequence of pathophysiological changes that correspond roughly to preclinical, mild cognitive impairment (MCI) and dementia stages, it is critically important to clarify the extent to which research participants in AD and normal brain aging studies have biomarker evidence of AD. There is a critical need to increase the number of research participants in Arizona's well known longitudinal cohorts and other studies who are characterized in terms of biomarker evidence of fibrillar A β and PHF tau burden, cardinal features of AD, neurodegeneration and, eventually, comorbid diseases. There are now several PET radiotracers that can be used to measure fibrillar A β and PHF tau burden, including several that are available in Arizona. Unfortunately, it typically costs about \$3000-4000 to generate each of these tracers, which along with the cost of the PET scans themselves, have made it unaffordable to conduct A β and PHF tau PET scans in a larger number of research participants.

[18F] florbetaben is a neuropathologically validated, FDA-approved radiotracer that has been used in the acquisition of fibrillar A β PET scans. [18F] PI-2620 is a promising second-generation radiotracer that has been used in the acquisition of PHF tau PET scans. Unlike other PET tracers, it is possible to produce up to 30 florbetaben or PI-2620 doses from a single batch, introducing the possibility to conduct many PET scans from a single batch, dramatically reduce the radiotracer cost associated with each PET scan and increase the number of PET scans that one might be able to afford in future studies.

From its inception, the NIH- and Banner Health-supported Cyclotron and PET Radiotracer Production Facility at Banner Alzheimer's Institute (BAI) was intended to provide a dedicated resource of PET tracers for research studies in Arizona. This state-of-the-art Cyclotron and Radiochemistry Laboratory operates in compliance with FDA approved USP Chapter <823> and, unlike commercial radiotracer production facilities, is fully dedicated to the development of PET tracers for research studies. In this application, we propose to purchase and install the equipment

and supplies, capitalize on our resources, time and expertise to establish the procedures needed to produce and ensure the quality of these PET radiotracers, capitalize on a special research licensing arrangement with Life Molecular Imaging (LMI) to use multiple research doses from a single batch, and provide a foundation to dramatically increase the affordability and use of A β and tau PET scans in our research participants.

This project will be part of a more extensive effort to dramatically increase the affordability and use of A β and tau PET scans for research studies in Phoenix and Tucson (e.g., in as many as 500 participants per year if we can work through the other associated costs and provide the funding) as early as July 1, 2019. We believe this effort will dramatically improve the value, productivity and impact of Arizona's internationally recognized longitudinal cohorts, including prospective brain donors in the Arizona ADCC, other prospective brain donors in the Brain and Body Donation program, and an increased number of cognitively unimpaired APOE4 homozygotes, heterozygotes and non-carriers in the APOE Gene Dose Program. It will also increase the value, productivity and impact of new studies of AD and normal aging, such that the findings can be used to help secure a greater number of NIH grants.

Since these PET tracers have a radioactive half-life of 110 min, we will not only be able to conduct as many as 10 PET scans on the two scanners at BAI from a single batch, but as many as 4 PET scans in Tucson from that same single batch, transporting those doses to that PET location by car.

This project is intended to help increase the value, productivity and impact of our studies, galvanize our ability to secure competitive research grants at a time in which there is an unprecedented level of NIH funding for AD research, and help to recruit and retain additional researchers to Arizona in support of these and related efforts.

Proposed One-Year and Long-Term Outcomes:

We propose to secure the licensing arrangement, purchase and install the equipment and supplies, optimize the radiotracer production and QA/QC procedures for florbetaben and PI-2620, secure INDs for the use of these tracers in our research studies, and provide the foundation to use these tracers in Phoenix and Tucson by July 1, 2019.

Meantime, we will be seeking other ways to maximize the affordability of PET scans and the number of florbetaben and PI-2620 PET scans in our research participants. At this time, we will aim to conduct florbetaben and PI-2620 PET scans in as many as 500 research participants per year.

Year End Progress Summary:

By December of 2018, BAI has processed the capital equipment request to purchase the synthesis unit to produce the florbetaben and the PI-2620 as well as ancillary quality control equipment needed. The ancillary equipment was received but the synthesis unit is still being built and should be ready to ship (from Europe) in early 2019. BAI made the initial payment for the synthesis unit (\$73,242) in 2018 and the remaining 2 payments will be made prior to shipping and again once it is installed. An invoice for the quality control equipment was received in late December and processed for payment in January 2019 (\$47,867).

Once the production equipment is installed and tested by the manufacturer, the radiochemistry staff will begin working on the tracer development process, the regulatory documentation and staff training process. A final independent audit will then be scheduled to ensure we are ready to produce these PET tracers for project use. Our expectation is that this PET tracer development process will take about 5-6 months to complete once the synthesis unit is installed and validated.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

A shared resource for the evaluation of blood-based biomarkers of amyloid- β plaque deposition. Willemijn Jansen, PhD, Eric M. Reiman, MD, Kewei Chen, PhD, Kathryn DeMarco. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; University of California Irvine; University of Wisconsin; Karolinska Institute; Maastricht University; Arizona Alzheimer's Consortium.

Specific Aims: We here aim to promote the further evaluation of blood-based amyloid- β biomarkers by galvanizing the effort to newly discovered biomarkers through creating a foundation for a central repository of blood samples and clinical data. Specifically, we aim to: **1. Promote the further development of a blood-based amyloid- β screening or pre-screening test for early AD detection.** A blood-based screening test with high sensitivity and specificity for amyloid- β positivity could be the basis for a rapid and inexpensive blood screening test to identify people at high risk of developing Alzheimer's disease. A blood-based pre-screening test will help to reduce the number of people that need an invasive PET scan or lumbar puncture in order to identify amyloid positive and negative persons for AD prevention trials and the study of cognitive aging without amyloid. We postulate that at least one of the plasma biomarker assays will have sufficient accuracy (e.g., at least 80% sensitivity for a specificity of at least 50%) to further advance AD research and care, and we postulate that our network will accelerate the evaluation of these and future blood-based biomarkers. **2. Examine the impact of age range, APOE4 gene dose, clinical severity, amyloid assessment modality and cut-off on the performance of the identified blood-based biomarkers for amyloid- β positivity across different cohorts.** The influence of age range, APOE4 gene dose, clinical severity, amyloid assessment modality and cut-off on the performance on the sensitivity, specificity and accuracy of the newly developed blood-based biomarker for amyloid positivity will be characterized and compared. We postulate that at least one of the developing assays will have sufficient accuracy independent of age, APOE4 gene dose, and clinical severity. **3. Create a foundation for a central, shared, user-friendly resource of blood samples and participant-level data.** This data and samples sharing initiative will provide access to help other organizations to evaluate a blood-based amyloid- β test. Blood samples and data of persons with known amyloid- β status can be requested by research groups to test locally developed promising amyloid- β blood-based biomarkers in a rapid fashion. We hypothesize that blood samples and clinical data of 5,000 persons will be secured and expended by two independent research groups during the year of this pilot grant, creating a foundation for further development of the resource.

Background and Significance: The progressive nature of AD posits a huge burden on the ones affected, their families and caregivers. The increasing prevalence also poses a major challenge for the wider society and health care systems and has great economic impact. There is an urgent need to prevent AD. Preventive therapies need to be introduced prior to cognitive impairment and made available to the widest range of patients possible. Several prevention trials using anti-amyloid treatments have started, and more are on the way. Development of a blood-based biomarker for amyloid- β positivity would allow for rapid screening of large populations for prevention trials. A blood-based marker of amyloid- β could also be utilized for pre-screening to determine who should or should not be referred for additional costly PET or CSF measurements. Once effective treatment is found, demands for a blood-based biomarker will even increase. The proposed pilot study will provide a foundation for the evaluation of such a blood-based biomarker and thereby accelerate the development of an Alzheimer's prevention therapy. At this moment,

several blood biomarkers with great potential for screening or pre-screening of amyloid- β positivity are in the pipeline. Large and diverse samples for the rapid evaluation of newly developed biomarkers with great potential is absolutely needed to confirm results across centers and study participants. This resource can be leveraged in an easy, accessible way by the worldwide research community and will have a profound impact on the prevention of AD. As there are currently over 500 million older adults worldwide, this will result in billions of saved dollars. Also, the infrastructure for samples and data as well as the findings resulting from this study can be utilized as a valuable resource to employ or build on for researchers within the AD field.

Preliminary Data and Plan: We will include blood samples and clinical data of persons with normal cognition, mild cognitive impairment (MCI) or dementia. Selected participants will have stored plasma samples and corresponding amyloid- β PET imaging, CSF or neuropathology data available that were acquired within two years of plasma sampling. Participants will be included from ongoing studies. At this stage, we have secured commitment of the following well-characterized studies*:

- Arizona APOE study (n=200; PI: Eric M. Reiman, MD)
- Brain and Body Donation Program (n=180; PI: Thomas Beach, MD)
- The 90+ study (n=280; PI: Claudia Kawas, MD)
- Wisconsin Registry for Alzheimer's Prevention study (n=1000; PI: Sterling Johnson, PhD)
- BIOMARKAPD study (n=500; PI: Bengt Winblad, MD, PhD)
- DESCRIPA study (n=200; PI: Pieter Jelle Visser, MD, PhD)

*numbers provided are an indication

Other centers that have data available on amyloid- β burden will be recruited through existing connections formed in the Amyloid Biomarker study, a data pooling initiative initially aimed at determining the prevalence of amyloid- β positivity in CSF or on PET for which I am the central coordinator. In total, we aim to include samples and data of 5,000 participants in the first year.

Blood samples and clinical data

Blood samples and clinical data will be acquired retrospectively. Blood samples are stored locally, and as pre-analytical procedures are center-specific extensive documentation will be requested in this regard. Depending on the plasma and/or serum quantities required to test a specific blood-based biomarker for amyloid- β positivity, we will request and ship aliquots from our partners. Clinical data on demographics (age, sex and education), genetic markers (*APOE* genotype), clinical severity (normal cognition, MCI, dementia), amyloid- β positivity level and assessment modality (in vivo: standard uptake value ratio (SUVR) on PET, $a\beta$ 42 concentration in CSF, postmortem: CERAD neuritic plaque score at neuropathological examination) will be requested. These data will be harmonized and pooled across sites and matched with the results from the blood-based biomarker assay tested. We will develop protocols in order to optimize sample and data sharing. All de-identified samples and data will be shared according to the appropriate institutional guidelines, HIPAA guidelines, and material transfer agreements between collaborating researchers and institutions.

Promising blood-based biomarkers

After development of the sample and data sharing structure, the performance of blood-based biomarkers can be tested. Several research groups have recently published findings on very promising blood-based biomarkers of amyloid- β positivity or are in the process of developing a promising blood-based marker based on earlier results. Initially, targeted analyses will be performed by two research groups with the aim of replicating and extending the findings of earlier studies performed by these groups. This includes plasma biomarkers of Amyloid- β 42 and the Amyloid- β 42/40 ratio measured by refined mass spectrometry assays (C2N Diagnostics; Roche).

These promising markers show high sensitivity and specificity for amyloid- β positivity and great test-retest reliability and are ready to be tested in a large population.

Statistical analyses

Brain amyloid- β burden measured by PET, CSF or neuropathological examination and dichotomized according to center-specific cut-offs will be used as the reference amyloid- β burden. Generalized Estimating Equations (GEE) modelling will be used to examine the association between each blood-based biomarker and reference amyloid- β burden. GEE allow for the analysis of binary correlated data such that we can account for the clustering of participants within studies. To evaluate the performance of blood-based biomarkers in predicting reference amyloid- β burden, we will conduct receiver operating characteristic (ROC) analyses. The area under the curve (AUC), and the best values for the sensitivity, specificity and accuracy at an optimal cut-off point will be used to calculate the performance measures. The optimal cut-off points will be determined by Youden's index, which optimizes biomarker performance when equal weight is given to sensitivity and specificity.

$$\text{Sensitivity} = \text{TP}/(\text{FN}+\text{TP})$$

$$\text{Specificity} = \text{TN}/(\text{TN}+\text{FP})$$

$$\text{Accuracy} = (\text{TP}+\text{TN})/(\text{TP}+\text{TN}+\text{FP}+\text{FN})$$

TP = true positive, TN = true negative, FP = false positive, and FN = false negative

We will use GEE to build a prediction model to examine the influence of age range, APOE4 gene dose, clinical severity, amyloid- β assessment modality and cut-off on the associations between plasma biomarkers and reference amyloid- β burden. Then, we will examine the performance of the blood-based biomarkers by adjusting our ROC analyses for these variables and evaluate the effects of these variables on the sensitivity, specificity and accuracy of the blood-based biomarkers for amyloid- β positivity.

Proposed One-Year and Long-Term Outcomes: The infrastructure for samples and data sharing resulting from this study will form the basis for a prospective multicenter study submitted as a competitive NIH R01 grant submitted through Banner Alzheimer's Institute that promotes the discovery and development of blood-based biomarkers for AD. We will use the experience gained in this pilot study to optimize and harmonize study protocols to collect blood samples, PET images, and CSF in a harmonized fashion; to overcome issues in compiling informed consent and material and data transfer agreements; to develop a strong data management plan in order to keep the data structured and data flow as accurate and continuous as possible; and to form a scientific review committee to evaluate proposals for scientific merit and to decide on issuing of data and samples. Results as well as experience gained from this pilot study will be very useful in applying for a competitive R01 grant through NIH.

Year End Progress Summary: Since receiving this award, progress has been made in several key areas including fluid biomarker and related data collection and sharing efforts, primarily with the Arizona APOE study cohort, with much promise that continuing these efforts will aid in further development of a blood-based amyloid- β screening or prescreening test for early AD detection. Much of the initial funding period has been spent establishing and building relationships with collaborators external to Banner Health to obtain access to other cohort data and samples as well as promote blood-based biomarker testing and create a foundation for a shared resource of blood samples and participant-level data.

Thus far, agreements have been established with Banner Health and C2N Diagnostics in order to identify the key Arizona APOE study participants who have provided blood plasma samples to share with collaborative researchers while recognizing those participants who have accompanying cross-sectional amyloid- β data obtained via PET or CSF measures within one year

of plasma sample collection. Arizona APOE study participants meeting these criteria have been identified and total roughly 130 participants. The first sample sharing plan has been established between C2N Diagnostics and Banner Health for the Arizona APOE study cohort which is due to take place in March 2019 with anticipated plasma amyloid- β analysis results available in April 2019. Results will be linked to existing data and analyzed for the aims of this proposal. For the remainder of the funding period and beyond, we hope to apply these efforts more expeditiously with the other intended cohorts of the original proposal in order to more rapidly complete the necessary agreements and share data and samples with C2N Diagnostics.

During the past few months, promising amyloid blood assays have been developed at VU University Medical Center in Amsterdam, the Netherlands and the National Center for Geriatrics and Gerontology in Japan. We have established connections with these groups and are exploring possibilities to share blood samples of the Arizona APOE cohort to be tested in these newly developed assays, as well. The network we have built during the project period will form the basis and “proof of concept” for future grants.

Project Progress Report
Banner Sun Health Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 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 and Apolipoprotein E4 (APOE4) Gene Dose Programs. Thomas G. Beach, MD, PhD and Edward Zamrini, MD (co-PIs), Geidy Serrano, PhD, Kathryn Demarco, David Weidman, MD, Lucia Sue, Richard J. Caselli, MD, Charles H. Adler, MD, Donald Saner, MS, Eric M. Reiman, MD. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Mayo Clinic Arizona; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. To develop a repository of cerebrospinal fluid (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 develop a repository of CSF, plasma, and PBMC samples linked to brain imaging and neuropathology data from well characterized, longitudinally assessed, and consenting participants in Arizona's APOE4 Gene Dose Program.
3. 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 Findings: The Arizona Brain and Body Donation Program (BBDP) provides an invaluable scientific resource of longitudinal cognitive, motor, clinical, and genetic data from >800 living older adults who have standardized annual assessments, consent to brain (and frequently body) donation, and provide a resource of unusually high-quality brain tissue, postmortem CSF and blood samples (which differ in some respects to samples that are acquired in life) and neuropathological data after they die. The program includes but is not limited to research participants with the clinical features of Alzheimer's disease (AD) or related disorders and cognitively and neurologically unimpaired older adults with support from the National Institute on Aging (NIA)-supported Arizona 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, 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. This year the project will include brain imaging of a subset of subjects, with MR, amyloid PET and tau PET, allowing cross-comparison of multiple AD biomarkers.

The Arizona APOE4 Gene Dose Program provides an invaluable scientific resource of longitudinal data from initially cognitively unimpaired research participants with two, one and no copies of the APOE4 allele, the major genetic risk factor for AD. The program includes nearly 200 participants who were initially late-middle-aged participants with a first degree family history of dementia who are followed every two years with a battery of clinical ratings, cognitive tests, FDG,

amyloid and now tau PET scans, and MRIs, who have provided plasma, serum and PBMC samples that are stored at Mayo Clinic, and who have begun to provide CSF samples with support from a longstanding NIA grant. It also includes more than 200 other participants, with or without a family history and through youngest to oldest adult ages, who are followed using state and organizational Arizona Alzheimer's Consortium funds, and who have not yet provided CSF, plasma and serum samples. CSF and blood samples in state-supported APOE4 Gene Dose participants would increase the value of the Arizona APOE4 Gene Dose Program in several ways, including a) the chance to detect and track the earliest fluid biomarker changes associated with the predisposition to AD, b) clarify the extent to which they are associated with subsequent cognitive decline and clinical progression, c) help to distinguish the cognitive changes associated with preclinical AD from those associated with aging in the absence of AD pathology, d) help researchers clarify the extent to which emerging AD biomarkers could be detected at earlier ages, and e) provide promising endophenotypes to help in the clarification of AD risk factors.

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 BBPD and APOE4 Gene Dose Programs, 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. We proposed to acquire up to 100 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.

To date since 2015, we have obtained blood samples from 650 participants, 260 this funding period (as of February 22, 2019). By clinical diagnosis, the collected blood samples are from 439 non-demented controls, 108 subjects with mild cognitive impairment, 51 subjects with a clinical diagnosis of dementia due to possible or probable Alzheimer's disease, 120 subjects with Parkinson's diseases and 29 with other diagnoses. It is projected that we will meet our 2018-2019 goal of collecting blood samples from 400 BBPD 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 40 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.

Due to the low successful rate on obtaining CSF by lumbar puncture a decision was made to not bring any BBPD subject for CSF donation until securing proficient personnel that could perform lumbar puncture with a higher successful rate. We have now identified proficient personnel and will start collecting CSF samples in April 2019. It is projected that by the end of this funding period we will have CSF from fifteen subjects.

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. BBPD 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.

Longitudinal biofluid samples from 70 subjects enrolled in the APOE imaging cohort (CSF, plasma, and serum) have successfully been transferred from BAI to BSHRI. No subjects have yet been referred to BAI for this project from the APOE cohort. However, it is anticipated that blood and CSF will be obtained from 50 participants by the end of September 2019. This year the repository transferred four hundred plasma and CSF samples collected from fifty subjects from the Arizona APOE4 Gene Dose Program. Samples were transferred to the laboratory of Dr. Zlokovic at University of Southern California to understand the vascular contribution to dementia and AD, and to C2N Diagnostics to demonstrate the sensitivity and specificity of a new refined mass spectrometry assays that could measure Amyloid- β 42 and the Amyloid- β 42/40 ratio.

Brain Imaging. We proposed that ten subjects that have also contributed blood and CSF will receive MR, 18F Flortaucipir PET and 11C PiB PET scans. For 11C PiB, IV administration of 15 mCi +/- 10%, 4 x 5 min dynamic emission will be followed by a 50 min delay from injection to scan. For Flortaucipir, we will use the same radiotracer dose, radiotracer uptake period, and scanning period that were used in previously published studies and our own preliminary work, including a 4x5-min dynamic emission scan in 3D mode following IV administration of 9.25 (+/- 10%) mCi of Flortaucipir and an 80-min uptake period. Both Florbetapir and Flortaucipir scans will be performed on our GE Discovery 710 PET/CT system at Banner Alzheimer's Institute and for both, emission images are reconstructed with OSEM reconstruction using 3 (for Flortaucipir) or 4 (for PiB) iterations and 24 subsets and a 3 mm (for Flortaucipir) or 0 (for PiB) Gaussian filter and use of the CT to correct the images for radiation attenuation and scatter. During this funding year we harmonized all the Arizona Alzheimer's consortium biofluid collection and bioimaging protocols, modified IRBs for this modification and re-consented more than forty subjects to do the new procedures, from which ten are cognitively normal subjects. To date we have scheduled MR, 18F Flortaucipir PET and 11C PiB PET scans for six subjects and it is projected that we will be close to meeting our 2018-2019 goal of collecting imaging data from ten subjects.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Project Proposal

A Human Brain Single-Cell Suspension Resource. Geidy Serrano, PhD (PI), Thomas G. Beach, MD, PhD (Co-PI), Lih-Fen Lue, PhD, Matthew Huentelman, PhD (Co-I's), Brafman, PhD (Consultant) and colleagues from each of the participating Alzheimer's Consortium sites. Banner Sun Health Research Institute (BSHRI), Banner Alzheimer's Institute (BAI), Mayo Clinic Arizona, University of Arizona, Arizona State University, Translational Genomics Research Institute, and Arizona Alzheimer's Consortium.

Specific Aims:

1. Develop, optimize and standardize a method for producing single-cell suspensions from rapidly-autopsied human brains, allowing the analysis of proteins, RNA and DNA from single cells and phenotypically-specified cell populations.
2. Biochemically characterize single cells and phenotypically-specified populations of cells from single-cell suspensions created with an optimized standardized method (from Specific Aim 1).
3. To provide the foundation of a shared resource of separated cells to researchers within and outside Arizona.

Background and Significance: Biochemical analysis of human neurodegenerative brain tissue, 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. 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.

Year End Progress Summary:

Specific Aim 1: Develop, optimize and standardize a method for producing dissociated-cell suspensions from rapidly-autopsied human brains, allowing the analysis of proteins, RNA and DNA from dissociated cell s and phenotypically-specified cell populations.

Creation of dissociated-cell suspensions

After trying multiple methods using various combinations of enzymatic and mechanical dissociation techniques, as well as time and temperature differences, we decided on what we thought resulted as the best approach for ***Hypothermic cell dissociation*** which aimed to minimize molecular changes caused by processing, by cold processing. The hypothermic approach uses enzymatic digestion with Accutase for 4 hours at 4°C in fresh tissue minced with a razor blade, followed by mechanically disrupted by repetitive pipetting. Myelin, neuropil and other cellular debris removal is done by using different densities of percoll and centrifugation.

To date, 211 autopsies have been performed by the BBDP since the funding start date for this continuing project (July 1, 2016). Of these, tissue from 84 subjects has been used to process

cells using the hypothermic dissociation protocol. In this current funding year (beginning July 1, 2018), we have obtained cell suspensions using the hypothermic protocol from 20 autopsies. On average we are now collecting 16.0 million cells/gram of tissue. Final suspensions are aliquotted for tissue banking in cryopreservative solution and stored at -80°C and for quality control (QC) assessments.

Phenotypic characterization of cells from dissociated cell preparations by H&E and IHC

A subset of cell pellets were embedded in paraffin, sectioned and stained with H&E (Figure 1), or drop slightly fixed in 70% methanol and stained with H&E for physiological examination. Each examined dissociated cell suspension always presents a diverse population, which included neurons (N), astrocyte (A), microglia (M), oligodendrocytes (O) and endothelial cells (E) (Figure 1; *left*). In order to estimate the percentage of each cell type a neuropathologist examined and counted each cell type in four random selected areas in each randomly selected cell pellets from a total of six cases. Forty five percent of the cells counted were neurons, followed by 25% astrocytes, 21% microglia, 5% oligodendrocytes and 4% endothelial cells. Another method to assess cell types is immunohistochemistry. To further confirm whether major cell types and cell specific antigens are still present, the paraffin-embedded cell pellets were immunohistochemically stained with antibodies specific for neurons (Neu- N), astrocytes (glial fibrillary acidic protein, GFAP) and microglia (Iba1). Examination of stained cell pellets prepared with the hypothermic approach show cells stained with all three antibodies.

Specific Aim 2: Biochemically characterize dissociated cells and phenotypically-specified populations of cells from single-cell suspensions created with an optimized standardized method. Characterization of RNA expression from dissociated cell preparations by qPCR and whole gene sequencing.

RNA extraction from dissociated cell suspensions and its correspondent adjacent whole cortical homogenates were done on twelve random selected cases. RNA samples were then probed using qPCR for cell-type-specific RNA for neurons (NEuN), astrocytes (GFAP) and microglia (Iba1), in addition to housekeeping genes that will allow us to compare expression across cases (GAPDH and Actin). The Huentelman laboratory at Translational Genomics Research Institute (TGen) used the same RNA samples to do whole transcriptome sequencing and run differential analyses using a paired design comparing Cell Sorted vs Homogenates.

A delta-delta approach was used for the qPCR analysis. Our results suggest that neuronal NEU-N and astrocyte GFAP RNA expression does not seem to be different between dissociated cell suspensions as compared to the whole homogenates, while RNA expression of the well known microglia protein IBA1 seems to be upregulated in the dissociated cell suspensions.

Furthermore, more than 11,626 gene transcripts were successfully sequenced at TGen and classified either as being mainly expressed in neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, or mixed (in two or more cell types). Then we counted the total number of transcripts specific for each category/cell type and analyzed and calculated the percentage of genes that were either overexpressed in the dissociated cell suspension when compared to the homogenates, down-regulated or did not show any substantial differences. Both sets of RNA generated data suggest that our methodology used to generate dissociated cell preparation, despite using hypothermic conditions, probably affects gene expression. This observation is particularly more noticeable in microglia specific genes, where almost 50% of the sequenced genes showed up-regulation in the dissociated cell preparations as compared to the whole cortical homogenates.

Phenotypic characterization of cells from dissociated cell preparations – FACS. To further determine what cell types are present in the cell suspensions, fluorescence-activated cell sorting (FACS) was used. This method also provides aliquots of “pure” populations of cells (P), depending on the antibodies used. The Civin laboratory acquired a new cell sorter (Bio-Rad S3E; with 488 and 647 wavelength) by the end of 2017 and during 2018 ran multiple experiments trying to optimize staining of cell with low artifactual staining and sorting of cells (S) with RNA that could be further analyzed by qPCR. Antibodies targeting cell types included neuronal marker NeuN, MAP2, neurofilament and SM32; astrocyte marker GFAP and microglia markers IBA1 and LN3. Multiple antibodies tested were already labeled with fluorescent molecules that will be activated by the sorter, but antibody testing also included non-fluorescent primary antibodies which were later incubated with fluorescent-labeled secondary antibodies. Once cell types were identified using the most suitable antibodies, cells were sorted as “pure” population of cells and the rest of the cell types. Sorted cells were used to extract RNA and 100 ng from each sample was used for qPCR. Actin was used as a housekeeping gene, and probes for MAP2 GFAP and IBA1 were used to confirm the presence of cells of interest or enrichment in the “pure” sorted group when compared to the remaining population sorted in each experiment. Our analysis approach used delta-delta calculation, where any $2^{(\Delta\Delta)}$ values above one represents enrichment or over expression of specific genes in the pure population when compared to the rest of the population.

Discussion and Future Plans

1. Further FACS experiments with different antibodies are needed to improve cell enrichment.
2. Further analysis of cell suspensions using next generation RNA sequencing (RNA-Seq) and the 10X Genomics droplet-based approach. Challenges so far have been adapting the protocols used in the TGen labs, which have been based on cells derived from cell culture or peripheral blood, to cells obtained from dispersion of solid tissue such as brain. We are currently collaborating with another expert in the field, Dr. Fryer, whose laboratory is already proficient using 10x in whole cells from mouse brain. As scRNAseq from whole cells (rather than nuclei) is potentially the method that will give the greatest advances in the understanding of cell-type-specific gene expression changes.
3. A methods paper is still under preparation because of the complexity of the experiments, but we project it will be submitted before the end of this funding period so that user-researchers will have confidence in the methods used to prepare the cell suspensions.
4. After a methods paper has been published, in the next year of funding, one or more high-profile projects should be undertaken, to further establish the importance of the general approach and to further awareness of the resource among the neurodegenerative disease scientific community. We are currently working in getting the necessary parameter to sort cells based on pathological proteins of interest, to further sequence and compared to non-pathological cells.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Establishing a bank for human subject-derived microglial and fibroblast primary cell cultures. Lih-Fen Lue, PhD (PI), David Brafman, PhD, Thomas G. Beach, MD, PhD, Geidy Serrano, PhD (Co-I's). Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

1. To isolate, characterize, and bank microglial cells.
2. To isolate, characterize, and bank fibroblasts.
3. To generate hiPSC lines from patient fibroblasts.

Background and Significance: Genetically engineered AD mouse models have played an important role in pointing to many key mechanisms in AD. However, transgenic mouse model-based research has not translated to effective human therapeutics. The transgenic mice models lack the genetic, epigenetic, and transcriptomic heterogeneity present in human diseases and are typically not representative of "sporadic" AD. Research in human subject-derived models is needed. Currently, there are two types of human cell sources which have been used for producing human brain cell models: differentiated cells reprogrammed from induced-pluripotent stem cells (iPSC) and primary brain cells isolated directly from postmortem brains. To facilitate progress in human cell-based basic and clinical research, it is crucial to ensure a continuous supply of primary cell cultures covering a broad range of neuropathologically-characterized brain heterogeneity. This goal can only be achieved with a dedicated prospective program at a suitable center with rapid autopsy of large subject numbers as well as standardized clinical and postmortem research examinations. The Brain and Body Donation Program (BBDP) at the Banner Sun Health Research Institute (BSHRI) provides invaluable autopsy human tissues for us to build a sustainable program for banking viable cells using postmortem brain and skin tissues. The initial effort will concentrate on microglia and scalp fibroblasts. There is a great demand for microglia directly isolated from patient's brain, to investigate inflammatory mechanisms and for anti-inflammatory drug development. Skin fibroblasts are the most accessible cell types that have been successfully made to iPSC or directly trans-differentiated to neural cells such as neurons and astrocytes. While fibroblasts are easy to obtain at many places, the advantage of using fibroblasts banked at BBDP is that they will be linked to deep phenotyping through associated neurological, neuropsychological, and histopathological data.

Preliminary Data and Plan:

Specific Aim 1: To isolate, characterize, and bank microglial cells. This aim will (1) establish a shorter procedure for isolation of microglia, (2) characterize isolated cells with cell-type specific markers, (3) compare the effects of various cryogenic reagents on viability preservation during storage, and (4) bank cells. The isolation procedure for microglia will be based on our previously published procedure with further modification. The procedure requires 5 hours for isolation, followed by a 24-hour selective adherence procedure to obtain high purity of microglia. We will replace the selective adherence step by a magnetic beads-separation procedure using magnetic columns (less shear force). We will select a suitable cryoprotectant that gives a combination of highest survival rate and best RNA quality after cells are thawed from the frozen state. A set of phenotypic and functional features will be used to characterize cells, using flow cytometry and qPCR for cell type-specific genes.

Specific Aim 2: To isolate, characterize, and bank fibroblasts. This aim will (1) modify the core procedure to increase the efficiency of fibroblast harvest; (2) characterize the cells using flow cytometry analysis; (3) assess revival rate in relation to type of cryoprotective reagents, and (4) bank cells. We have previously used a conventional procedure to isolate fibroblasts from epidermis of scalp tissues collected at autopsy. The procedure involves long-term *in vitro* expansion from primary epidermal and dermal cell mixed culture. We had used this procedure to isolate the fibroblasts from 15 cases in the past. In this proposal, we will test a recently published procedure to shorten the time to obtain pure epidermal fibroblasts. This procedure involves use of Y-27632, an inhibitor of Rho-associated protein kinase to treat cell cultures, enhancing epidermal cell selection and reducing dermal cell inclusion [29;30]. We will use flow cytometry and qPCR to confirm the specificity of the fibroblasts. Various types of cryoprotectant will be tested for best survival rate and RNA integrity. Once the procedure and reagent are standardized, cells from 10-15 cases will be banked.

One-year outcome and long-term goal: We anticipate to establishing optimal protocols for microglia and fibroblast banking and at least 15-20 cases of cells banked for long-term storage.

Specific Aim 3: To generate hiPSC lines from patient fibroblasts. For generation of hiPSCs from patient fibroblasts we have adapted our previous published protocol for reprogramming patient skin fibroblasts (Cell Rep. 2014 Dec 11;9(5):1770-1780). Briefly, expanded fibroblasts will be transduced with 4 non-integrating sendai viruses each expressing Oct3/4, Sox2, Klf4, c-Myc. After 3 days, transduced cells will be plated onto mitotically arrested mouse embryonic fibroblast (MEF) feeder cells. HiPSC colonies will begin picked 15-21 days after transduction. Isolated hiPSC colonies will be cultured in hiPSC expansion medium (DMEM/F12 with 10% knockout serum replacement supplement with FGF2 and ascorbic acid). Loss of sendai virus will be determined after passage 10 by immunostaining with anti-sendai virus antibody. HiPSC lines will be analyzed for (i) characteristic hiPSC cell morphology, (ii) expression of pluripotency markers OCT4, NANOG, and SOX2 (iii) ability to differentiate *in vitro* populations representative of the three main germ layers, and (iv) a normal complement of 46 chromosomes. For each patient, a total of 3 clonal hiPSC lines that fulfill these criteria will be expanded and cryopreserved.

Year End Progress Summary:

Autopsy cases that have been collected and processed during this funding period: We started cell isolation for this project in late August of 2018 after the new cell facility was set up. Up to the end of January 2019, we had processed a total of 16 autopsy cases for this project; averaging 3 autopsy cases per month. Among these cases, 6 cases were used for isolation of both microglia and fibroblasts. The other cases were either for microglia alone or fibroblasts alone. The clinical diagnoses of these cases were 6 normal controls (NC), 4 Alzheimer's disease (AD), 4 Parkinson's disease (PD), and 2 mild cognitive impairment (MCI). All cases have demographic information, postmortem delay intervals, last MMSE and UPDRS, and ApoE genotypes available. Some of the cases have neuropathological diagnosis completed. ApoE genotype is an important feature for this cell bank. Among 12 cases that fibroblasts have been isolated, there were 2 subjects with ApoE ϵ 3/4 genotype, but the rest of the cases were 3/3. We have not had cases with ApoE ϵ 4/4 yet or any cases with the ϵ 2 allele. We anticipate meeting the proposed goals of banking cells from 15-20 cases by the end of funding period in June.

Procedure optimization: One of the goals of this project is to establish the procedures that can be suitable for routine isolation of postmortem microglia (Aim 1) and fibroblasts (Aim 2) at BSHRI. At the initial stage of the program, it is crucial to carry out optimization and standardization of the procedures. We summarize what has been done towards this goal below.

Human microglia: Postmortem brain slices of frontal cortical tissues, approximately 50-75 gm, were collected at the time of autopsy and immersed in Hibernate media-A until cell isolation procedure. Cells were isolated through the procedures of mechanical and enzymatic dissociations, gradient centrifugation, and removal of blood vessels and endothelial cells. Once

these procedures have been established, we tested three ways of cell preparation for banking: (1) Banking cryoprotected mixed glial cells. In previous two years, we had been part of postmortem single cell suspension project. In that project, mixed glial cells were not separated into individual cell types before cryoprotection. The rationale was that mixed glial cells could give options for downstream application in the user's lab. For example, sorting microglia using different set of markers. (2) Banking cryoprotected CD11b antibody-selected microglia: this approach selects microglia cells by CD11b antibody-conjugated microbeads before cryoprotection. To obtain CD11b antibody-selected microglia, this selection procedure was added after removal of blood vessels and endothelial cells. We tested two different CD11b antibodies for selection and compared the isolation efficiency with other microglia cell-surface markers (CD33 and TREM2). The antibodies were used with EasySep PE release magnetic separation procedure (StemCell Technology). (3) Banking cryoprotected microglia purified by adherence property. This procedure has been used by us over the last two decades for obtaining microglia at > 95% purity. For microglia selection procedure in (2), we are still testing more cases to compare cell yield, purity, and viability. The characterization of the isolated cells using cell-specific markers (CXCR3, CD33, and TREM2) at protein and RNA levels is ongoing. The characterization will be completed at the end of funding.

Scalp Fibroblasts: We had previously established a procedure for isolating fibroblasts from postmortem scalp tissues. At the beginning of this new project, we explored whether abdominal skin could be a better source for growing fibroblasts, because we could have a larger size of the tissues for cell isolation. After testing abdominal tissues, we found that scalp tissues were still a better source for our use, because abdominal skin samples have a thinner dermal layer and thicker fatty hypodermis compared scalp. Thus, we will continue using scalp tissues as the source of fibroblasts. We then further optimized the procedure to obtain scalp explants; and optimized culture condition and medium supplements. Briefly, the scalp tissue provided to us is typically a 1-2 cm² strip, ranging from 2.5 g to 4.5 g. After washing tissues three times vigorously in the buffer containing anti-mycotic agents, we removed the fatty layer. The dermal layer was gently separated from the epidermal layer and minced to 1 mm² pieces. The tissue pieces were then plated to cell cultures plate for adherence. Time required for adherence and cell outgrowth from explants varied between cases. We had two autopsy cases that failed to adhere. Cells growing out of the explants were a mixture of keratinocytes, fibroblasts, and vascular cells. When reaching confluency, cells were passaged into flasks for expansion. We typically expand cells until passage 3. Once they reached confluency at passage 3, cells were trypsinized and counted. Cells for cryo-storage were resuspended in cryoprotectant and stored at -80°. Depending on total cell yield from each case, we have been able to bank 3-10 vials of 0.5-1 million passage 3 fibroblasts. Fibroblasts were characterized at RNA and protein levels with cell type markers including fibroblast surface protein and vimentin. **hiPSC:** We have harvested scalp fibroblasts from 9 ApoE ε3/3 carriers and 3 ApoE ε3/4 carriers. Cells from selected cases with known ApoE genotypes are to be used by Dr. Brafman for hiPSC induction as proposed in Aim 3 in next few months.

Progress Summary: We have successfully established procedures for routine isolation of scalp fibroblasts and microglia from autopsy cases. Cells which have been stored in cryoprotectant will be available as shared resources for AAC research scientists and scientists throughout the national and international community, once characterization is completed. During this past year, we supported, with letters of support for human microglia and fibroblast cultures, and two NIH grant proposals by Dr. Rita Sattler at Barrow Neurological Institute.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Clinicopathological Study Initiation for Incidental REM Sleep Behavior Disorder in Sun City, Arizona. David Shprecher, DO, MSci (PI), Thomas G. Beach, MD, PhD (Co-PI), Charles H. Adler, MD, PhD (Co-PI), Eric M. Reiman, MD, Richard J. Caselli, MD, Shyamal H. Mehta, MD, Joseph Hentz, MS, Geidy Serrano, PhD, Brad Boeve, MD, Ron Postuma, MD (Co-I's). Banner Sun Health Research Institute; Banner Alzheimer's Institute; Mayo Clinic Arizona; Mayo Clinic Rochester MN; McGill University; Arizona Alzheimer's Consortium.

Specific Aims:

1. Enroll subjects with probable or confirmed REM Sleep Behavior Disorder (RBD) into the Banner Sun Health Research Institute Brain and Body Donation Program, a longitudinal clinicopathological study of normal aging and neurodegenerative disease in Sun City, Arizona.
2. Conduct formal sleep studies to determine the proportion of subjects with probable RBD, based on the Mayo Sleep Questionnaire and clinician review, that have polysomnogram-confirmed RBD.

Background and Significance: Idiopathic rapid-eye-movement (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 approximately 50% of those with RBD will develop either parkinsonism or dementia within 10 years, with 80% or more converting after 20 years. The mean time interval between RBD onset and cognitive impairment or parkinsonism is 6-7 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). There are currently no preventative treatments for PD or DLB, and prevention trials have not been feasible due to the low incidence rates and absence of clear clinical predictors of disease development. RBD subjects, however, with their high rate of progression to a synucleinopathy, are ideally suited for prevention trials. Recruiting for prevention trials from sleep clinics would be convenient but will be limited by the relatively small numbers of definite iRBD subjects that come to medical attention, especially if, as expected, multiple agents and trials will be needed. Probable RBD (pRBD) can be identified using the RBD single item questionnaire but it is not completely clear yet, from a community-based population, what proportion of these will be confirmed by PSG. Recruiting pRBD directly from the elderly population would be expected to generate the needed subject numbers for prevention trials, as RBD has been estimated to be present in about 0.5%-17% of older adults, however, there has never been a true population survey for the prevalence of RBD in the United States. Existing data comes almost entirely from subjects identified after presentation to a healthcare organization and are thus a selective and possibly distinct subset of RBD. The results of our population survey of a single Sun City zip code (our funded AAC project from 2015-2016) were presented at the International Movement Disorders Society meeting in Hong Kong, October 2018 and the study manuscript is under review for publication. We designed the survey using the RBD single item question (RBD1Q) for probable RBD (pRBD) and the

Innsbruck RBD Inventory for high-likelihood RBD (HL-RBD). Attempts by telephone and mail were made to administer it to 1000 individuals in the Sun City, Arizona zip code. Of 3,000 individuals contacted, there were 484 respondents (response rate 16%), who were 96.7% Caucasian, mean age 78 (SD 8.5.) Of these, 48 (9.9%) endorsed pRBD by RBD1Q, 7 with history of PD or other potential cause of RBD. 16 (4%) had HL-pRBD, 3 with history of potential secondary cause. Previous research suggests that 66% of HL-pRBD respondents will have polysomnogram confirmed RBD. A subset of the pRBD subjects identified by this study were invited to enroll in the Banner Sun Health Research Institute Brain and Body Donation Program (BBDP) and asked to undergo a formal sleep study with PSG. Survey-based research did not appear to be an adequate strategy for recruitment of individuals with iRBD into clinical research studies.

Preliminary Data and Plan: The principal investigators are recognized experts in the clinical and neuropathological evaluation of synucleinopathies and have published multiple studies of preclinical markers including RBD. Dr. Shprecher has previously undertaken broad-based surveys of neurological illness, including a mail-out survey for the presence of RBD in 7,888 subjects in Salt Lake City, UT, to which 1,344 respondents included 13% that indicated the presence of dream enactment behavior (manuscript in preparation). Co-PI Dr. Adler is Co-Director of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and leads the clinical assessments of all enrolled subjects. Over 800 subjects are examined annually and Dr. Adler has published extensively on the clinical biomarkers seen in PD, AD, and other neurodegenerative disorders. Co-PI Dr. Beach is Co-Director of AZSAND and 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. Between 80 and 110 autopsies are done each year, allowing the rapid acquisition of relatively large numbers of new subject, and autopsies are obtained in more than 90% of those enrolled. Tissue is made available to investigators worldwide, with more than 150 tissue transfers each year. Drs. Reiman and Caselli will also participate in this program, given the relevance of RBD to the preclinical study and prevention of DLB, and the opportunity to leverage resources from the Arizona AD Core Center.

Experimental Design and Methods:

Specific Aim 1: Enroll subjects with probable or confirmed REM Sleep Behavior Disorder (RBD) into the Banner Sun Health Research Institute Brain and Body Donation Program, a longitudinal clinicopathological study of normal aging and neurodegenerative disease in Sun City, Arizona. Subjects with pRBD or PSG-confirmed RBD will be recruited from the greater Phoenix region through outreach community lectures, advertising and personal contact with metropolitan area sleep clinics. Additionally, subjects from our community survey in Sun City that answered positively to the dream-enactment behavior question will be invited to enroll into the BBDP. Once enrolled, subjects will receive the standard annual cognitive and movement disorder assessments, including all the assessments that are part of the National Institute on Aging Alzheimer's Disease Centers Uniform Data Set, part 3. Upon death, subjects will be autopsied through the BBDPs rapid autopsy protocol and receive a complete neuropathological examination. Tissue will be banked as a shared resource for researchers within and outside of Arizona.

Specific Aim 2: Conduct formal sleep studies to determine the proportion of subjects with probable RBD, based on the Mayo Sleep Questionnaire and clinician review, that have polysomnogram-confirmed RBD.

A subset of the pRBD subjects enrolled into the BBDP will be asked to undergo a formal sleep study with PSG. We have budgeted for 10 sleep studies but if more subjects agree to have a study, we will use non-award funds to have up to 20 subjects done.

Proposed One-Year and Long-Term Outcomes: Establishment of a cohort of prospectively-assessed RBD subjects will be used as preliminary data to obtain NIH, PCORI, and/or Michael J. Fox Foundation grants to enlarge the cohort, conduct directed studies of clinical progression biomarkers, and potentially begin prevention trials to slow or stop progression to PD or DLB. As the principal investigators have a long-established record of obtaining federal and non-federal out-of-state funding, this project has a high probability of leading to larger, long-term state revenue inflow and increasing local employment.

We are requesting an additional year of funding to cover the cost of 15 nights of diagnostic research polysomnograms at \$1500 per night (total \$22,500). About half of subjects are expected to need two nights to capture enough REM sleep to make a diagnosis, so this would cover diagnostic evaluations for about 10 subjects.

Year End Progress Summary:

Aim 1: As of February 2019, we have enrolled a total of 5 individuals with polysomnogram-confirmed REM Sleep Behavior disorder into our longitudinal research program.

Aim 2: The funds from our prior academic year's funding period were very helpful in generating the study participants now scheduled for polysomnograms. In order to promote recruitment for the study, Dr. Shprecher has (in the past academic year) given three outreach lectures in the past academic year specifically for the recruitment arm of this study, entitled "Important Links Between Sleep and Brain Health" in Sun City West and Trilogy-Vistancia (Peoria, AZ); five outreach lectures on "Hope through Parkinson Disease Research" in Maricopa county, and a Neurology grand rounds lecture, entitled " Dreaming: A Prevention Strategy for Lewy body Disorders" at Banner University Medical Center-Phoenix.

As of February 15, 2019, we have completed two research polysomnograms and have 11 individuals scheduled or pending scheduling research polysomnograms. We plan to present our preliminary findings of the study in abstract form and prepare for publication this year. Our site is now a member of the International REM Sleep Behavior Working Group. We plan to consider a collaborative research application based upon findings of this pilot study through this group.

As a result of our recent work, we have been invited to participate in a grant application under review to add our site to existing NIH award R34AG056639, "Neuroprotective treatment trial planning in REM sleep behavior disorder" to fund clinical assessments of participants with idiopathic RBD in our observational research study (Brain and Body Donation Program).

Project Progress Report

Barrow Neurological Institute
At St. Joseph's Hospital and Medical Center

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

The Role of Nicotinic Acetylcholine Receptors (nAChRs) in Mediating Neuroinflammation and Amyloid-Induced Alterations in Potassium (K⁺) Channel Functional Expression in Basal Forebrain Cholinergic Neurons (BFCNs). Andrew A. George, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims: This project will test the hypothesis that amyloid-beta (A β), interacting with select nicotinic acetylcholine receptor (nAChR) subtypes, induces microglial polarization, leading to increased neuroinflammation and BFCN hyperexcitability through functional regulation of voltage-dependent potassium (K⁺) channels.

Background and Significance: Cholinergic neurons of the basal forebrain provide widespread innervation of the hippocampus and cerebral cortex, and play important roles in cognitive function, especially memory consolidation. BFC neuronal loss is a relatively early feature of Alzheimer's disease (AD). However, it is unknown why these cholinergic neurons selectively degenerate. Recent evidence suggests that nAChRs play a crucial role in the pathogenesis of this disease. A β binds to α 7-containing nAChRs with a high affinity, modulating receptor function in a concentration-dependent manner. In transgenic mouse models of AD, elevations in A β lead to up-regulation of α 7-containing nAChR and is strongly correlated with increased seizure rates. In humans, seizures and subclinical epileptiform activity are more frequent in early AD stages, and individuals in the asymptomatic preclinical stage of AD exhibit septo-hippocampal hyperactivity. Interestingly, mice overexpressing A β exhibit hippocampal CA1 hyperexcitability and increased seizures associated with alterations in dendritic potassium (K⁺) channels. Modulation of K⁺ currents have been linked to AD pathogenesis, contributing to neural dysfunction and degeneration. For example, voltage-gated A-type K⁺ channels are upregulated during early stages of AD, resulting in increased hippocampal CA1 firing rates. Expression of KCNQ/M-potassium channels (I_m) and SK-type Ca²⁺-activated K⁺ channels (both involved in regulating spike afterhyperpolarization) are functionally altered in the presence of A β .

Additionally, non-neuronal mechanisms may contribute to the astatic activity of BFCNs during the early stages of AD. For example, activated microglia in AD generate inflammatory mediators, such as cytokines, that can enhance neuronal excitability. Furthermore, A β -induced rises in astroglial intracellular Ca²⁺ can result in glutamate release and subsequent activation of neuronal NMDARs, resulting in neuronal hyperexcitability hippocampal pyramidal neurons. Glutamate released from astrocytes can also act on presynaptic metabotropic glutamate receptors (mGluRs), increasing the probability of transmitter release in glutamatergic terminals. Thus, diverse mechanisms could contribute to network dysfunction in Alzheimer's disease.

The long-term goal of this project is to identify pharmacotherapeutic targets to abate neurodegeneration of basal forebrain cholinergic neurons (BFCNs), a population of neurons selectively lost in the early development of Alzheimer's disease (AD). Evidence has long supported the conclusion that neuroinflammation is associated with AD pathology as individuals with AD are at an increased risk of immune system dysfunction, show upregulation of pro-inflammatory makers in the brain, and a higher incidence of epileptiform activity. Given these findings, it remains reasonable to consider that AD etiopathogenesis, in at least some cases, involves amyloid- β (A β)-induced pro-inflammatory signaling directly or indirectly leads to BFCN hyperexcitation and subsequent degeneration.

Specific Aims and Project Description:

Aim 1) To test the hypothesis that A β selectively activates α 7-containing nAChRs leading to microglial-mediated pro-inflammatory signaling, which results in BFCN hyperexcitation through the functional downregulation of K⁺ conductances. The proposal's aim will use organotypic forebrain slice cultures from transgenic mice expressing enhanced green fluorescent protein (EGFP) under the exclusive control of the choline acetyltransferase (ChAT) promoter. BFCN whole-cell current clamp recordings will be used in combination with well-established nAChR and K⁺ channel pharmacology to delineate the relationship between A β isoforms, α 7 nAChR activation and functional modulation of K⁺ channels (e.g. A-type, M-type (I_m) and SK-type) as they relate to alterations in BFCN intrinsic excitability. Single-cell intracellular content will be isolated from electrophysiologically interrogated neurons and used as a substrate for RT-PCR determination of K⁺ channel expression levels. Subsequent to whole-cell recordings, organotypic slices will be collected and subjected to flow cytometric analysis and fluorescence-activated cell sorting (FACS) to determine the activity of resident and infiltrating immune cells in the presence or absence of A β . Cell-specific immune-markers will distinguish monocytes/macrophages /microglia and neutrophils. Resident microglia will be distinguished from infiltrating monocytes/macrophages and activated microglia and proinflammatory monocytes/macrophages. Using ELISA assays, organotypic culture media will be collected and analyzed for cytokine activity and correlation will be drawn between A β administration, nAChR activation, and characterization of K⁺ channel functional modulation and BFCN intrinsic excitability.

Proposed One-Year and Long-Term Outcomes:

Accumulation of A β has been shown to cause neural inflammation, leading to the activation of microglia around A β plaques and, in turn, can lead to 1) increased neuronal instability and 2) subsequent epileptiform activity (as observed in both humans with AD and mouse models of AD). Given these findings, the ultimate goal of this study is to understand the effects of A β /nAChRs interactions on mediating neuroinflammatory processes that can influence the intrinsic properties that regulate neuronal excitation. The preliminary findings from this award will lay the foundation for NIH funding opportunities into the identification of pharmacological targets to stabilize neural activity by increasing the survival of specific neuronal populations that selectively degenerate during AD.

Year End Progress Summary:

Using cell-attached single-channel electrophysiology, we provide evidence that oligomeric A β directly activates both α 7 and α 7 β 2 nAChR subtypes and preferentially alters α 7 β 2-containing nAChR single-channel kinetics by enhancing α 7 β 2 nAChR open-dwell times. These results demonstrate for the first time a direct functional interaction between A β and pure populations of heterologously expressed α 7 and α 7 β 2 nAChR subtypes with fixed receptor stoichiometries. Additionally, using an *ex vivo* mouse model of AD, we demonstrate that BFCNs chronically exposed to oligomeric A β exhibit neuronal hyperexcitation manifest as an increase in action potential firing rate. This A β -induced enhancement in BFCN action potential firing rate is mirrored by alterations in the intrinsic mechanisms that govern adaptations in neuronal spike frequency. Furthermore, we show that oligomeric A β significantly reduces the amplitude of the action potential afterhyperpolarization (AHP) in cholinergic neurons recorded from the medial septum/diagonal band (MSDB) and the horizontal diagonal band (HDB). Using well-established nAChR pharmacology, we show that this effect that is dependent upon α 7 β 2 nAChR activation. Finally, we provide evidence that A β alters specific features of BFCN action potential waveform. BFCN whole-cell patch-clamp recordings reveal that chronic oligomeric A β administration reduces the maximal rate of voltage change during action potential depolarization, attenuates action potential peak amplitude of upon subsequent spike formation and increases the maximal rate of action potential repolarization. In continuation of this study, basal forebrain slices have

been harvested and single-cell suspensions from the basal forebrain are currently being analyzed for microglial polarization, astroglia activation, and levels of pro-inflammatory makers. We predict a strong correlation between amyloid load, BFCN hyperexcitability and the activation of microglial cells and astrocytes in the basal forebrain. We will continue our examination into the role of $\alpha 7\beta 2$ nAChR subtypes in driving pro-inflammatory signaling by pharmacologically manipulating these receptor subtypes using compounds that selectively modulate $\alpha 7\beta 2$ nAChRs.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Cortical tau pathologic signature: A biomarker for Down syndrome with and without dementia. Sylvia E. Perez, PhD, Bin He, MD, Elliott Mufson, PhD, Paul Coleman, PhD. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) We will test the hypothesis that an increase in the number of frontal cortex pyramidal neurons bearing phosphorylated (AT8, pS422) and truncated (MN423, TauC3) tau differentiate demented from non-demented individuals with Down syndrome (DS) using quantitative immunohistochemically techniques. We also hypothesize that hereditary early onset familial Alzheimer's disease (EOFAD) and DS with dementia (DSD+) cases will display higher numbers of cortical NFTs containing phosphorylated pS422 and truncated MN423 compared to non-demented individuals with DS (DSD-).
- 2) We will test the hypothesis that an up-regulation of classes of genes related to apoptosis and downregulation of tau phosphorylation, amyloid and glutamatergic phenotype transcripts will be greater during the evolution of NFTs within frontal cortical pyramidal neurons in DSD+ and EOFAD compared to DS without dementia by combining Tau pS422, TauC3 and MN423 immunohistochemistry with single cell gene technology.

Background and Significance:

The phosphorylation of tau prevents its binding to microtubules and under pathological conditions, tau is hyper-phosphorylated, adopts abnormal conformations and self-assembles into paired-helical filaments (PHF), the main component of NFTs. Consequently, these tau alterations result in microtubule destabilization, loss of tau function and the formation of NFTs. NFTs are a pathological hallmark of a group of adult neurodegenerative diseases clinically characterized by dementia and designated as tauopathies, including AD and DS. Individuals with DS display intellectual disabilities early in life but by the fourth through sixth decade are at a greater risk for AD like dementia coincident with increases in the A β plaque and NFT pathology. These lesions are associated in part with the overexpression of genes located on the chromosome HSA21, including the amyloid precursor protein (*App*) that encodes the precursor of A β , APP, as well as the dual-specificity tyrosine phosphorylation-regulated kinase 1A (*Dyrk1A*) and the regulator of calcineurin 1 (*Rcan1*), which promote aberrant phosphorylation of tau. APP is cleaved by β and γ -secretases generating A β species, the main component of amyloid plaques, which occurs prior to NFT formation in DS. Although PET imaging studies have associated A β detection with cognitive decline in DS, these findings remain controversial. On the other hand, NFT pathology in DS similar to AD, displays a stronger correlation with dementia, suggesting a more prominent role for tau/NFTs in the development of dementia in individual with DS.

Recently, a linear model for NFT evolution has been proposed, and can be observed using antibodies directed against specific phosphorylation, conformation and cleavage tau epitopes that reveal pretangle, intermediate and late stages of NFT development during the progression of AD. For example, tau phosphorylation at serine 422, at serine 202 and threonine 205 and tau conformational at residues 155-244 and 305-314 were identified as early pretangle events using pS422, AT8 and Alz50 antibodies, respectively, whereas conformational tau change occurs after phosphorylation of tau. While tau truncation at aspartate 421 (by caspase 3) and at glutamic 391 detected with TauC3 and MN423 antibodies, respectively, occurs later during NFT formation in AD, and are associated with cell apoptosis and cell death. Whether similar pathological tau signatures occur in DSD-, DSD+ and EOFAD and whether they are link to cognitive decline is

unknown. Our group has been at the forefront of the single gene profiling of cortical and subcortical neurons during the progression of AD. By contrast, there are no single cell gene expression studies of neurons marked by site specific tau posttranslational modifications in DS with and without dementia or EOFAD. Here, for the first time, we will apply this type of analysis to DS with and without dementia compared to EOFAD. These studies further open the door to transcription drug discovery aimed at slowing or preventing tangle pathology in human tauopathies.

Virtually nothing is known about tau/NFT signatures and their affect upon gene expression in either DS D+, DSD- and EOFAD. The research proposed focuses on combining site specific tau biomarkers with single cell gene array technology to define tau based signatures related frontal cortex glutamatergic pyramidal neurons, a region severely affect by NFT pathology and understudied in DS and EOFAD. Data will generate new tau/NFT drug targets and biomarkers with possible translation to sporadic AD.

Preliminary Data and Plan:

Aim 1. We hypothesize that phospho and truncation tau markers are increased in the frontal cortex layer III and V neurons of demented DS and EOFAD compared to non-demented DS. Relative numbers of frontal cortex layer III and V neurons immunostained with antibodies against AT8, pS422, Alz50, TauC3 and MN423 NFTs will be quantified using a modification of an unbiased stereology procedure. Briefly, three frontal cortex sections will be singly immunostained using AT8, pS422, Alz50, Tau C3 and MN423 tau antibodies (1:1000-1:5000) as previously reported. Additional sections will be doubly immunostained with either early phosphorylation (pS422, rabbit IgG antibody) or conformation (Alz50, mouse IgM antibody) and late truncated tau markers (TauC3 or MN423, monoclonal antibodies) to determine the progression of NFTs in layers III and V of the frontal cortex. Sections will be counterstained with Gill's Hematoxylin for cytoarchitecture NFT counts in cortical layers, and imaging will be performed as previously described.

Aim 2. We hypothesize that phospho and cleaved tau protein markers in cortical NFTs will be associated with an up-regulation of classes of genes related to cell apoptosis and a down-regulation of transcripts related to tau phosphorylation, amyloid and glutamate in DSD+ and EOFAD compared to non-demented DS. Single population expression profiling using custom-designed microarray analysis will be evaluated using the same cases used in Aim 1. Fixed sections will be single immunostained using pospho pS422 and truncated MN423 and TauC3 tau markers. Labeled cells will be micro-aspirated using a Zeiss laser capture microscope, mRNA will be extracted as previously reported and custom-designed microarrays will be employed to identify mRNA changes. The current array platform includes cDNAs/ESTs for ~864 genes relevant to neurodegeneration, cell survival, cell proliferation, apoptosis, epigenetics and more.

Six Month Progress:

Here, we applied quantitative immunocytochemistry and fluorescent procedures to characterize NFT pathology using antibodies specific for tau phosphorylation (pS422, AT8), truncation (TauC3, MN423), and conformational (Alz50, MC1) epitopes, as well as A β and its precursor protein (APP) in frontal cortex (FC) layers V and V, which displayed consistently tau pathology, as well as in striatal tissue from DSD+ and DSD- cases. Expression profiling of single pS422 labeled FC layer V and VI neurons was also determined using laser capture microdissection and custom-designed microarray analysis. We found that cortical and striatal A β plaque burdens were similar in DSD+ and DSD- cases. In both groups, most FC plaques were neuritic, while striatal plaques were diffuse. By contrast, FC AT8 positive NFTs and neuropil thread densities were significantly greater in DSD+ compared to DSD-, while striatal NFT densities were similar between groups. FC pS422-positive and TauC3 NFT densities were significantly greater than Alz50 labeled NFTs in DSD+, but not DSD- cases. Putaminal, but not caudate pS422-positive NFT density, was significantly

greater than TauC3-positive NFTs. In the FC, AT8+pS422+Alz50, TauC3+pS422+Alz50, pS422+Alz50, and TauC3+pS422 positive NFTs were more frequent in DSD+ compared to DSD- cases. Single gene-array profiling of FC pS422 positive neurons revealed a downregulation of 63 of a total of 864 transcripts related to A β /tau biology, glutamatergic, cholinergic, and monoaminergic metabolism, intracellular signaling, cell homeostasis and cell death in DSD+ compared DSD- cases. These observations suggest that abnormal tau aggregation plays a more critical role in the development of dementia in DS.

The profile of vulnerable FC pyramidal layer V and VI neurons between DSD- and DSD+, suggests that these two groups have similarities as well as differences in neuropathological and gene expression signatures that may be used to develop therapeutic interventions that arrest cognitive decline in this population that represents a unique genetic model of early AD. This data is a great foundation to the research proposal that would be submitted to NIH.

Year End Progress and Long-Term Outcomes:

In addition, we are examining the evolution of tau pathology in the frontal cortex tissue from EOFAD cases. Expression profiling of single pS422 labeled FC layer V and VI neurons will be also determined using laser capture microdissection and custom-designed microarray analysis in EOFAD tissue.

In collaboration with Dr. Paul Coleman at ASU-Banner Neurodegenerative Disease Research Center we are investigating the role of epigenetics in the onset of dementia in DS and EOFAD.

To decipher the mechanism involved in tau and neuronal degeneration in DS, we will collaborate with Dr. Sattler, a well renowned ALS researcher from Barrow and an expert in the field of induced pluripotent stem cells (iPS). In this study, we will differentiate fibroblasts from DS donors with and without dementia into iNeurons and will characterize the cultures by immunostaining to determine alteration in neuronal morphology (dendritic tree, spine density, and synapse density), neuronal marker protein expression (MAP2) and neuronal activity (action potential firing rates) between this two groups. This research will be part of our proposal to NIH.

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Complement-Mediated Mechanisms of Post-stroke Cognitive Dysfunction. Andrew Ducruet, MD, Saif Ahmad, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims: 1) Test the hypothesis that increased expression of C3aR exacerbates the progression of vascular contributions to cognitive impairment and Dementia (VCID). 2) Test the hypothesis that increased expression of C3aR exacerbates the progression of VCID.

Background and Significance: For several decades, the majority of cognitive decline has been attributed to AD. This view has evolved with the understanding that Vascular Dementia (VaD) comprises up to 20% cases of dementia, while vascular causes contribute in more than 50% of cases. Therefore, the NINDS Stroke Progress Review Group in 2012 cited "the prevention of VCID (Vascular Contributions to Cognitive Impairment and Dementia)" as a major research priority.

Recanalization of major blood vessels by thrombolysis/ thrombectomy remains the only therapy for stroke. However, long-term vascular dysfunction in the small penetrating arteries and microvascular no-reflow may lead to chronic cerebral hypoperfusion (CCH), demyelination and dementia after stroke. Reduced cerebral blood flow (CBF) remains one of the earliest findings of "leukoaraiosis", an imaging correlate of the severity of VCID that results in white matter damage (WMD). Stroke survivors remain at high risk of VCID and dementia, and pass the threshold of cognitive decline earlier than in the course of normal aging.

WMD remains the pathological hallmark of VCID, often visualized in the periventricular regions and centrum semiovale. Several clinical and preclinical reports suggest that post-stroke immunomodulation and the resultant cerebrovascular dysfunction cause BBB disruption, neuroinflammation, and chronic WMD leading to cognitive decline. Complement activation plays a significant role in the progression of post-stroke WMD, AD and age-related cognitive decline. We previously reported that the expression of central complement component C3 is increased after stroke in the brain, and the post-stroke cleavage of C3 exacerbated the disruption of BBB. Exogenously administered C3a disrupted vascular integrity and increased the stroke injury; and pharmacological inhibition of its receptor was neuroprotective.

Preliminary Data and Plan: Our novel data now shows that C3aR expression is significantly increased in the "brain endothelium" after photothrombotic (PT) stroke in wild type (WT) mice as well as in ischemic human brain tissue from stroke patients. Others have shown that WT mice subjected to bilateral common carotid artery stenosis (BCAS), the most accepted and valid model of CCH, leads to cognitive decline, and later recapitulates AD-type pathology. Furthermore, our collaborator's interesting data from aged mice subjected to partially-humanized embolic clot (eMCAo) model of stroke also demonstrates that motor function in aged mice recovers substantially during long-term follow up after stroke, while their cognitive performance and outcomes decline. Our finding is in agreement with clinical reports that a substantial population of stroke survivors suffers from cognitive impairment although their motor functions may recover. Of particular interest to this proposal, mice subjected to either BCAS- or eMCAo-models of brain ischemic injuries showed significantly increased expression of C3aR during chronic follow-up, supporting our hypothesis that persistently unregulated C3aR expression may cause vascular dysfunction, neuroinflammation and exacerbate the progression of dementia after

stroke. Since ischemic stroke remains the leading cause of adult disability, there is an immediate need to address and treat post-stroke VCID, which may prevent the later development of dementia and AD-type pathology. Therefore, our central hypothesis is that the increased C3aR expression due to brain ischemia will exacerbate the progression of VCID. Our long-term goal is to understand the molecular mechanism of VCID and to facilitate translation of therapeutics to prevent the progression of dementia. We therefore propose the following SPECIFIC AIMS:

SPECIFIC AIM 1: Test the hypothesis that increased expression of C3aR exacerbates the progression of VCID. We will utilize the murine bone marrow (BM) irradiation chimera model of WT>C3aR^{-/-} to demonstrate the functional and pathophysiological role of C3aR expression in the resident-tissue vs. circulating cells. We will test our hypothesis in two different models, i.e., PT model of stroke and BCAS model of VCID. Mice subjected either injury model will be followed for at least 4-wks to test them on a battery of behavioral tests, imaging for WMD and CBF, tissue biochemistry and histopathological studies in the brain. Blood will be also collected for FACS-analysis of immune responses.

SPECIFIC AIM 2: Test the hypothesis that targeted inhibition of C3aR in the brain endothelium protects BBB integrity and prevents VCID progression. For this Aim, we will utilize the contract services at Emory University (Emory Transgenic Core) to generate C3aR^{flox/flox} mice. Prior to PT/BCAS injuries, we will utilize brain-endothelium specific adeno-associated virus 2 Cre (AAV2^{Cre}) for targeted transfection into the brain endothelium to specifically deplete brain endothelial C3aR expression. Mice will be subjected to injury and followed for behavioral, imaging, biochemical and histopathological outcomes as above in Aim 1.

Proposed One-Year and Long-Term Outcomes: This project will foster our goal to learn and bring novel expertise to the BNI such as a model of BCAS, novel genetic resources (such as brain endothelium specific AAV2) and C3aR^{flox/flox} mice. We have assembled a team of experienced researchers for long-term collaboration. The innovation lies in the proposed studies, such as differentiating the role of tissue-resident vs. circulating C3aR, use of AAV2^{Cre} which will help us to bypass the long-waiting Cre-LoxP breeding time, and finally the genetic depletion and study of brain endothelium specific C3aR in stroke and VCID for the first time. With this pilot funding, our goal is to generate sufficient preliminary data from Aim1 to apply for multiple VCID/ dementia R01 grants to the NINDS and NIA. Accomplishment of Aim 2 will help us to develop novel genetic tools to strengthen our future NIH funding applications.

Year End Progress Summary: We have successfully developed the model of BCAS in our laboratory and are currently evaluating the long-term histologic, imaging findings, and functional sequela of VCID in this model. We are also currently developing the protocol to generate the bone marrow irradiation chimera model for use in both PT model of stroke and the BCAS model of VCID. For aim 2, we have successfully obtained the C3aR flox-flox mouse and are currently breeding and genotyping these mice. We will then utilize the endothelial specific adeno-associated virus 2 Cre to specifically deplete endothelial C3aR expression in these same models. We are also working to obtain the brain endothelial specific Cre mouse which we will cross breed with our C3aR flox mouse to generate a brain endothelial specific knockout of C3aR.

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Genotypic and phenotypic signature profile of ALS dementia iPSC cortical neurons. Rita Sattler, PhD, Kendal Van Keuren-Jensen, PhD, Jennifer Levey, BS, Ileana Lorenzini, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Establish a genetic and phenotypic signature of hiPSC differentiated cortical neurons (hiPSC-CNs) from ALS patients with dementia: fALS with and without dementia; sALS with and without dementia; fFTD without ALS; healthy control
 - 1a) Perform RNA seq analysis on mature, differentiated hiPSC-CNs
 - 1b) Perform functional phenotypic characterization of hiPSC-CNs: neuronal morphology (dendrite branching and lengths); synapse density; neuronal firing and susceptibility to cell stress

Background: Amyotrophic lateral sclerosis (ALS) is known as the most common motor neuron disease defined by loss of upper motor neurons in the motor cortex and lower motor neurons in the spinal cord. Variances in genetics, pathology and clinical symptoms have contributed to the notion that ALS is no longer simply considered a motor deficit disease, but instead a heterogeneous disease with a significant contribution of degeneration in non-motor brain areas. Specifically, the discovery of several new genes in familial ALS (fALS), including C9orf72, Ubiquilin2 and TBK1, confirmed the overlapping disease phenotype with frontotemporal dementia (FTD). But even in sporadic ALS (sALS), it is assumed that 30-50% of ALS patients show cognitive and behavioral symptoms in addition to motor deficits, which could ultimately lead to the necessity of combination therapies for ALS patients, affected by symptoms of muscle weakness and cognitive impairments. Cognitive dysfunction observed during normal ageing is known to parallel selective loss of synapses and changes in spine density and morphology. The degree of synapse loss in Alzheimer's disease (AD) strongly correlates with cognitive decline, even more than the amount of plaque, tangles or neuronal loss, and a recent study of ALS postmortem tissue confirmed increased synapse loss in the prefrontal cortex of patients with reported cognitive impairments compared to ALS patients without cognitive deficits. In addition, studies in UBQLN2 mice showed impaired synaptic and intrinsic excitability in CA1 pyramidal cells before neurodegeneration occurs. Our preliminary data using patient-derived induced pluripotent stem cells (iPSC) differentiated into cortical neurons from fALS/FTD patients carrying the C9orf72 mutation confirm similar impaired excitability, in addition to decreased synapse numbers, dendritic arborization and dendrite length. We hypothesize that similar cellular phenotypes are present in patient-derived cortical neurons from sporadic ALS subjects with dementia.

Significance: The cognitive health of patients influences their participation in therapeutic interventions, the acceptance of patient-centered care, the making of end-of-life decisions, and concomitant with all of the before mentioned, increases the caregiver burden, especially if it precedes motor neuron dysfunction. It is therefore critically important to understand the mechanisms leading to cognitive impairments in ALS, to be able to uncover novel therapeutic targets for therapeutic development that address these disease symptoms. Few studies have addressed the mechanisms of cognitive impairments in ALS patients with dementia, especially in sporadic ALS. We are in a unique position to investigate some of these unknowns given our expertise in iPSC differentiations and phenotypic cellular analyses. We have initiated a close collaboration with Dr. Kendall Van Keuren-Jensen at the Translational Genomics Research

Institute (TGen) in Phoenix, AZ who will oversee the RNA-seq analyses of our cultured neurons, in addition to the bioinformatics analyses. We will take advantage of existing patient iPSC lines generated through efforts of the Answer ALS initiative, and we will be able to compare the findings in cortical neurons to those obtained from motor neurons differentiated from the same patient-derived iPSCs.

Progress to date:

We initiated our studies using existing hiPSC lines from familial FTD patients carrying the C9orf72 mutation (see below). In addition, we just purchased sporadic ALS iPSC patient lines with and without clinically documented dementia, as well as familial C9orf72 ALS/FTD patient lines. All of these new lines are currently being propagated and are in the process of being differentiated into cortical neurons.

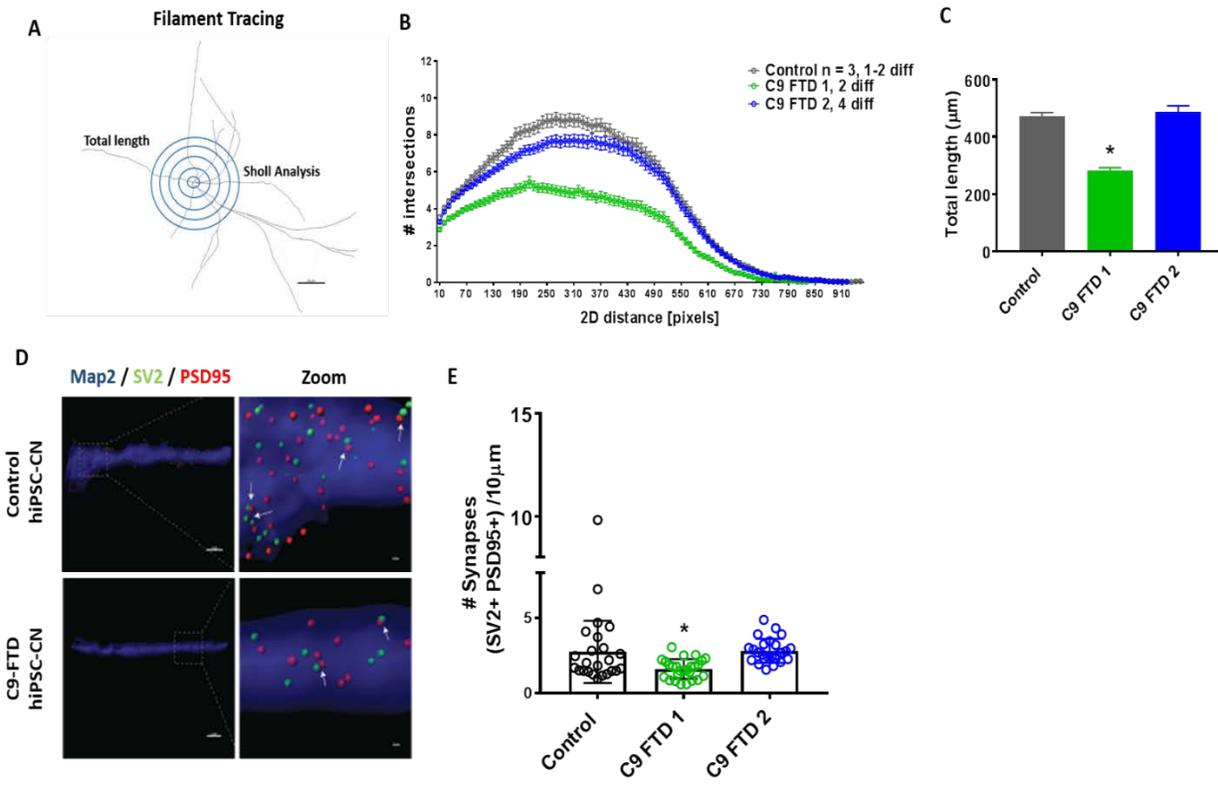


Figure 1. Changes in morphology in C9 FTD hiPSC-CNs. (A) Representation of a neuronal filament tracing used for Sholl Analysis. (B) The average number of dendrite intersections in hiPSC-CNs was reduced in C9-FTD (N=2) when compared to control (N=3); $p < 0.0001$ (Two way ANOVA followed by Tukey’s multiple comparison). (C) A decrease in total length was observed in one of the C9-FTD patient lines ($p < 0.001$), which is also the one showing a stronger branching deficit. (D) 3D reconstruction of Map2+ dendrites, SV2 pre-synaptic marker and PSD95 post-synaptic marker. (E) SV2+/PSD95+ synapses are compromised in C9-FTD cortical neurons ($p < 0.002$ for C9-FTD 1).

1. C9-mediated decreased dendritic branching and dendrite length, and decreased synapse number in vitro. Preliminary data from our laboratory using 2 C9orf72 FTD patient iPSCs differentiated into cortical neurons (hiPSC-CNs) suggest that even as a monoculture, cortical neurons from C9-FTD patients show decreased dendritic arborization as measured by Sholl analysis and decreased dendrite length (Figure 1 A-C, $n < 30$ neurons, $p < 0.0001$), which we hypothesize will be exacerbated in the presence of microglial cells. In addition, we observed a decrease in synapse numbers, as defined by co-localization of pre- and postsynaptic marker proteins (SV2⁺/PSD-95⁺) (Figure 1 D-E, $p < 0.002$). Interestingly, the patient line with the most

severe dendritic branching deficits (C9-FTD1) also shows a more severe decrease in dendrite length as well as synapse numbers, suggesting that there is a linear correlation between these phenotypic readouts, albeit the variability between patient lines.

2. Decreased neuronal firing in C9-FTD hiPSC-CNs.

If reduced numbers of synapses reflect a reduction in synaptic strength, we would predict altered synaptically driven neuronal activity in these C9-FTD cortical neurons. To test this hypothesis, we measured

spontaneous electrical activities of hiPSC-CNs using a microelectrode array (MEA) system. The mean firing rate of spontaneous action potentials, resembling *in vivo* field recordings, of hiPSC-CNs was analyzed for 3 healthy controls and 2 C9-FTD patient lines. HiPSC-CNs were plated in MEA tissue culture plates. Electrical activities were measured three times a week from each individual well throughout neuronal differentiation and maturation. Using two patient lines, the mean firing rates of C9-FTD CNs are significantly reduced at 60-70 DIV ($p=0.0148$; Figure 2), suggesting that the repeat expansion reduces neuronal activity in C9-FTD hiPSC-CNs.

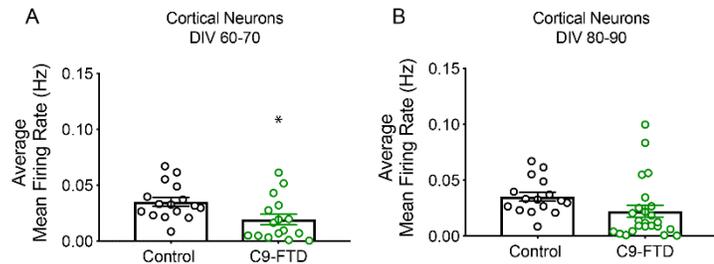


Figure 2. Decreased mean firing rate in mature C9 FTD hiPSC cortical neurons. MEA analysis was performed throughout neuronal differentiations. Two time points were chosen to represent the altered neuronal firing, div 60-70 (A) and div 80-90 (B). N (number of patient lines) = 2-3; n (number of differentiations per line)= 1-3. * $p=0.0076$

Proposed One-Year and Long-Term Outcomes:

We have just purchased sporadic ALS patient hiPSC lines, which will be analyzed similarly to the data shown above. We have also started isolating RNA from individual lines. We will continue with RNA isolation on the newly differentiated lines, and will then perform the proposed RNA seq analyses. The data will be compared to existing RNA seq data bases on human postmortem frontal cortex ALS patient autopsy tissue. The goal is to identify overlapping altered pathways and genes, which can then be manipulated in the iPSC neuronal cultures for future mechanistic studies using CRISPR/Cas9 for gene knockdown or lentiviral gene overexpression vectors.

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Multimodal Biomarkers of Alzheimer's Disease: Combining advanced MRI biomarkers with clinical, genetic, and structural imaging biomarkers. Ashley M. Stokes, PhD, Leslie C. Baxter, PhD, Richard Caselli, MD, Anna Burke, MD, Yi Su, PhD, Matt Huentelman, PhD, Marwan Sabbagh, MD. Barrow Neurological Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims: 1) Extend the neuroimaging biomarker battery to include genetic and clinical characterizations. It is well recognized that multiple factors contribute to the etiology of Alzheimer's disease, highlighting the importance of a multimodal biomarker approach. We previously developed a multi-parametric MRI battery, which incorporated advanced MRI methods sensitive to vascular, cellular, metabolic, and molecular characteristics with standard structural MRI. We hypothesize that extending our set of biomarkers to include clinical and genetic biomarkers will improve our accuracy for differentiating between AD stages.

2) Develop advanced analysis methods for combining multimodal biomarkers that differentiate between each stage of AD, from preclinical to MCI to clinically diagnosed AD. Each of the selected biomarkers has individually shown promise for interrogating a unique aspect of the AD pathological cascade. We hypothesize that developing advanced analysis methods to combine these biomarkers will improve our specificity and sensitivity to each stage of AD.

Background and Significance: The proposed set of biomarkers provide unique and complementary information that reflects the underlying AD pathology, where each metric was chosen for its sensitivity to a known abnormality related to AD. The addition of genetic and clinical information provides a more comprehensive characterization of AD pathology. In addition, there is a lack of consensus on how to combine and interpret data generated by multimodal approaches. The development of biomarker combination strategies, specific for AD pathology, represents a highly innovative aspect of this proposal. The proposed research aims to develop a clinically-relevant set of biomarkers that can be combined to identify patients likely to benefit from early AD prevention trials. The optimal biomarker combination will also shed new insights into the underlying molecular and functional changes that occur in the earliest phases of AD. To date, most of the work using these advanced biomarkers has primarily focused on method development or proof of concept studies, whereas the studies proposed herein represent the first prospective studies aiming to combine and leverage these functional biomarkers as they correlate to the clinical AD trajectory. Combining these unique biomarkers will allow us to improve our diagnostic accuracy. Thus, the proposed studies represent a significant advancement in AD neuroimaging techniques, providing a more comprehensive, non-invasive strategy with which to characterize neurobiological abnormalities.

Preliminary Data and Plan: Leveraging our previous AARC awards, we have acquired cross-sectional multi-parametric MRI data in 35 subjects (12 normal controls, 11 MCI, and 12 AD) with longitudinal follow-up in 80% of these subjects thus far. These subjects were

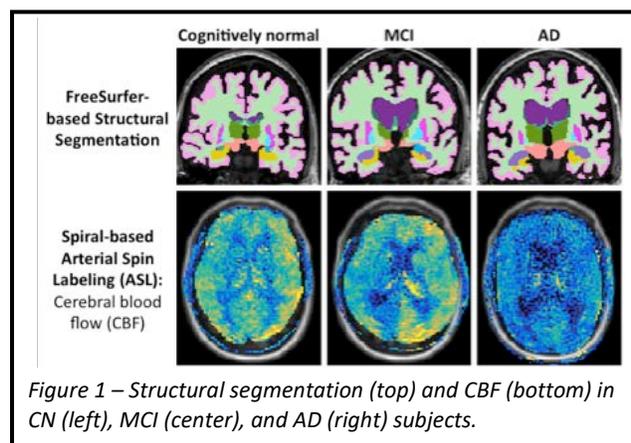
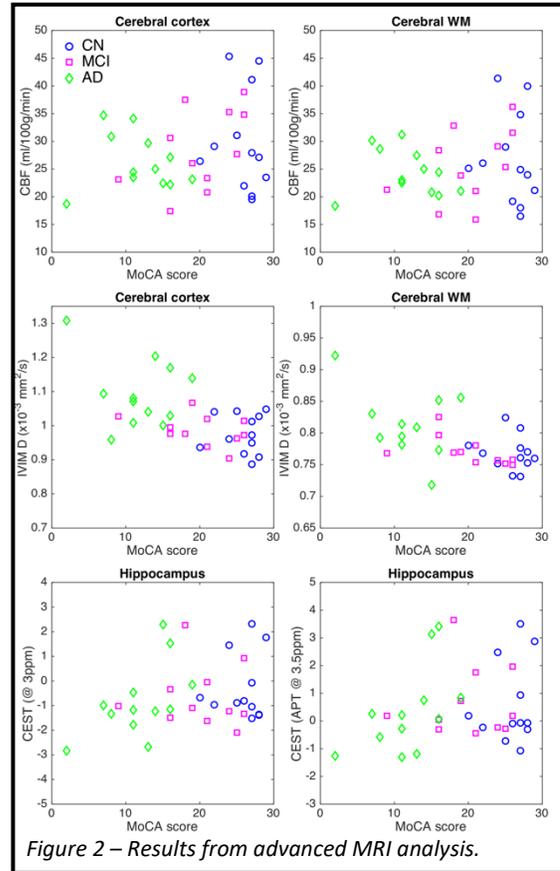


Figure 1 – Structural segmentation (top) and CBF (bottom) in CN (left), MCI (center), and AD (right) subjects.

recruited through a consortium-mediated collaboration between the BNI and Mayo Clinic (Richard Caselli). Figure 1 demonstrates an example set of images from cognitively normal (left), MCI (center), and AD (right) subjects. The top row demonstrates structural segmentation to extract volumetric parameters, while the bottom row shows maps of cerebral blood flow (CBF), where the MCI subject demonstrates regional perfusion deficits and the AD subject exhibits global hypoperfusion. From our initial cross-sectional cohort, regional analyses (Figure 2) showed lower perfusion for the AD subjects in both cerebral cortex and cerebral WM, though these results were not significant. The perfusion-insensitive (IVIM-D) diffusion coefficient showed significant differences in the cerebral cortex, with increased diffusion in the AD subjects ($p = 0.002$ for CN vs. AD and $p = 0.004$ for MCI vs. AD). These results may indicate altered microstructural characteristics. GluCEST was reduced in the AD subjects; additionally, APT-CEST showed lower CEST signal in the AD subjects, suggesting altered protein content in these patients. Longitudinal analysis is underway to quantify changes in our advanced functional biomarkers for blood flow, microstructure, and molecular species. The inclusion of more advanced metrics provides an advantage over the ADNI study and lays the foundation for the addition of more advanced biomarkers in future iterations of the ADNI protocol.



Each of these methods has individually shown promise for interrogating a unique aspect of AD pathology. Multi-parametric imaging has several advantages, including co-localization and integration of multiple complementary features to optimize diagnostic accuracy. Several methods to combine multi-parametric parameters have been previously proposed, including machine learning methods (4–6), but none have been widely accepted or validated, and none have been applied to the specific biomarkers proposed herein. This study serves to fill that gap in knowledge.

Proposed One-Year and Long-Term Outcomes:

The prior years of funding have laid the foundation for this study by establishing the baseline and biological trajectory of this advanced multi-parametric imaging battery. We plan to apply for funding through NIA/NIH. This pilot funding will allow us to continue data acquisition for the longitudinal study, expand our biomarker battery (genetic and clinical), and initialize our development of advanced biomarker combination strategies. Future funding applications will further expand our biomarker battery to include PET imaging for detection of tau (AV-1451), amyloid (PIB), or hypometabolism (FDG), which could provide additional insight into the correlations between advanced MRI and these abnormal protein deposits that are indicative of AD-underlying causes of dementia.

Year End Progress Summary (through February 1, 2019):

Aims 1 and 2: We have acquired cross-sectional MRI data in 42 subjects and longitudinal MRI data in 21 subjects thus far (with the remaining already scheduled, anticipated for scheduling, or

replaced), along with cognitive testing using our expanded battery (MoCA, FAST, HVL, trail-making, digit symbol, and digit span forward/backward). We have collected a corresponding 15 dried blood samples for genetic biomarker analysis. The MRI data includes high-resolution structural images, CEST, ASL, DWI, and SWI. Both cross-sectional and longitudinal data analysis are ongoing. For the diffusion and perfusion fraction parameters from DWI, we performed voxel-based analysis using a two-way ANCOVA model with the family-wise error (FWE) rate controlled at 0.05 for multiple comparisons. Post-hoc comparisons with Bonferroni correction revealed significant differences in both diffusion and perfusion fraction between the AD and CN groups and the AD and MCI groups, while no significant differences were found between the MCI and CN groups for either parameter. Moreover, we observed a significant correlation between diffusion and MoCA score in the anterior cingulate. We are in the process of performing statistical analysis of our cross-sectional data, in preparation for publication. In addition, we are continuing to acquire data in the remaining subjects over the next few months and are continuing to enroll new subjects for cross-sectional analysis.

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Mechanisms of amyloid- β -induced excitotoxicity. Ronald J. Lukas, PhD, Andrew A. George, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aim: In the project period, we will complete determinations at the single channel level whether soluble, oligomeric amyloid- β (oA β) acts as does the natural neurotransmitter, acetylcholine (ACh), to activate function of a novel nicotinic acetylcholine receptor (nAChR) subtype containing $\alpha 7$ and $\beta 2$ subunits ($\alpha 7\beta 2$ -nAChR) uniquely expressed naturally on basal forebrain cholinergic neurons (BFCN) that perish early in Alzheimers disease (AD).

Background and Significance: AD is a catastrophic, dementing, neurodegenerative disorder projected to afflict over 16 million US citizens by 2050. Pathological processes that lead to AD remain unknown, and clinical trials based on the fibrillar amyloid- β (fA β) hypothesis have failed. However, the cholinergic hypothesis of AD, based on early loss in disease of BFCN and their input to memory centers, and the amyloid hypothesis of AD, based on the early elevation of oA β in ultimate AD patients, remain viable.

In published studies, we have found that unusual $\alpha 7\beta 2$ -nAChR are present uniquely on mouse BFCN and on human BFCN that die in AD. $\alpha 7\beta 2$ -nAChR are different than the typical, homomeric, $\alpha 7$ -only-nAChR subtype and the nAChR subtypes that contain $\beta 2$ subunits along with non- $\alpha 7$ α subunits found elsewhere in the brain. In prior work, we also have found that exposure to fA β or oA β induces hyperexcitation and death of mouse hippocampal neurons via effects on some form of nAChR containing $\alpha 7$ subunits ($\alpha 7^*$ -nAChR, where the "*" indicates the known or possible presence of other subunits along with $\alpha 7$ and is meant to include homomeric $\alpha 7$ - and heteromeric $\alpha 7\beta 2$ -nAChR). Human hippocampal neuronal death is a hallmark of AD and more generally of memory loss.

More recently, we have found that oA β exposure in organotypic cultures of different regions of the mouse basal forebrain induces, within days, hyperexcitation of identified cholinergic neurons that culminates in BFCN death. Thus, we have evidence linking oA β exposure to BFCN death, which would be a proximal cause for loss of cholinergic signaling critical to memory and for cognitive decline in AD. This finding also merges amyloid and cholinergic hypotheses of AD. Moreover, these effects are attenuated when mouse BNFC $\alpha 7\beta 2$ -nAChR are blocked pharmacologically or if BFCN organotypic cultures are prepared from mice in which the nAChR $\beta 2$ subunit has been genetically deleted. Furthermore, we have initial, intriguing and surprising findings that human $\alpha 7^*$ -nAChR subtypes, such as those found on BFCN neurons, have direct interactions with oA β . That is, exposure to oA β activates single channel activity of heterologously-expressed, human $\alpha 7\beta 2$ -nAChR, just as does exposure to ACh itself.

Importantly, this suggests the **overarching hypothesis** that these direct interactions involve A β -mediated increases in responding of nAChR that leads to toxic, electrical hyperactivity of nerve cells and then to cell death. These findings illuminate new strategies for blocking these effects of A β , thus protecting cells from damaging excitotoxicity, and perhaps preserving memory circuitry and abilities.

Specific Aim and Project Description: The project's aim is to confirm and extend our preliminary findings that both oA β and ACh activate opening of $\alpha 7\beta 2$ -nAChR single channels by using electrophysiological recording and pharmacological approaches. Single channel recording of heterologously-expressed, human $\alpha 7\beta 2$ -nAChR in SH-EP1 human epithelial cells will be done to confirm that channel conductances and open dwell times are indistinguishable for responses

to the two ligands. Additional studies will characterize sensitivity of channel opening to blockade by the non-competitive antagonist, mecamylamine, and by the competitive antagonist, methyllycaconitine, and to augmentation by the positive allosteric modulator, PNU 120596.

Proposed One-Year and Long-Term Outcomes: Within the year of project support, we proposed finishing the planned studies and submitting the results for publication. We would publish single channel studies along with our observations concerning $\alpha\beta$ -induced excitotoxicity in mouse BFCN. Looking to the intermediate term, this contribution would be used to underscore significance of applications for large-scale, external funding of extensions of this work. If results show that methyllycaconitine in particular blocks effects of both $\alpha\beta$ and ACh, then they would point to interaction of β at nAChR agonist binding sites. If the competitive antagonist studies are negative, they would suggest that β causes nAChR channel opening via a novel process. In the long term, success in these studies would point to potential therapies involving timely application of $\alpha\beta$ -nAChR modulators. Extended studies, for example, would be done to determine whether presumed, maladaptive, abnormal activation of $\alpha\beta$ -nAChR by elevated $\alpha\beta$ levels as seen early in AD could be blocked by entities that would not prevent normal functional activation of ACh by that much-smaller ligand. Questions then would turn to whether such ligands could slow or even stop neuronal degeneration and cognitive decline. Perhaps ligands suitable for brain imaging could be used to assess early losses of BFCN, when disease modification strategies would be implemented.

Year End Progress Report: We are pleased to indicate that we have achieved all of our goals in this pilot project. We have shown that heterologously-expressed, human $\alpha\beta$ -nAChR single channel events and bursts of events are elevated by acute exposure to either ACh or $\alpha\beta$. Responses to either ligand are virtually entirely blocked by exposure to either mecamylamine or methyllycaconitine. That blockade in turn is reversed upon exposure to PNU 120596. All of these findings strongly indicate that $\alpha\beta$ has direct, functional effects at $\alpha\beta$ -nAChR. As of February, 2019, we are preparing a manuscript to report these findings along with our data showing $\alpha\beta$ -induced, $\alpha\beta$ -nAChR-mediated excitotoxicity of mouse BFCN. We expect that this work will be accepted for publication by June, 2019. Meanwhile, we also will continue to do experiments funded by the AARC award doing single channel recording from BFCN in slice cultures. This work is challenging, but success in those efforts will support applications for more extensive, external funding, and it will close the loop between our studies of mouse and human $\alpha\beta$ -nAChR: $\alpha\beta$ interactions while also validating the mouse BFCN model as one for studies of effects on cell health and survival as in AD.

Importantly, α -nAChR roles in excitotoxic cell death have precedent (Orr-Utreger et al. 2000, J Neurochem 74:2154; Lukas et al., 2001, Eur J Neurosci 13:1849). For another example, motor neuron numbers in adult vertebrates are about double those earlier in development. Cholinergic collaterals terminating on near-by motor neurons competing for the same motor pools are more active for motor neurons successfully stimulating muscle cells and receiving retrograde trophic signals. Losers in that competition for targets lack such trophic support and undergo excitotoxicity as winners become more active. Application of α -nAChR antagonists in the spinal cord prevents such “programmed” motoneuronal death by blocking collateral-mediated activation of motor neuronal excitotoxicity (Hory-Lee and Frank, 1995, J Neurosci. 15:6453). A similar strategy might be therapeutic in AD.

We hypothesize that BFCN and HC neuronal hyperexcitation serves to “erase engrams” at the cellular level, contributing to demise in memory, and then leading to cell death. The project has clear, medical significance, because it addresses molecular and cellular mechanisms that lead to neuronal demise and viably and explains the emergence of AD symptomology. Timely application of $\alpha\beta$ -nAChR antagonists might be a viable treatment to preserve cholinergic and cholinceptive neurons in early AD patients. The project also has scientific significance, in its

novel observations concerning sites and mechanisms of A β action in modifying important signaling via nAChR.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Hispanic Enrollment in Alzheimer's Research Trials (the HEART Program at BNI). Meredith Wicklund, MD, Anna D. Burke, MD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

This funding supports repurposing Dr. Leslie Baxter's funding for the *Insula Dysfunction in Frontotemporal Dementia and Autism* Project, which will be eliminated due to her departure from Barrow Neurological Institute (BNI) to establish the Hispanic Enrollment in Alzheimer's Research Trials, to be known as the HEART Program at BNI. HEART is designed to increase recruitment and retention of Hispanic subjects in the Arizona Alzheimer's Disease Core Center and other research protocols by removing unique cultural barriers and increasing awareness and access to meet the defined program goals.

Project Description:

The Alzheimer's Disease and Cognitive Disorders Program at Barrow Neurological Institute (BNI) has been an active contributor to the Arizona Alzheimer's Disease Core Center study for a number of years. Historically, the program was led by Leslie Baxter, PhD who recently departed BNI. Her departure has enabled us time to reflect on how we will be best positioned in the future to contribute to the AADC. We propose reallocation of Dr. Leslie Baxter's project funds to establish a novel new initiative, the HEART Program within the Alzheimer's Disease and Cognitive Disorders Division of Barrow Neurological Institute under the direction of Meredith Wicklund, MD and Anna Burke, MD.

BNI has recognized more than 200% growth in our outpatient clinic volume from 2016 to 2018 for which Hispanics contribute to more than 38% of our total patient population. Given the culturally dense volume seeking care at BNI, we believe now is an ideal time to leverage our unique Hispanic patient population and dedicate a program aimed at increasing Alzheimer Research Trial opportunities within Arizona.

The HEART Program will include an outreach objective and an ADCC clinical core and/or research project recruitment and retention plan. The 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. We will plan 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.

Specific Aims:

1. Implementation of the HEART Program to include a formal development plan outlining internal and external outreach strategies to increase recruitment and establishment of organizational

infrastructure, resources, and written translational materials to promote trial retention while recognizing unmet needs of a large Hispanic speaking community seeking care within Maricopa County.

2. To forge a close working relationship with members of our Hispanic American 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.

Progress Summary:

The creation of the HEART program focuses on establishing the necessary infrastructure to efficiently recruit, evaluate, and retain Hispanic participants into the clinical core. During the FY19 funding period, we have:

1. Hired a clinical research coordinator who is fluent in Spanish. By the end of FY19, she will be trained and certified in administering psychometric testing in Spanish.
2. Hired a research assistant who has been designated to the ADCC and HEART program. She will be involved in ongoing outreach and communications with study participants and potential participants to improve the rates recruitment and retention.
3. Created Spanish language tools, informational materials, and caregiver supports to support patients and care partners struggling with Alzheimer's disease and related dementias.
4. Our staff has attended and presented at 3 minority focused seminars and will be attending three additional memory screenings and community events in order to provide information regarding the ADCC trial.
5. Identified 5 potential Hispanic participants for the ADCC who will undergo the screening process for the trial.

These and other activities will position us to significantly increase the number of Hispanic participants in the NIA-sponsored AD Center Clinical Core (ADCC) and other relevant research studies during the next funding period—an effort that will be made in collaboration with David Coon and his colleagues in the ADCC Outreach and Education Core, and with Richard Caselli and his colleagues in the ADCC Clinical Core, such that we and the other clinical core sites have at least 100 actively enrolled Hispanic participants in the ADCC Clinical Core by July 2020.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Advanced MR Imaging and Genetic Biomarkers of Arizona Native Americans. Ashley M. Stokes, PhD, Leslie C. Baxter, PhD, Anna Burke, MD. Barrow Neurological Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims: Aim 1: Establish a dataset of advanced MR imaging biomarker data on aging individuals from programs that have strong ties to urban Native Americans, including Banner Alzheimer's Institute. While structural MRI is known to change with later disease progression, advanced MR imaging of microvascular blood volume (using intravoxel incoherent diffusion), blood flow (using arterial spin labeling (ASL)), molecular species (using chemical exchange saturation transfer (CEST)), and iron deposition (using susceptibility-weighted imaging (SWI)) may provide specific signatures of disease progression. We hypothesize that the corresponding vascular or molecular changes could be an early indicator of brain changes associated with dementia, MCI or AD, prior to morphological changes.

Background and Significance: The proposed set of biomarkers provide unique and complementary information that reflects the underlying AD pathology, where each metric was chosen for its sensitivity to a known abnormality related to AD. We previously characterized these biomarkers in a non-targeted population of aging adults with and without cognitive impairment. In that cohort (**Figure 1**), we observed high correlation between IVIM-DWI metrics, which are sensitive to both perfusion and diffusion, and clinical cognitive metrics (namely, the Montreal Cognitive Assessment (MoCA)). Group differences were observed regionally using a voxel-based analysis approach, with significant correlations in the frontal lobe, left and right cerebral white matter, and right cerebral cortex. In addition, further investigation into MoCA sub-domains revealed voxel-wise IVIM correlations between caudate and both attention and concentration and memory and concentration and memory sub-domains. We sought to characterize these and other imaging metrics in a population of Arizona Native Americans. The proposed research is significant because it a) targets an under-studied ethnic group in Arizona for whom higher rates of diabetes and hypertension place them at higher risk for cerebrovascular changes that negatively affect brain health. Given the inclusion of vascular-related parameters, this approach may provide novel insight into neurological changes that differential impact their risk of developing dementia. The proposed studies aim to examine the relationship between multi-parametric, advanced imaging signatures of cerebrovascular and brain changes, genetics, and general health in Arizona Native Americans. Each MRI metric has been used, individually or in

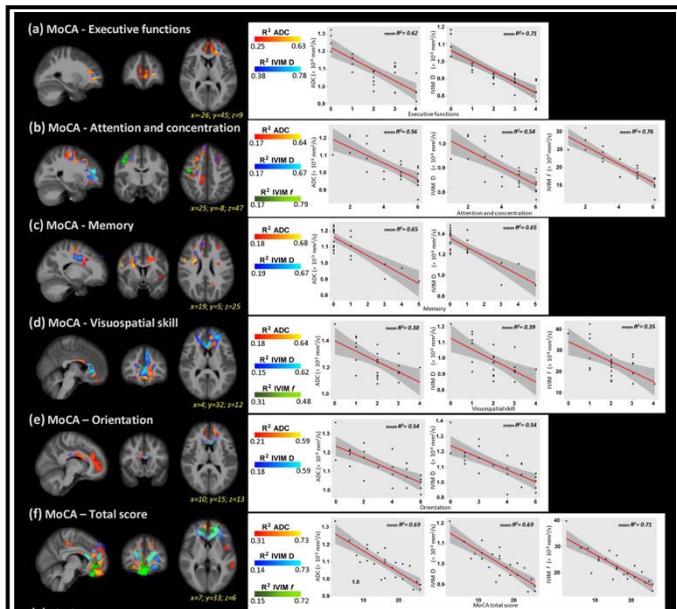


Figure 1 – Voxel-based correlations between cognitive assessment tests and VBM/ADC/IVIM images. The plots, with the relative mean of R^2 , represent the correlations of the average values inside the significant clusters.

pre-clinical proof of concept studies, to characterize advanced AD status, but, to our knowledge, no study has combined these complementary metrics nor have they been used to study subtle changes that may impact health in Native Americans. This project represents the first prospective study aiming to combine and leverage these functional biomarkers as they correlate to risk factors that can affect cerebrovascular health. Combining these unique biomarkers, along with genetic biomarkers, will allow us to improve our knowledge of these health risk factors affect brain health. The proposed study will provide invaluable data on an under-studied group that are important and unique to Arizona.

Preliminary Data and Plan: These preliminary data are presented with the permission of Dr. Ashley Stokes, who has obtained them from her current AARC award (7/1/2016-6/31/2017), from which she has acquired multiparametric data in 35 subjects (12 normal controls, 11 MCI, and 12 AD).

These subjects were recruited through a consortium-mediated collaboration between the BNI and Mayo Clinic (Richard Caselli). Figure 1 demonstrates an example set of images from cognitively normal (left), MCI (center), and AD (right) subjects. The top row shows structural segmentation using FreeSurfer, which permits extraction of parameters relating to regional volumes and cortical thickness. The middle row shows maps of cerebral blood flow (CBF) using ASL, where the MCI subject demonstrates regional perfusion deficits and the AD subject exhibits global hypoperfusion. The bottom row shows minimum intensity projections from SWI, which can be used to highlight and quantify cerebral microbleeds.

Subjects will be recruited from area practices with aging populations and via community flyers and from community events. Data acquisition will match the baseline study and will be performed at the Keller Center for Imaging Innovation using a dedicated research 3T Philips MRI. Structural MRI will be performed using well-established data collection methods, and morphometric features will be quantified using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>). CBF, SWI, and CEST data will be measured using the imaging methods described above. We will use our collaboration with programs that have strong community ties to recruit urban Native Americans. We will also obtain DNA samples for genetic assays (including APOE and genome-wide SNP array genotyping) (co-Investigator Matt Huentelman, TGen). Advanced analysis methods for combining biomarkers will be developed with the collaboration of Yi Su (Co-Investigator, Banner Alzheimer's Institute).

Proposed One-Year and Long-Term Outcomes:

Although this study focuses on single time point imaging, the publication of this study will lay the foundation for a longitudinal study that establishes the imaging and genetic phenotypes of Native Americans from Arizona. The data obtained through this award can be used as pilot data for larger grant applications through the National Institute on Aging (NIH/NIA) for members of the Arizona Consortium.

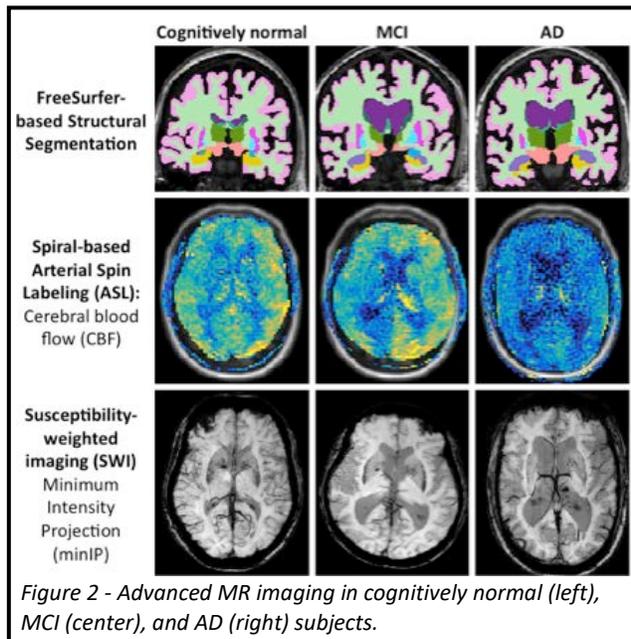


Figure 2 - Advanced MR imaging in cognitively normal (left), MCI (center), and AD (right) subjects.

Year End Progress Summary (through April 1, 2019):

Aim 1: We have been working with MedStar and other area facilities with strong ties to the Native American community. We have attended several outreach activities and have been actively recruiting for this study. We reduced our initial recruitment goal from 100 subjects to 50 subjects, as well as added a pilot sub-study to investigate vascular biomarkers using a novel MRI perfusion imaging method. We are hoping to acquire the remaining data over the next three months.

Project Progress Report
Critical Path Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Facilitating User Accessibility to Regulatory-Endorsed Drug Development Tools for Alzheimer Disease. Daniela J Conrado, PhD, Jackson Burton, PhD, Volker D Kern, PhD, Klaus Romero, MD, Stephen P Arnerić, PhD. Critical Path for Alzheimer's Disease (CPAD); Critical Path Institute; Arizona Alzheimer's Consortium.

Specific Aims: The long-term goal of this effort is to help optimize the design of clinical trials investigating drugs to treat the different stages of the AD continuum. The central hypothesis is that open-access and regulatory-endorsed quantitative tools based on a large database of clinical studies in the AD continuum can inform several aspects of clinical trial design including (a) type of design (e.g., parallel, cross-over, delayed-start, adaptive), (b) selection of trial participants, (c) determination of trial size, (d) determination of trial duration, and (e) selection of endpoints and/or biomarkers. The Critical Path for Alzheimer's Disease (CPAD) consortium previously developed a clinical trial simulation (CTS) tool for trials in mild-to-moderate AD, using the longitudinal AD Assessment Scale-Cognitive sub-scale (ADAS-Cog). The tool was endorsed by the FDA (fit-for-purpose) and EMA (qualification opinion) in 2013 (1), and updated with additional data. This effort was supported by a previous AAC grant (2017/2018). CPAD has recently completed the development of a model to describe the longitudinal progression of the mild cognitive impairment (MCI) stage of the AD continuum. This model has received a letter of support from EMA ([LINK](#)) and is under FDA review. CPAD is planning the continuation of its long-term goal of optimizing clinical trial design by focusing on user accessibility and adoption of these tools by means of three specific aims:

Aim 1. To develop a user-friendly clinical trial enrichment (CTE) tool to optimize the design of clinical trials to evaluate therapeutic candidates intended to treat MCI.

Aim 2. To develop real-time solutions for the efficient application of the clinical trial simulation features of the CTE and CTS tools that are accessible to members of drug development teams and regulators.

Aim 3. To develop a comprehensive, continued training mechanism for AD researchers on the use and application of the CTS and CTE tools, including computational efficiency solutions.

Background and Significance: AD is the main cause of dementia and one of the great public health challenges (2). There is an urgency to develop drugs that slow, halt or reverse the pathophysiological process leading to AD. Such drugs are known as disease-modifying therapies (DMT) and would be most helpful if targeted at earlier disease stages before the clinical symptoms are readily apparent. Memantine was the last drug to be approved in 2003, characterizing an AD drug development failure rate of 99.6% within 2002 and 2012 (3). Of these unsuccessful trials, 70% of compounds were intended as DMT, 14% were symptomatic cognitive enhancers, and 13% were to treat neuropsychiatric and behavioral symptoms (4). Multiple challenges and issues have been suggested to explain the failures of AD clinical trials (5–7) which include (a) lack of predictability of animal models, (b) poor characterization of the maximum tolerated dose, (c) failure to meet one or more of the “three pillars” (i.e., brain penetration of drug, target engagement, pharmacological activity), (d) inaccurate disease diagnostic, (e) suboptimal selection or trial participants, (f) inadequate dose selection, (g) inadequate trial size and/or duration, and (h) inappropriate selection of endpoints and/or biomarkers.

Pharmacostatistical modeling and simulation can help with several of the trial design-related issues leading to failure of clinical trials (8) thereby increasing the likelihood of a clinical trial to demonstrate efficacy of an efficacious drug. The quality and impact of such models depend on the quality and size of the data used for development. Recognizing the importance of gaining insights from past AD trials and applying the learnings to future drug development programs, CPAD integrated patient-level placebo data from placebo-arm AD clinical trials, data from the AD Neuroimaging Initiative (ADNI) observational, and summary level information from trials in AD to develop the CPAD CTS. Besides the natural disease component, this tool carries clinical trial (e.g., placebo effect and dropout) and drug effect components. To the best of our knowledge, this is the most comprehensive CTS tool for AD, and the only one endorsed by the FDA and EMA in this disease area. Briefly, the tool can simulate different scenarios, such as parallel versus delayed start design, different study duration, sample size, drug effect size, statistical power, and enrichment strategies (e.g., biomarker-driven). In the previous grant, the CPAD CTS statistical framework was updated to account for additional datasets acquired in the CPAD database. The new tool utilizes patient-level data exclusively and accounts for the additive allele effect of APOE- $\epsilon 4$ and concomitant medication use on progression rate. A user-friendly interface was developed for this updated tool that provides users with functionality to optimize clinical trial design. Motivated by our long-term goal, CPAD recently completed the development of a quantitative model that describes the progression of the MCI stage of the AD continuum. The model describes the time course of the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), including several predictors of disease progression rate. Such a model, when transformed into a CTE tool, will help inform several aspects of trial design such as selection of trial participants, enrichment and stratification approaches. This model has received a letter of support from EMA ([LINK](#)) and is under FDA review.

A considerable bottleneck for adoption of these tools by clinical trialists are the computationally intense requirements to carry out clinical trial simulations. For example, large numbers of trials must be simulated to perform power calculations, often requiring several hours to several days on a desktop computer. Reducing this time is critical to align with the real-time processes and decisions that go into trial design. Cloud computing technology has potential to address this need by allowing users to remote login to high performance computing platforms for trial simulation. Several companies have the infrastructure in place to provide such a service, but significant effort is required to interface such a tool with a cloud environment.

Preliminary Data and Plan: AD mild-to-moderate CTS tool: The update to the CTS tool was carried out using patient-level data exclusively from 15 clinical studies in mild-to-moderate AD within the CPAD database and individuals diagnosed as mild-to-moderate in the ADNI-1 database yielding a total of 4,726 subjects. Based on prior knowledge and/or clinical interest, pre-specified covariates were baseline age, sex, apolipoprotein-E-encoding gene (APOE) genotype, and concomitant medication use. The Richards model, a generalized logistic model, was used to describe the nonlinear time course of ADAS-Cog scores. A graphical user interface (GUI) was developed using *Shiny*, a package from RStudio that allows to build interactive web pages with the open-source statistical programming platform *R*. *RStudio* is a free and open-source integrated development environment (IDE) for *R*. The GUI provides users with a simple interface to customize patient and trial design characteristics, and then allows simulation of clinical trials under those conditions. Users can calculate statistical power through those simulations based on the patient and trial characteristics chosen. Details of the work including parameter estimates and additional details on the GUI were summarized in a poster presented at the 2018 AAC Annual Scientific Conference and the completed results are being prepared in a manuscript (9).

Disease progression model for MCI: Data was utilized from three sources – the ADNI-1 and ADNI-2 observational studies, and the Investigation Into Delay to Diagnosis of Alzheimer's

Disease With Exelon (InDDEx) trial control arm – yielding a total of 1,051 amnesic MCI subjects with 7,860 CDR-SB timepoints in the screening-to-48 months interval. The model was built using ADNI data (N=702), with InDDEx being reserved for external validation. The time course of CDR-SB was described by a non-linear mixed-effects model. Based on prior knowledge and/or clinical interest, pre-specified covariates were: baseline intracranial volume-adjusted hippocampal volume (ICV-HV), sex, baseline mini-mental-state-examination (MMSE), baseline age, and APOE genotype. Of the evaluated models, the one following a Richards curve was most appropriate to describe the nonlinear time course of CDR-SB scores. This model has received a letter of support from EMA ([LINK](#)) and is under FDA review.

Methods: The patient-level data from ADNI and the additional studies in the CPAD database are to be remapped to current AD CDISC standards and quality checks performed. Once completed, the curated data are to be analyzed to determine if the relevant model variables, are well represented in the data, i.e., sufficient numbers of studies measured these variables. A final file of the key variables, including the relevant longitudinal measurements, will be created to be used for the statistical analysis. This will be developed to specifically contain data on APOE- ϵ 4 allele counts and concomitant medication use, i.e. stable background medication use. The update to the CTS will be performed by incorporating expanded APOE- ϵ 4 allele counts and concomitant medication use, i.e., stable background medication use, as covariates into the parameter describing rate of disease progression within the model. The purpose of this is to capture variability associated with these covariates and quantify their predictive accuracy on disease progression. The overall statistical model will then be used to generate new estimates on the parameters which can be used to perform simulations. The GUI for the CTS will be accomplished by using *Shiny*, an open source package in *R* used to generate interactive user interfaces. This interface will allow users to see real-time predictions of disease progression for input parameters and produce summary level statistics for specific clinical trial design settings. A user guide will be developed that contains thorough explanations of the tool, with information relevant to clinical trial simulation and case studies will be provided to facilitate self-guided learning.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes:

1. Create a fully-functioning open access CTE for the MCI stage of the AD continuum. The CTE will include a user-friendly graphical interface to warrant the widespread use of the tool.
2. Create a beta release of the CPAD trial simulation solutions that will allow the AD research community and clinical trialists to use the AD CTS and CTE tools in a computationally efficient manner.
3. Create a comprehensive curriculum that covers the essential abilities for the adequate use and application of the tools.

Long-term outcomes:

1. Explore the possibility of updates or amendments to the existing regulatory endorsement under the Fit-For-Purpose Initiative at FDA and under the Qualification of Novel Methodologies in drug Development at EMA, for the CTS and GUI platforms data.
2. Expand the CTE tool for the MCI stage of the AD continuum with data from clinical trials to allow a description of placebo effect, and clinical trial dropout. The resulting AD expanded CTS tool will be also submitted to the FDA and EMA for regulatory review.

- Expand the CPAD AD integrated database to include data from observational studies and clinical trials in AD Stage 1 and 2 when these become available. Such data will be used to develop CTE and CTS tools for the respective AD disease stages.
- Deploy the training mechanism, to facilitate the use and application of the tools by AD researchers.

Year End Progress Summary:

Aim 1: A user-friendly CTE tool was developed to optimize the design of clinical trials to evaluate therapeutic candidates intended to treat the MCI stage of the AD continuum using *Rshiny* (**Figure 1**). The GUI provides users with a simple interface to optimize clinical trial design by customizing patient and trial design characteristics, and then allows simulation of clinical trials under those conditions. Covariates for the patient population include baseline intracranial volume-adjusted hippocampal volume (ICV-HV), sex, baseline mini-mental-state-examination (MMSE), baseline age, and APOE genotype. Users can calculate statistical power through those simulations based on the patient and trial characteristics chosen. This work has received the ACoP9 Quality Award and was presented (oral and poster M033) at the Annual Conference on Pharmacometrics (ACoP9) in October 2018 in San Diego, CA.

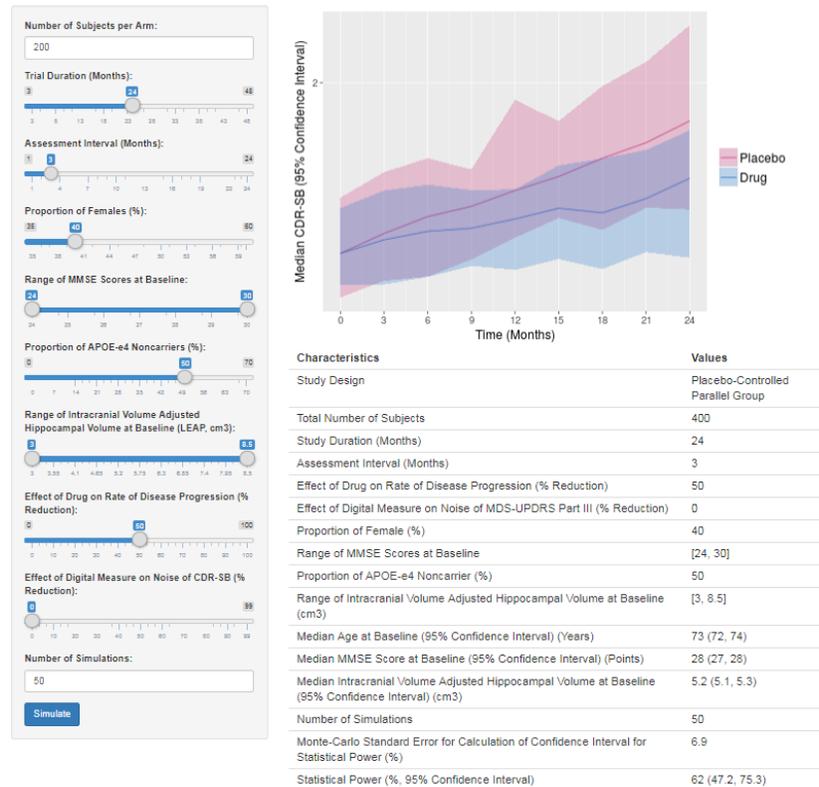
Aim 2: As part of the computational solutions for efficient application of the tools, efforts were first taken to make the tools widely available by implementing the GUI versions of the CTE and CTS tools on the shinyapps.io platform. The tools can be accessed and used here: [CTS tool](#), [CTE tool](#). These web-based app approaches allow anyone with an internet connection to access and use the tools. Further, because the tools are hosted on a separate computing infrastructure, it permits the use of high-performance computing to address the computational bottlenecks associated with clinical trial simulation. A construct was developed for interfacing the CTE and CTS tools with high performance computing capabilities using Amazon Web Server (**Figure 2**). The construct outlines the methodology that will allow a user to access graphical processing units (GPU) to significantly reduce the time to simulate several clinical trials. Users will not have any requirements to access the GPU as it is intended to be completely behind the scenes and seamless. Current efforts are being directed at the implementation of the construct.

Figure 1. GUI for the aMCI tool

Hippocampal Neuroimaging-Informed Amnesic MCI Clinical Trial Simulator



Simulate clinical trials on patients with amnesic mild cognitive impairment



Aim 3: Several different mechanisms have been utilized for continued training on the use and application of the tools. As seen on the CTE web app, documentation is available that described various aspects of the tool and its use. This initial documentation will undergo continued updates as the underlying tool is modified and refined. Accompanying documentation for the CTS tool is in development. In conjunction, a manuscript is being developed that emphasizes the use and application of the CTS tool. A poster was presented at the ACoP9 in October 2018 in San Diego, CA highlighting the GUIs, how to access them, and the construct for the computational efficiency solutions.

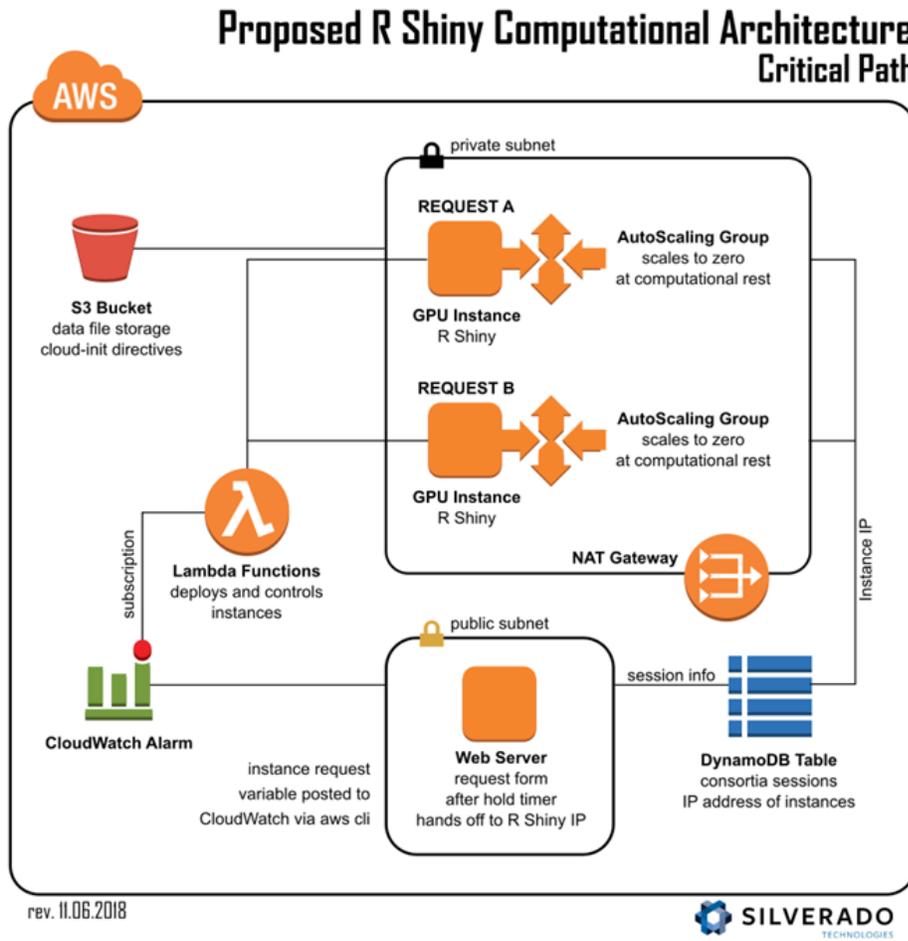


Figure 2. Construct for GPU acceleration for AD and MCI tools

Project Progress Report

Mayo Clinic Arizona

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Normal and Pathological Aging (Preclinical Alzheimer's Disease). Richard J. Caselli, MD, Dona E.C. Locke, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Project Description: Cognitively normal individuals age 21-99 (most age 45-70) undergo 1) APOE genotyping to categorize their relative risk for developing Alzheimer's disease; 2) longitudinal neuropsychological and behavioral assessments; and 3) serve to create a biorepository for DNA, serum, plasma, viable frozen lymphocytes, and immortalized cell lines to determine what factors divert individuals from normal to pathological aging/Alzheimer's disease with the intent of identifying optimal timing of treatment and new potential therapeutic targets for preventing this divergence (prevention of Alzheimer's disease). This "APOE Cohort" also serves as a core resource for multiple collaborative projects within our site and for the consortium.

Specific Aims:

- A. To maintain and grow a unique cohort of human aging in which we characterize the effect of APOE gene dose (a risk factor for Alzheimer's disease) on age-related changes in:
 1. Mentation (neuropsychological measures of cognition and behavior; subjective assessments by observers and self; sleep parameters)
 2. Brain Imaging (structural brain changes [MRI], functional [FDG-PET], amyloid-PET, tau-PET)
- B. To correlate longitudinal changes on each of these measures with clinical outcomes (mild cognitive impairment, Alzheimer's dementia, non-Alzheimer's dementia)
- C. To characterize the influence of other demographic, genetic, epigenetic, and health factors on cognitive aging trajectories
- D. To create a biobank of serum, plasma, DNA, frozen viable lymphocytes, and immortalized cell lines of this cohort.
- E. To function as a core resource collaboratively supporting other investigators
- F. To support, where appropriate, activities of the NIA funded Arizona Alzheimer's Disease Center

Background and Significance: Even at the earliest clinical stages of Alzheimer's disease (AD), amyloid pathology has nearly peaked yet neither symptoms nor brain atrophy correlate well with amyloid burden. Failed anti-amyloid therapies have been blamed on being started too late, resulting in new disease modifying strategies that begin during the preclinical, asymptomatic stage. Our work to date has helped to define and characterize the preclinical stage of AD, differentiating normal from pathological aging. Themes of our current research include 1) identification of preclinical disease modifying attributes (genetic, medical, demographic, and others), 2) extension of preclinical testing and precision medicine into the clinical practice domain, and 3) integration of multiple data sources into predictive algorithms.

Preliminary Data: To date we have completed APOE genetic testing on over 2800 participants from which were selected our study population for further testing. We have completed one or more epochs of neuropsychological testing on 788 individuals (table 1) including 451 APOE e4 noncarriers, 240 e4 heterozygotes, and 97 e4 homozygotes (table 2). Of these, 609 have completed two or more epochs of testing, with followup durations of up to 22 years (average is over 9 years) providing data for longitudinal studies. We have nearly 3000 plasma and serum samples on roughly 375 individuals, and DNA on all. 497 have immortalized cell lines established

including all with brain imaging. We established memory aging trajectories for each of 3 APOE genotypes (1), and subsequently on all remaining cognitive domains (2) providing a baseline upon which we are able to distinguish normal aging from preclinical Alzheimer’s disease, and the differential impact of modifying factors such as cardiovascular risk factors (3) preclinical amyloid deposition (4) and personality factors (such as proneness to stress) (5) thus generating new hypotheses about amyloid’s pathophysiologic role. We have further published TOMM40 related memory trajectories and have found a qualitatively and quantitatively different effect than for APOE (6). We have also completed a lorazepam “memory stress test” comparing the impact related to APOE and TOMM40 genotypes (7).

Table 1

Epoch	n	months followup
1	818	0
2	624	30.09 (13.09)
3	485	60.24 (20.25)
4	416	87.86 (25.38)
5	342	112.77 (28.22)
6	273	136.33 (28.94)
7	217	158.53 (29.19)
8	140	175.91 (23.62)
9	101	191.98 (24.67)
10	62	213.90 (21.86)
11	43	224.63 (20.05)
12	27	239.26 (21.21)
13	11	254.00 (15.61)

Table 2

	All	e44	e34	e4NC	Notes
followup entire cohort					
-n	819	100	250	459	
-months	92.40 (81.40)	95.05 (76.68)	94.54 (82.59)	92.27 (81.68)	
followup for > 1 epoch					
-n	622	83	191	348	
-months	121.52 (71.92)	114.52 (69.58)	124.24 (72.57)	121.70 (72.20)	
2018 enrollments (n)	30	3	11	8	8 pending APOEs

Year End Progress Summary:

1. The results of our computerized cognitive paradigm, the Parra binding task, did not prove to be superior to “conventional” memory tests in distinguishing APOE e4 carriers from noncarriers (findings presented at the Alzheimer Association International Conference in Copenhagen, 2015)
2. Whole exome sequencing and bioinformatics analysis in our first 14 nonfamilial young onset dementia patients was well tolerated, disclosed only a single unexpected genetic risk factor (for

- Parkinson's disease) amidst hundreds of benign variants and variants of unknown significance (findings presented at the American Academy of Neurology in Boston, 2017, and provided support for the hypothesis that lower genetic diversity is a risk factor for nonfamilial young onset dementia.
3. Analyses of responses to the autism questionnaire have been completed and support the existence of a broad autism phenotype in roughly 5% of the adult population, and its correlation with subjective cognitive impairment
 4. Published the effect of TOMM40 and APOE genotype on a lorazepam "stress test" for memory (7)
 5. Longitudinal personality assessments in individuals with incident MCI showed the beginning of personality changes with increased Neuroticism and reduced Openness that lay the foundation for subsequent behavioral disorders (8).
 6. Collaborated with ASU investigators on a new MRI morphologic metric sensitive to very early stage AD (9-12)
 7. Presented our initial analyses of predictive changes in longitudinal FDG-PET, MRI volumetry, and memory test trajectories in MCI progressors vs nonprogressors (13).

Experimental Designs and Methods: Responders to local media ads undergo APOE genotyping (a blood test); APOE e4 carriers are matched by age, gender, and education to a noncarrier. Screening tests (Folstein MMSE, Hamilton Depression Scale, Neurologic exam, psychiatric interview) confirm reported normality. Blood for the biorepository is obtained at entry for storage of plasma, serum, and DNA. Neuropsychological (and related) testing is performed every 2 years under age 80 and annually over age 80. Individuals developing MCI or AD are rolled over into the NIA-ADCC study.

Proposed One-Year and Long-Term Outcomes: In addition to maintaining the ongoing evaluation of this important cohort, our goals for the next one year include:

1. Extend our genetic study of unexpectedly young onset dementia patients with whole exome sequencing and bioinformatics analysis of a large gene set encompassing identified risk genes for Alzheimer, disease, frontotemporal lobar degeneration, and Parkinson's disease to examine 3 specific goals:
 - a. do "minor" genetic variants contribute to nonfamilial young onset dementia
 - b. how disclosure of genetic results to patients and families impacts clinical care (e.g., does it lead to CLIA lab confirmation of research results; does the absence of a highly pathogenic variant such as a PSEN1 mutation offer solace to families concerned about familial transmission)
 - c. is genetic diversity as reflected in excess heterozygosity and standardized homozygosity scores a risk factor for nonfamilial young onset AD
2. evaluate the results of an autism questionnaire with regard to
 - a. the prevalence of a "broad autism phenotype" (BAP) in our cohort members, and whether they "fit" a previously described BAP phenotype., and
 - b. whether a BAP phenotype impacts subjective cognitive impairment, age-related cognitive decline and the risk for incident MCI and dementia alone or in conjunction with APOE e4
3. Compare the longitudinal trajectories of FDG-PET, MRI volumetrics, and neuropsychological tests in patients with and without eventual progression to MCI and dementia to determine how long in advance of diagnosis trajectories significantly deviate from the nonprogressor group.
4. Support our collaborative projects
5. Maintain the shared plasma/serum biobank resource
6. Continue to strategically merge, where appropriate, data from this project with the NIA P30 Alzheimer's Disease Center data to create a much larger dataset encompassing the entire adult lifespan and all stages of cognition including young adulthood, middle age, and elderly normal stratified by APOE genotype and other demographic properties, as well as MCI and dementia.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Predicting Cognitive Decline in Cognitively Unimpaired Individuals. Cynthia M. Stonnington, MD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Project Description: Cognitively unimpaired 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 project will capitalize on the existing longitudinal data base of imaging, neuropsychological testing, and genetic testing to establish how a clinician might use a combination of such data to identify pre-clinical predictors of disease and to determine the probability of developing disease for any given individual patient.

Specific Aims:

1. To identify participants in our longitudinal study of aging who have baseline imaging and have shown evidence of cognitive decline by having developed incident MCI.
2. To preprocess MRI scans using cortical thickness, i.e., Freesurfer, and grey matter volume, i.e., SPM, methods, as well as surface multivariate tensor-based morphometry (mTBM) and grey matter morphology signatures to study important structural MRI AD biomarkers. Compare region of interest and whole brain differences between decliners and nondecliners for each of the methods.
3. To develop methods to predict decline using FDG PET, MRI, amyloid imaging, genetic, and neuropsychological data by creating training sets of baseline data from participants with decline and from participants who have at least two epochs of data and show no decline.
 - a. Examine the statistical power in distinguishing the two groups using Receiver Operating Curve (ROC).
 - b. Examine prediction accuracy by using machine learning methods.
4. To evaluate additional genetic markers contributing to risk for cognitive decline, including BDNF Val66Met polymorphism.

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. Anti-amyloid therapies have all fallen well short of expectations to date, for the generally held reason that they are started too late, and that for a disease modifying agent to be effective it must be started during an earlier, preclinical stage, i.e., before patients develop symptomatic memory loss. Preclinical AD is superficially indistinguishable from normal aging. We therefore plan to develop methods to differentiate normal from pathological aging by combining imaging-based biomarkers, neuropsychological, and genetic data to better identify those individuals on the cusp of symptoms and therefore most likely to benefit from treatment.

Preliminary Data.

1. From a total of 139 ADNI participants who were diagnosed as MCI and had baseline FDG PET and MRI imaging data, 78 (75.8±7.0 years old) developed incident AD during the subsequent 36 months, and the remaining (75.3±8.0) did not during the same period. FDG PET measured glucose uptake, MRI measured hippocampal volume and ADAS-mod at

baseline all distinguished MCI converters from non-converters, but, using ROC, the sensitivity and specificity showed increased statistical power when these modalities were combined (sensitivity=82%, and specificity=80%).

2. From our longitudinal APOE data base of cognitively normal individuals, we have identified 21 individuals with baseline FDG PET and MRI and neuropsychological data who subsequently developed incident MCI, along with 180 in the same age cohort who remain cognitively normal also had FDG PET and MRI and neuropsychological data.
3. From our longitudinal APOE data base of 180 cognitively normal individuals with baseline FDG PET and MRI and neuropsychological data, we have identified 18 who show evidence of cognitive decline but have not yet developed MCI or AD.
4. From our longitudinal APOE data base, we identified 14 individuals with amyloid imaging data who also had evidence of cognitive decline but remained cognitively normal and matched by age, sex, APOE status, and education to 14 individuals who did not show any cognitive decline. At $P < .005$ (uncorrected), decliners had significantly greater evidence of fibrillar A β burden in comparison to nondecliners (1)
5. From our prospective cohort study of aging, we examined baseline CMRgl, Pittsburgh B (PiB) PET measured amyloid burden, and subsequent rate of change in cognition from 114 CU adults (59 with PiB PET) who had been both BDNF and APOE4 genotyped. Among APOE4 carriers, BDNF Met carriers had significantly higher frontal CMRgl and slower decline of frontal CMRgl over time than the BDNF val/val group but no significant differences in decline of cognitive scores. The BDNF effects were not found among APOE4 noncarriers. Increased amyloid deposition was positively correlated with areas of greater cerebral metabolism.

Experimental Designs and Methods: From our ongoing, longitudinal normal and pathological aging study, identify: 1) all participants with baseline imaging exhibiting cognitive decline according to definitions used in our prior studies; and 2) all participants with baseline imaging who developed incident MCI.

Both the FDG PET and PiB PET Distribution Volume Ratio (DVR) baseline images will be coregistered to MRI baseline images, and the MRI Dartel normalization will be used to normalize the MRI and PET data. For PiB PET scan data, the well-known graphical analysis Logan method and an automatically labeled cerebellar region-of-interest will be used to compute parametric brain images of the PiB DVR, a measure of fibrillar A β burden. Together with the effects of age and sex, partial volume effect corrected PET kernel matrices will be created separately for segmented grey matter, cortical thickness, Dartel normalized MRI and PET images, APOE e4 genotype, and cognitive test score data. Regions of interest will be determined from published data that used a data set independent of ours.

For mTBM methods we will segment each baseline MRI scan with FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>), parameterize the hippocampal and ventricle surfaces as described previously, and generate the surface multivariate morphometry statistics (MMS) consisting of mTBM and radial distance (RD).

Firstly, we will examine the statistical power in distinguishing the two groups using Receiver Operating Curve method. Secondly, we will apply machine learned decision trees to various sets of features from brain imaging, genetic, and neuropsychological data. We will then test diagnostic and prognostic performance using different maximum number of features. Specifically, we will construct a collection of overlapping patches on the surface as the initial sparse coding dictionary. Stochastic Coordinate Coding will then be applied to learn a dictionary and sparse codes. We will use the max-pooling algorithm on the newly learned high-dimensional features to obtain a final set of low-dimensional features. Finally, an AdaBoost classifier will be applied to categorize aMCI and cognitively unimpaired individuals with 5-fold leave-one-out cross

validation adopted to evaluate classification accuracy, sensitivity, specificity, positive and negative predictive values.

Proposed One-Year and Long-Term Outcomes: Produce computerized systems capable of diagnosis or prognosis for individuals who are cognitively normal based on chains of reasoning that a clinician can evaluate.

Year End Progress Summary: We previously described 79% sensitivity and 78% specificity prediction of imminent clinically significant decline using standard automated brain mapping algorithmic programs, binary logistic regression and leave-one-out procedures (*Stonnington CM, Chen Y, Savage CR, Lee W, Bauer Iii RJ, Shariieff S, Thiyyagura P, Alexander GE, Caselli RJ, Locke DEC, Reiman EM, Chen K (2018) Predicting Imminent Progression to Clinically Significant Memory Decline Using Volumetric MRI and FDG PET. J Alzheimers Dis 63:603-615*). Here, we aimed to improve prediction with the same data set but using hippocampal surface multivariate morphometry statistics (*Shi J, Thompson PM, Gutman B, Wang Y, Alzheimer's Disease Neuroimaging I (2013) Surface fluid registration of conformal representation: application to detect disease burden and genetic influence on hippocampus. Neuroimage 78:111-134*) combined with patch-based sparse coding algorithms. For the latter, we chose a random forest algorithm. Random forests are a combination of tree predictors such that each tree depends on the values of a random vector sampled independently and with the same distribution for all trees in the forest. This algorithm adapts a learning process called "feature bagging." In this process, we selected a random subset of the features for several times and then trained a decision tree for each subset. If some features are strong predictors for the response, they are selected in many decision trees and thus made correlated. In comparison with Decision trees, Random forests have the same bias but lower variance, which means it overcomes the drawback of overfitting caused by the small data set. For our sparse surface features, when the training number becomes smaller, diversification becomes more subtle, and the method can better detect these subtle differences. Figure: Patch-based sparse coding system. (a) Surface Multivariate Morphometry Statistics. (b) Generate patches and randomly select patches on the surface. (c) Dictionary Learning and Sparse Coding. (d) Sparse Patch-based Features got from (c). (e) Max-Pooling to resize the features in (d). (g) Classification by using random forest classifier with the features after Max-pooling.

From a prospective cohort study in Arizona, 18 cognitively unimpaired adults who subsequently progressed to the clinically significant memory decline within 2 years (progressors) were matched for age, sex, education, and apolipoprotein E4 allele dose to 20 adults who remained cognitively unimpaired for at least 4 years after baseline visits (nonprogressors) (TABLE 1). The same inclusion criteria and methods were then applied to the Alzheimer's disease Neuroimaging Initiative (ADNI) data set, resulting in a sample of 18 progressors and 34 nonprogressors who were older and had a greater percentage of males and non e4 carriers than the Arizona participants (TABLE 2). We achieved 95% prediction accuracy in the Arizona cohort (TABLE 3) and 90% accuracy in the ADNI cohort (TABLE 4). Combining the two cohorts (36 progressors and 54 nonprogressors) achieved 85% prediction accuracy, 86% sensitivity, and 83% specificity (TABLE 5). While our findings should be considered preliminary, sparse coding together with the surface multivariate morphometry may be applied to individual volumetric MRIs to predict imminent progression to clinically significant memory decline with great accuracy.

Table 1

Characteristics Progressors and Nonprogressors at the Time of Baseline Scan (Arizona Cohort)

	Progressors (n=18)	Nonprogressors (n=20)	P-Value
Sex (M/F)	7/11	7/13	0.80
$\epsilon 4$ Genotype (N)	13:03:02	13:04:03	0.89
% (HM:HT:NC)	(72:17:11)	(65:20:15)	
Age	68.75 \pm 4.65	66.76 \pm 3.29	0.13
Education	16.44 \pm 1.69	15.50 \pm 3.33	0.29

Sex and genotype p-values were calculated by chi-squared tests, Age and education p-values were calculated by t-tests. HM= $\epsilon 4$ homozygote; HT= $\epsilon 4$ heterozygote; NC= $\epsilon 4$ non-carrier.

Table 2

Characteristics of Progressors and Nonprogressors at the Time of Baseline Scan (ADNI Cohort)

	Progressors (n=18)	Nonprogressors (n=34)	P-Value
Sex (M/F)	15/3	22/12	0.16
$\epsilon 4$ Genotype (N)	0:07:11	0:07:27	0.16
% (HM:HT:NC)	(0:39:61)	(0:21:79)	
Age	79.64 \pm 4.16	77.82 \pm 3.65	0.11
Education	15.83 \pm 3.07	16.61 \pm 2.48	0.32

Table 3

Experimental Results: Arizona Cohort (Leave-One-Out Cross-Validation)

<i>Hippocampal</i>	<i>MMS</i>	<i>MMS_left</i>	<i>MMS_right</i>
Accuracy	0.95	0.76	0.66
Sensitivity	0.94	0.71	0.78
Specificity	0.94	0.83	0.39

Table 4

Experimental Results: ADNI Cohort (Leave-One-Out Cross-Validation)

<i>Hippocampal</i>	<i>MMS</i>	<i>MMS_left</i>	<i>MMS_right</i>
Accuracy	0.90	0.72	0.65
Sensitivity	0.87	0.67	0.50
Specificity	0.94	0.33	0.06

Table 5

Experimental Results: Combined Cohorts (5-fold cross-validation)

<i>Hippocampal</i>	<i>MMS</i>	<i>MMS_left</i>	<i>MMS_right</i>
Accuracy	0.85	0.75	0.80
Sensitivity	0.86	0.77	1.00
Specificity	0.83	0.70	0.50

We are completing the manuscript of this study to submit for publication.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Reduced Genomic Diversity as a Risk Factor for Accelerated Cognitive Aging and Alzheimer's Disease. Richard J. Caselli, MD, Matthew Huentelman, PhD, Li Liu, MD. Mayo Clinic Arizona; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Project Description: Whole exome sequencing will be performed on members of the Arizona APOE Cohort and scores will be generated for observed heterozygosity and standardized homozygosity, both reflections of relative genetic diversity. Genetic diversity scores will be correlated with cognitive performance, cognitive trajectories, and clinical outcomes.

Specific Aim: To assess the impact of genetic diversity of cognitive aging and the risk for Alzheimer's disease by correlating relative rates of heterozygosity and homozygosity on a genome-wide basis, as well as in a targeted panel of previously described susceptibility loci with cognitive performance, trajectories, and clinical outcomes in members of the Arizona APOE Cohort.

Background: How well adapted we are to the environmental and physiological stresses that affect our health generally depends on our genetic diversity as a species and as individuals. Inbreeding lowers fitness-related characteristics and this inbreeding depression is predominantly caused by the accumulation of deleterious recessive mutations reflected in the higher fitness of heterozygotes compared with homozygotes (1). The onset of AD prior to age 65 is unusual, but familial clustering of such cases has led to the discovery of highly penetrant genetic variants that converge on cerebral amyloid aggregation, and more recently weaker variants reflecting multiple mechanistic pathways, but all known genetic associations together still do not account for the majority of AD heritability because most of the missing genetic risk resides in common, ostensibly benign variants which occur on every autosome (2,3). Applying the principle of inbreeding depression (4,5), we hypothesized that lower heterozygosity would influence human cognitive aging and susceptibility to AD.

Preliminary Data: We performed whole exome sequencing and determined heterozygosity scores in two small independent cohorts of nonfamilial young onset AD patients. We found, in both cohorts that reduced heterozygosity strongly influenced the risk for young onset AD. Excess homozygosity of thousands of variants with individually very weak effects could therefore be a potent susceptibility factor for nonfamilial young onset AD, and suggests future prevention strategies may require a personalized approach in which genomic and exposomic profiles are used to create vulnerability maps that will differ between individuals. We will apply the above analysis to whole exome sequenced samples to determine heterozygosity and homozygosity rates overall as well as for targeted genes previously reported to be associated with AD risk, and gene "clusters" of known relevant pathways, e.g., APP processing.

Methods:

Subjects. Members of the Arizona APOE Cohort (Project 1 described previously) who have consented for their stored DNA to be used for further research.

Genomic sequencing. Whole exome sequencing and analysis will be performed by Dr. Matthew Huentelman at the Translational Genomics Research Institute on these cases and control DNA samples.

Estimate genetic diversity: The genomic data will be provided to Dr. Li Liu at Arizona State University (adjunct appointment in the department of Neurology, Mayo Clinic Arizona) who will compute observed heterozygosity and standardized homozygosity scores (6) for the cases and controls. She will estimate genome-wide diversity by computing these indices using all polymorphic loci. We will also group loci based on allele frequency to examine patterns related to common variants or to rare variants.

Proposed One Year and Long-Term Outcomes: We will complete whole exome sequencing and bioinformatic analysis on an estimated 300 participant DNA samples to create the database from which longer term correlations will be determined including cognitive performance measures, cognitive trajectories (age related cognitive decline), and clinical outcomes including but not limited to Alzheimer's disease.

Year End Progress Summary:

1. Additional funding has been obtained that will allow us to expand this project to whole genome sequencing, and that proposal is currently going through the regulatory committees.
2. In the meantime, we have completed a related project. Genetic diversity reflected by the excess of heterozygosity score was determined from whole exome sequence data in 767 Late Onset Alzheimer's Disease (LOAD) patients and 653 octogenarian controls from the National Institute on Aging Alzheimer's Disease Centers. Genetic diversity of common variants (minor allelic frequency >15%) was higher in the controls than in the LOAD group, $p=0.006$. Genetic diversity reflecting many genome wide, ostensibly benign variants may be another risk factor for dementia.
3. We have also completed whole exome sequencing of an autopsied cohort of young onset dementia patients and octogenarian controls and data analysis is in progress.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Psychosocial Intervention Development for Those Living alone with Mild Cognitive Impairment. David W. Coon, PhD, Dona Locke, PhD. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims: To develop a psychosocial intervention to improve and maintain quality of life for patients who are living alone with Mild Cognitive Impairment.

Background and Significance: Approximately 15-20% of people age 65 and older have Mild Cognitive Impairment (MCI), a condition characterized by measurable changes in thinking abilities that are noticeable to both people with MCI and their family/friends. However, people with MCI can still carry out their everyday activities. A recent systematic review suggests that approximately 32% of people with MCI go on to develop Alzheimer's within 5 years (Ward, Tardiff, Dye, & Arrighi, 2013). Depression appears to be quite common among MCI patients (25% in community samples; 40% in clinical samples) (Ismail, Elbayoumi, & Fischer, 2017), and MCI patients have reported significantly lower psychological quality of life compared to their peers with normal cognitive functioning. Moreover, living alone with MCI appears to place these MCI patients at higher risk for poorer outcomes (Muangpaisan et al., 2008). To date, no evidence-based treatments have been identified that improve and maintain quality of life for people living alone with MCI. The two investigators for the proposed project run intervention programs for individuals diagnosed with MCI and/or early-stage dementia. Early-stage Partners in Care (EPIC), led by Dr. Coon as a partnership with ASU and the Alzheimer's Association, is a program focused on patients with early-stage dementia and their care partners. This group dyadic intervention includes education and skill-training workshops designed to reduced stress, enhance well-being, and help manage challenges by hearing the patient's voice in terms of care values and future care preferences. The HABIT Healthy Action to Benefit Independence and Thinking program, led by Dr. Locke at Mayo Clinic, is a cognitive rehab and brain wellness intervention for patients with MCI and a program partner. HABIT aims to support functioning, improved quality of life, and strengthen partnerships. EPIC and HABIT can be seen as companion programs as each involves different types of interventions. The HABIT program involves: (1) cognitive rehabilitation (2) support group for both patient and partner (3) wellness classes (4) cognitive exercise and (5) yoga. However, neither program is designed to support MCI patients who do not have someone to be their partner (e.g., individuals living alone with MCI with no local family members). Using our experiences with EPIC and HABIT as a frame, we want to respond to local and federal partner requests (e.g., the Alzheimer's Association, local Area Agencies on Aging, and the U.S. Administration for Community Living) to develop an intervention program for this population.

Preliminary Data: EPIC pilot results funded from a U.S. Administration Innovation grant showed significant changes in clinical symptoms (depression and other mood states), quality of life indicators (relationship functioning, self-efficacy, care preparedness), and social validity among EPIC patients and care partners when delivered by Alzheimer's Association staff under Dr. Coon's supervision (Coon et al., 2013). EPIC is the first group dyadic intervention to show positive outcomes for both early-stage individuals and care partners. Embedded into the community through the Alzheimer's Association Chapters in Arizona and Nevada, EPIC is currently being tested through an RCT funded by an NIA R01 (Coon, PI). The backbone of the HABIT program is a cognitive rehabilitation intervention, the memory support system (MSS). Master of the MSS helps improve memory ADL functioning, improves self-efficacy, reduces caregiver depression,

and helps prevent increases in partner burden compared to untreated individuals (Greenaway et al., 2012). Research evaluating the impact of the loss of one component of the HABILIT program (e.g., dyads receiving 4/5 of the components) suggests that various combinations of different components impact different outcomes (e.g., memory ADLs, quality of life, mood, self-efficacy) such that a synergy of multiple interventions may be most beneficial on a variety of patient and partner outcomes (Locke et al., 2018). When dyads who completed the HABILIT program with all 5 components were asked about the impact of HABILIT using a Likert scale format, patients agree to strongly agree that they learned tools to cope with memory loss and that HABILIT improved their ability to function despite memory loss, improved quality of life, and improved mood. Partners expressed similar satisfaction with the program for their own quality of life and mood (Locke & Chandler, 2018).

Experimental Designs and Methods: This project will be comprised of two phases to help finalize a protocol for a psychosocial intervention to help improve and maintain quality of life for people with MCI who live alone. Both Phase I and Phase II will involve a series of six focus groups (3 focus groups with people with MCI who live alone; 3 groups with providers who assist people with MCI). Focused interviews will also be available for those who are eligible but unable to attend one of the focus groups. Phase I focus groups will help to (a) determine the key needs and concerns of people with MCI who live alone; (b) introduce key components of both EPIC and HABILIT for review, comment, and potential adaptation for people with MCI who live alone; (c) gather outreach and recruitment strategies to help identify and enroll this population in a future intervention; and, (d) identify potential barriers to enrollment (e.g., inability to drive) and strategies to overcome those barriers. Prior to Phase II, qualitative analysis of focus group and focused interview transcripts will be used to help refine key components of a psychosocial intervention protocol (e.g. outreach and recruitment material, intervention components, etc.). Phase II focus groups and focused interviews will gather additional input to help to further refine (a) outreach and recruitment strategies; (b) screening and interview material; (c) intervention components and mode of delivery; and, (d) translate key needs and concerns into intervention outcomes for evaluation. Qualitative data analysis of Phase II will help to finalize the intervention protocol for pilot testing.

Proposed One-Year and Long-Term Outcomes: The proposed short-term outcomes would be the finalization of a protocol (outreach and recruitment, screening and interview, and intervention material) for a psychosocial intervention for people with MCI who live alone. In addition, the data analyses from the focus groups and focused interviews would yield both professional presentations at meetings like such as the Gerontological Society of America, the American Society on Aging, or American Psychological Association and the submission of the findings to venues such as *The Gerontologist (Practice Concepts Section)*, *the Clinical Gerontologist*, or *Dementia*. Based on the findings, the Co-PIs (Coon & Locke) would hope to submit an R21 or perhaps even a smaller R01 submission in 2019-2020, depending on the project's findings and other funding sources for a small intervention pilot.

Year-End Progress Summary: The project is on track for completion 6/30/19. Project protocol, screening tools, focus group and focused interview guides, recruitment material, and consents were developed for the current project. Informal feedback from professionals in the field combined with the experience of the investigators and their teams helped these materials. Focus groups and focused interviews with individuals living alone with MCI and professionals who assist them will be completed by year's end. Findings from these group and individual interviews will help to refine the screening tools, recruitment materials, quantitative interviews, and the overall intervention for people living alone with MCI to be implemented in a future intervention pilot.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Fluid Biomarkers for Neurodegenerative Disease Research. Richard J. Caselli, MD, Paul Coleman, PhD. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

1. To create a relational database that catalogues existing biobanked specimens and a link to the AZ consortium website's homepage.
2. To maintain and advance longitudinal collections of biofluids (plasma, serum, DNA, CSF) in members of the Arizona APOE Cohort, Alzheimer's Disease Center Clinical Core, and other AZ based research cohorts.
3. To explore project specific collections for Arizona investigator needs that may include (but not be limited to), for example, PAXgene tubes.

Background and Significance: There is a need for and considerable research activity among Arizona investigators striving to achieve a reliable biofluid based biomarker assay for Alzheimer's disease as well as other neurodegenerative disorders. Existing biobanking resources are not readily accessible to scientists even when actual biospecimens could be made available.

Preliminary Data, Experimental Design and Methods: To date plasma and serum samples from research participants have been banked in the Mayo Clinic Arizona biospecimens core lab and shared with Arizona based investigators at Arizona State University and Barrow Neurological Institute. Additionally, DNA samples from the Arizona APOE cohort stored in a Mayo Clinic Florida research lab will be transferred to the Mayo Clinic Arizona biospecimens core lab and made available for Arizona investigator (and other approved) uses. Other biobanking efforts exist at Banner Sun Health Research Institute Tom Beach), Banner Alzheimer's Institute (Eric M. Reiman), Translational Genomics Research Institute (Matt Huentelman), and Arizona State University (Josh LaBaer).

Proposed One-Year and Long-Term Outcomes:

1. Establishment of relational database cataloguing biofluid samples from existing research participants.
2. Transfer of major APOE Cohort DNA resource from Florida to the Mayo Clinic Arizona biobank.
3. Creation of a biofluids request and use committee.

Year End Progress Summary:

1. Limited progress was made creating a means to query the types of samples available in the Mayo biorepository but a major change in goals has curtailed further development at this stage (detailed below).
2. Transfer of major APOE Cohort DNA resource from Florida to the Mayo Clinic Arizona biobank has been completed
3. Creation of a biofluids request and use committee is pending a major change in the AARC's biofluids efforts in which Dr. Beach at BSHRI will assume leadership for this effective core resource and the current organizational methods that are utilized by the BSHRI brain and body donation program will be applied to biofluids.
4. During the course of the year a change in biofluid strategy was developed in conjunction with Drs. Beach and Reiman to transfer biofluid management to the Neuropathology Core, and utilize the allocated funds instead for imaging biomarkers in a select group of APOE Cohort members

who have transitioned to the stage of mild cognitive impairment. Five such individuals will undergo amyloid and tau PET with coregistered MRI to provide biomarker characterization.

Project Progress Report

Midwestern University

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Continuing Investigations into the Role of Microbes in the Development of Alzheimer's Disease. G. Jentarra, PhD (PI), T. B. Jones, PhD (PI), J. Vallejo, PhD, D. Jones, PhD, J. Kaufman, PhD, Weidang Li, MD, PhD, Fernando Gonzalez, PhD, P. Potter, PhD, Tony Tulloh, MD, Ashlesh Murthy, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Determine microbial load in additional tissue from patients with affected cognitive function (AD and mild cognitive impairment; MCI), as well as non-demented high pathology (HPC) and normal controls. DNA from serum, as a measure of bacterial load in blood, and tissue from the basal pons (a negative control) will be analyzed for bacterial and fungal DNA by 16S or 18S rRNA gene sequencing. Our hypothesis is that microbial load will correlate with cognitive function and pathology in AD and MCI patients, but be lower in HPCs, and lowest in normal controls.

Specific Aim 2: Use the 3xTg-AD and APOE4 TR mouse models to study the effects of infection with *C. pneumoniae* and *C. albicans*, which have been previously proposed to contribute to development of AD.

Aim 2.1: Determine whether AD pathology in transgenic mouse models will be induced or exacerbated following intranasal infection with *C. pneumoniae*, a pathogen previously implicated in AD. Aim 2.2: Perform intravenous fungal inoculation experiments using APOE4 TR mice, who may have a more permeable blood-brain barrier than APOE3 TR control mice. We predict that APOE4 mice might display aberrant microglial inflammatory signaling following infection. We hypothesize that infection might induce A β or tau pathology in the brains of APOE4 TR mice.

Background and Significance: Inflammation contributes to the pathogenesis of AD, as activation of various immune cells, particularly microglia, and production of cytokines both in the central nervous system (CNS) and the periphery have been reported. To date, no definitive triggering mechanism for AD has been identified. Gene alleles, such as APOE4, increase risk of AD. However, the mechanism underlying susceptibility to AD created by the APOE4 allele is unclear. It may be related to deficiencies of metabolism, altered immune function, or impairment of the blood-brain barrier, which could lead to inadequate or exaggerated immune response or entry of substances not normally found in the brain.

Many reports have identified a wide range of microorganisms in brain tissue in association with AD. These include spirochete type bacteria, HSV-1, and fungi/yeast, including various species of *Candida*. The chronic presence of any of these microorganisms in the brain may be sufficient to produce inflammation in AD. Historically, diseases are associated with a particular microorganism. However, in this case, many heterogeneous microorganisms have been associated with AD, leading us to hypothesize that the identity of the microorganisms is not as important as their chronic presence, which could drive a long-term inflammatory response.

The amyloid and tau pathology remain to be explained and there is reason to believe that these could be provoked by infection. A β is induced by the presence of an infecting microbe and has strong antimicrobial activity, involved in both pathogen agglutination and formation of channels/pores in microbial membranes. A β may therefore be produced to limit infection. Hyperphosphorylation of tau, which drives aggregation, may be also be induced by microbial infection, as has been demonstrated in cell culture experiments using HSV-1.

The experiments we are proposing will provide information about 1) whether microbial load is higher in AD and MCI tissues and is associated with pathology, 2) whether the presence

of infection can exacerbate AD pathology, including A β and tau, and 3) whether the risk for AD development conferred by the APOE4 allele is associated with decreased resistance to entry of microbes into the brain. These results could alter the way that AD is treated and lead to far more effective treatments, at both early and later stages.

Preliminary Data and Plan:

Aim 1: We previously analyzed tissue from the superior frontal gyrus (SFG) of our four subject groups in order to perform an unbiased survey of the bacterial DNA (by 16S rRNA gene sequencing) present in post-mortem brain tissue. Several hundred different bacteria were identified in those tissues, with AD tissue showing more diversity than other groups. This study is to be followed with a second analysis of tissue from the inferior temporal gyrus (ITG), an area heavily affected with AD pathology. Results of an additional analysis of bacterial DNA from the serum of subjects and from the basal pons (BP) of these subjects (intended to be a negative control, as it is free of pathology) were planned as the final steps in this series of experiments.

Aim 2: We hypothesized that 3xTg mice would display enhanced susceptibility to *C. albicans* infection that would manifest as a reduced ability to clear the organism from peripheral tissues and the brain. Further, we hypothesized that if amyloid and tau are induced as an anti-microbial response, these should be enhanced in inoculated mice compared with non-inoculated and wild-type controls. Survival/mortality rates were evaluated in 3xTg-AD mice after infection with *C. albicans*. At 6 months of age, C57BL/6 wild-type (WT) mice had 100% survival compared with 75% survival in 3xTg-AD mice ($p = 0.06$). At 12 months of age, the rate of survival of WT mice had decreased to 67% ($p = 0.06$ versus 6 months of age) while that of 3xTg-AD mice at 12 months of age did not change from that at 6 months ($p = 0.7$). Significant hepatosplenomegaly was observed in 3xTg-AD mice compared with inoculated WT mice ($p < 0.001$), an effect that increased in 3xTg-AD, but not WT mice, as the mice aged ($p < 0.0001$). Males were significantly more affected than females ($p < 0.001$). Collectively, these preliminary data suggest strain-, sex-, and age-dependent effects on the response to fungal infection.

Proposed One-Year and Long-Term Outcomes:

1. 16S rRNA gene sequencing data from three different sites in the brains of the same subjects will be compiled and analyzed for differences between groups and sites, and in relation to subject characteristics such as age, sex, brain pathology, etc. This data will be published as a set once it is complete. Additional experiments will follow up on any significant data from the study.
2. We used preliminary data from Aims 1 and 2 to submit an NIH R15 (AREA) proposal in February 2018, as well as a proposal to the Infectious Diseases Society of America, and to the CART organization. Another NIH grant submission is planned for June 2019.
3. Animal studies are on-going and upon completion, the data will be submitted for publication. We will utilize the outcomes of this study to design additional studies to further explore the mechanisms that initiate and drive plaque and tangle pathology.

Year End Progress Summary:

Aim 1: 16S rRNA gene sequencing data was acquired for the superior frontal gyrus and inferior temporal gyrus from all subjects. Technical discrepancies in the data were noted and addressed with the commercial sequencing lab that performed the analysis. They were unable to satisfactorily resolve the discrepancies. After establishing that TGen North in Flagstaff, AZ, had greater expertise in the analysis of these types of samples, all three sample sets (SFG, ITG, and BP) were sent to them for 16S rRNA gene sequencing analysis. Results are currently pending. While analysis of serum for bacterial DNA was also planned, we established that insufficient DNA

was available from serum and determined that whole blood, which is unavailable for these subjects, would be more informative for this analysis.

While resolving the sequencing issues, we continued our assessment of bacterial presence in the brain. ELISAs were used to measure lipopolysaccharide (LPS, a gram-negative bacterial product) in serum and brain tissue lysates from the superior frontal gyrus of our 48 subjects. We then followed up with analysis of lipoteichoic acid (LTA, a gram-positive bacterial product), in the same brain lysates. Serum levels of LPS were significantly different between normal subjects and patients with AD. Female subjects had significantly higher serum LPS than males. High levels of LPS were noted in the brain lysates of all subjects, and did not correlate directly with diagnosis. However, in patients with MCI, post-mortem interval correlated strongly with increased LPS, possibly indicating continued growth of microbes after death, which may reflect the activity level of the microbes before death and could be related to early cognitive impairment. Serum LPS levels were disconnected from brain LPS levels, suggesting that the LPS in the blood may not be the source of brain LPS. LTA levels in brain lysates were considerably lower than LPS levels but still easily detectable and relatively consistent between the subject groups.

Together, this data indicates that many bacteria may be resident in the brain and that their presence in general is not unusual. The pending sequencing data will be needed to see if there are differences in the types or numbers of different kinds of bacteria between subject groups. This data suggests that if microbes play a role in AD, it may be that the microbes are the triggers for immune response, but that the manner in which individual's brains respond to their presence may differ and may be influenced by the many risk genes associated with AD. We are following up this data with analyses of host responses in the same subjects to establish if they are responding differently.

Aim 2: During the past year we processed the tissues collected from 6- and 12-month-old C57 and 3xTg mice inoculated with *C. albicans* (i.v.) and sacrificed at 1, 3, 7, or 14 days post-infection. We have completed sectioning and staining of splenic and renal tissues from the 6- and 12-month mice for all inoculation groups. Tissues were stained with PAS to identify fungal organisms remaining in the tissues and Congo red was used to identify amyloid (confirmed by the presence of apple green birefringence under polarized light).

We have demonstrated the presence of uncleared *C. albicans* yeast cells (spleen) and hyphae (kidney) in 3xTg-AD mice at 12 months of age; this was more pronounced in male mice, consistent with previous findings of increased fungal burden in tissue homogenates. We were also able to determine that intravenous fungal inoculation induced amyloid in peripheral tissues, not just in 3xTg-AD mice, but also in C57/BL6 mice, as evidenced by the appearance of fatty oval casts and maltese crosses with apple green birefringence under polarized light. The deposition of amyloid was particularly prominent in and around blood vessels that also demonstrated increased Congo red staining, suggesting increased friability in blood vessels with amyloid deposition. APOE3 and APOE4 mice that are needed for the completion of these studies are currently being aged and will be infected when they have reached the target ages for the experiments.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Diabetic obesity results in cognitive impairment: Evaluation of the gut, brain and bone effects in response to exercise and genistein treatment-II. Layla Al-Nakkash, PhD, Tom Broderick, PhD, Jeffrey Plochocki, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims: We hypothesize that administration of genistein or exercise improves outcomes in the High-Fat Diet (HFD)-fed mice. We predict that both genistein supplementation combined with regular exercise has additive beneficial effects. We hypothesize that male and female mice respond differentially to genistein and exercise and likely via varied mechanisms.

Aim1: Determine ability of genistein and exercise to modify metabolic state in HFD mice.

Aim 2: Determine ability of genistein and exercise to modify microbiome of HFD mice.

Background and Significance: A diet rich in high energy food such as HFD is known to result in obesity and cognitive deficits. HFD is also associated with metabolic syndrome, a major contributor to insulin resistance, type 2 diabetes, cardiovascular disease, loss of bone mass, and inflammation, and is a risk factor for neurodegenerative diseases like Alzheimer's and dementia. Genistein, a naturally occurring isoflavonic phytoestrogen, has been previously shown to improve tissue function and demonstrates anti-inflammatory, neuroprotective, and bone-protective properties. Similar benefits have been demonstrated for moderate exercise.

Preliminary Data and Plan: Prior investigations from our laboratories have found genistein diet (600 mg genistein/kg diet for 4-weeks) increases ischemic tolerance and is cardioprotective, improves resistance to bone fracture, enhances jejunum chloride secretion, and reduces serum glucose levels in the obese and diabetic ob/ob mouse. We also found treatment with exercise in the diabetic condition similarly improves fracture resistance and serum glucose levels. Our experimental design used 50 male and 50 female C57BL/6J mice. Mice were randomly divided into the following treatment groups (10 mice/group): lean controls; HFD, HFD+exercise, HFD+genistein, and HFD+genistein+exercise. Thus, the study includes five test groups per sex. Tissues were collected at the conclusion of the 12-week diet and exercise study.

Aim1: Determine ability of genistein and exercise to modify metabolic state in HFD mice.

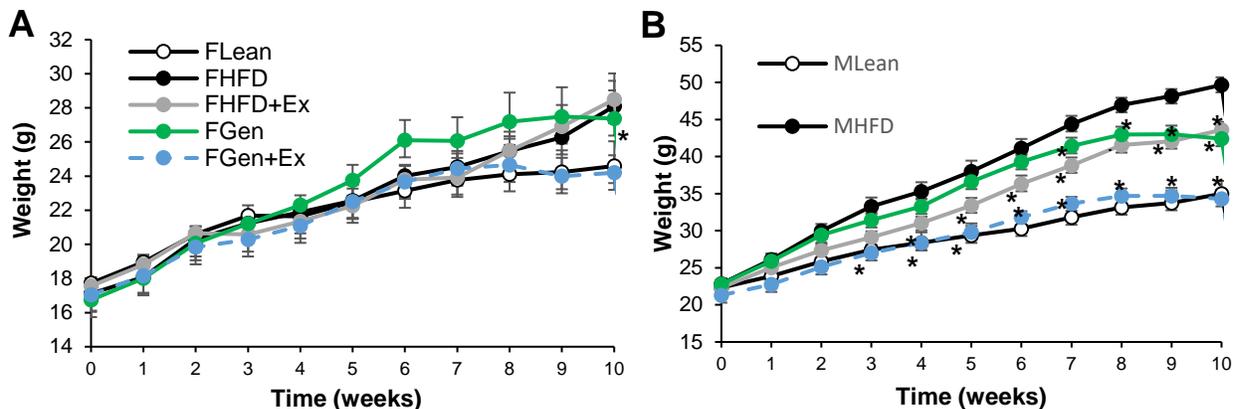


Fig. 1. Effects on body weight. A. Females: Mice fed high fat diet (HFD) or HFD+exercise (Ex), HFD+genistein (Gen) weight more than the HFD+Ex+Gen. n=10/group. **B. Males.** Mice fed high fat diet (HFD) weight more than those in the HFD+exercise (Ex), HFD+genistein (Gen) groups. Those in the HFD+Ex+Gen group have the most beneficial effects on weight-gain. n=8-10/group. Data are mean \pm SEM. * significant difference from HFD, $P < 0.05$

In female mice, the combination of HFD+Ex+Gen resulted in a significant 4g weight loss versus HFD alone (Fig. 1A). In male mice the effects of genistein-alone or exercise alone resulted in a 6 g weight loss compared to HFD, and in combination treatment a 15g weight loss compared to HFD was observed (Fig. 1B). We aim to correlate weight loss with serum markers of diabetic state, metabolism, overall health, satiety, and finally correlate these to markers of brain function.

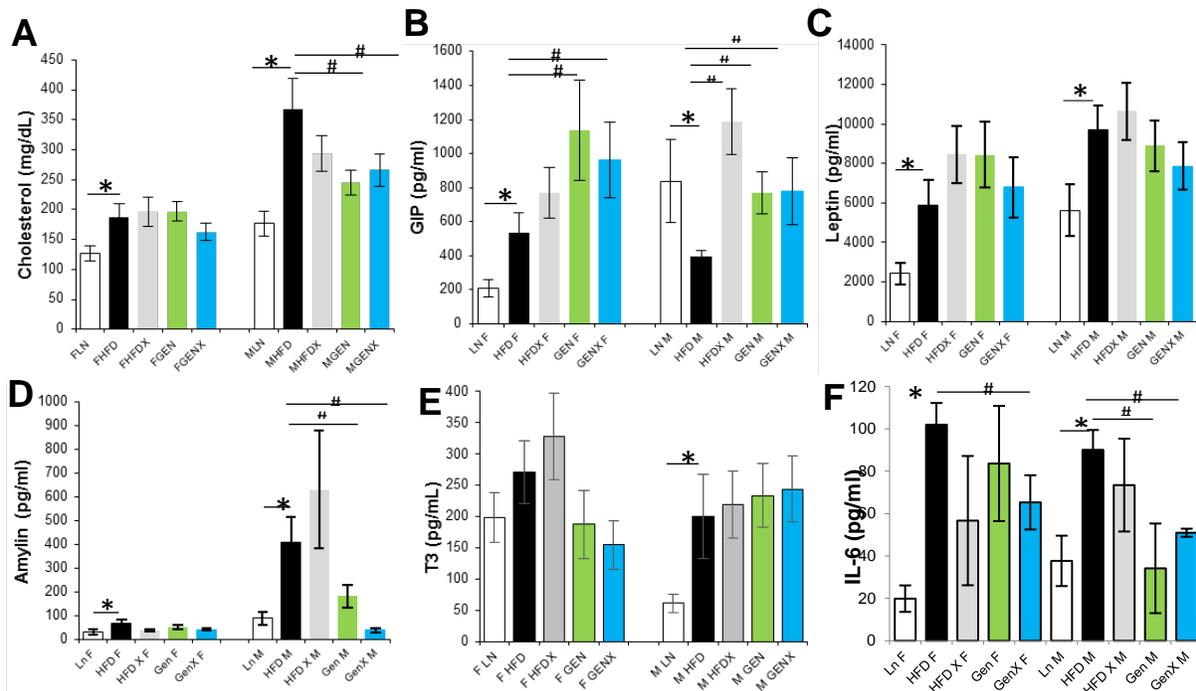


Fig. 2. Effects on serum profile. A. Cholesterol. As predicted HF/HS diet increased serum cholesterol in both female and male mice. Genistein and genistein/exercise significantly decreased levels in males only. **B. GIP.** GIP levels were increased in HF/HS females and decreased in HF/HS fed male mice. All treatments further increased GIP levels in males and females. **C. Leptin.** Leptin levels were increased by the HF/HS diet in males and females, and treatment had no effect. **D. Amylin.** Amylin levels were increased by HF/HS diet in both males and females and in males genistein and genistein/exercise returned levels back to leans. **E. T3.** T3 levels were significantly increased by HF/HS diet in males and there was no treatment effect. **F. IL-6.** IL-6 levels were increased by the HF/HS diet in both males and females, and genistein/exercise reversed this. (graph legend: open bar=lean, black=HF/HS, gray=HF/HS+exercise, green= HF/HS+genistein, blue=HF/HS+genistein+exercise). n=3-8/group. Data are mean \pm SEM. * significant difference from HFD, # significant treatment effect, $P < 0.05$

These data indicate that there are significant sex-dependent effects of genistein and exercise on key markers of health in serum: metabolic (cholesterol, T3), inflammation (IL-6), satiety and glucose regulation (amylin, leptin, GIP). The sex-dependent differences on weight gain are interesting, and we are excited to see how these differences translate to comparable benefits in bone, serum and brain health. We hypothesize that if weight is a predictor of Alzheimer's-like pathology, then the males will exhibit greater benefit attributed to exercise and genistein compared to female counterparts. We will evaluate differences between treatment groups in brain protein expression for markers of Alzheimer's pathology.

Recently, we determined a reversal of splenomegaly (associated with significant improvement in red-white pulp area) by exercise and genistein in this HF/HS model (*Buchan, St, Aubin, Fisher, Hellings, Castro, Al-Nakkash, Broderick & Plochocki. 2018. High-fat, high-sugar diet induces splenomegaly that is ameliorated with exercise and genistein treatment. BMC Res Notes. 11:752*). Moreover, we have shown that HF/HS induces metabolic changes in articular cartilage (EB 2019 abstract #1918) and improves fracture resistance (EB 2019 abstract #1917) and is reversed with low intensity exercise and genistein treatment. *Thus in the past year 1 manuscript has resulted from this funding.*

Aim 2: Determine ability of genistein and exercise to modify microbiome of HFD mice.

Evaluation for differences between treatment groups in microbiome: samples are currently being analyzed at ASU's microbiome core. We predict to complete work on this aim during the remainder of the current funding cycle and perform analyses during the upcoming months.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Effects of Norclozapine on beta Amyloid in Transgenic Mice- a potential new treatment option for Alzheimer's Disease? Pamela Potter, PhD (PI), Doug Jones, PhD (Co-I). Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Validate the effect of norclozapine on beta amyloid levels and pathology in the 3xTg-AD mouse.

Specific Aim 2: Treat mice with the delta opioid agonist SNC-80 to determine the effect of stimulating delta receptors on β -amyloid levels.

Background and Significance: The risk of Alzheimer's disease increases in patients who have been taking drugs that block cholinergic muscarinic receptors. Drugs in this class are used for multiple reasons: as antihistamines, to treat overactive bladder, for chronic pain, as antidepressants, as antipsychotics, and for irritable bowel syndrome. Stimulation of muscarinic receptors inhibits production of β -amyloid, the toxic peptide that accumulates in Alzheimer's Disease (AD). Administration of cholinergic antagonists increases deposition of β -amyloid in transgenic mouse models of AD. It has also been shown that lesion of cholinergic neurons in experimental animals increases production of β -amyloid. Treatment with muscarinic agonists could potentially decrease levels of β -amyloid and maintain G-protein coupling and function of muscarinic receptors.

The lack of selective muscarinic agonists that cross the blood brain barrier has hampered efforts to treat muscarinic dysfunction in AD. We observed that norclozapine, a metabolite of the antipsychotic clozapine, which is a partial agonist on M1 muscarinic receptors, decreased β -amyloid levels in transgenic mice who overexpress β -amyloid. In addition to being a partial agonist on M1 muscarinic receptors, norclozapine is also an agonist at delta opioid receptors. Thus, the benefit of norclozapine might be mediated by its opioid action, rather than via its muscarinic effect.

Preliminary Data and Plan: The current proposal was designed to compare the effects of norclozapine with those of the delta opioid agonist SNC-80, to differentiate which receptor causes the beneficial effect on β -amyloid levels that we observed. The muscarinic antagonists scopolamine and dicyclomine will be used to provide a negative control, which increases amyloid production. Scopolamine easily crosses the blood brain barrier and is known to accelerate the degenerative changes in one mouse model of Alzheimer's disease. Dicyclomine has been shown to increase β -amyloid in transgenic mice, so it will be used as another positive control. Sham-injected mice will be treated with sterile saline.

3x-Tg-AD mice have mutations of the human APP and presenilin genes, which make them more susceptible to increased formation of β -amyloid and tau, and they are a widely used animal model of AD. Dr. Douglas Jones, the project Co-I, is currently maintaining a breeding colony of these mice at MWU.

Proposed One-Year and Long-Term Outcomes:

1. Animal experiments will be completed and the data used for a publication regarding the effects of norclozapine versus SNC-80.

2. Informative data will also be used to design a larger study that may help to determine the potential usefulness of norclozapine in patient treatment.

Year End Progress Summary:

Thus far we have treated an initial group of fourteen mice with SNC-80, sterile saline, and dicyclomine. The brains from these mice are stored at -80°C to be analyzed with the rest of the mice that will be treated. We had to wait for another suitable cohort of mice to be born and grow to an appropriate age. Those mice are almost ready to be treated.

Thus we expect to be treating mice with norclozapine, scopolamine, norclozapine, SNC-80 and sterile saline to add to the number already treated. We expect to be doing treatments from the period March through May in order to reach sufficient numbers for analysis. When all treatments are completed, samples of brain tissue from all of the mice will be analyzed for β -amyloid₁₋₄₂. We have recruited a summer student who will be able to assist with treatment and analysis of the samples, and we expect to have the results of this study in June or July of 2019.

Project Progress Report
Northern Arizona University

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Longitudinal analysis of the gut microbiome-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 this work will be to understand the changes in the gut microbiome and metatranscriptome as an individual progress through amyloid- β deposition in the brain, and how that differs from healthy individuals over the same period. To accomplish this goal, we propose two interacting aims.

SA 1. Investigate composition and diversity of the gut microbiome longitudinally during progression of Alzheimer's Disease (AD) pathology in triple transgenic model of AD (3xTg-AD) and contrast this with control mice.

SA 2. Compare changes in the gut and brain metatranscriptome during progression of AD pathology in 3xTg-AD and control mice.

There is evidence that microbially-derived products (e.g. lipopolysaccharide) causes amyloid- β aggregation *in vitro*. Therefore, we hypothesize that the gut microbiome may influence AD development directly, through production of metabolites that cross the blood-brain barrier, or indirectly, through neuroinflammatory sequelae.

Background and Significance: The human body is host to trillions of microorganisms, collectively termed the human microbiome. Recent technological advances have vastly expanded our understanding of the human microbiome, and it is becoming clear that the human microbiome impacts diverse aspects of human health, including neurological health. It is well-established that pathogenic microbes can impact host behavior, such as altered fear response in rats infected with *Toxoplasma gondii* or increased aggression in mammals infected with rabies virus. There is increasing evidence that commensal host-associated microbiota can also impact the brain and even host behavior. Mechanistically, this may occur through stimulation of the vagus nerve, through microbially produced metabolites entering the circulatory system and possibly crossing the blood-brain barrier, or through microbially produced metabolites stimulating the immune system, among other mechanisms.

Preliminary Data: Recent work in humans suggests the composition and diversity of the gut microbiome differs in individuals with AD. AD patients were characterized by decreased gut microbiome richness (i.e., number of different types of microbes that are present) and decreased abundance of the bacterial genus *Bifidobacterium* relative to age-matched healthy controls. Work in transgenic mice supports the observation that gut microbiota differ in mice exhibiting AD pathology relative to wild-type mice, and illustrates a correlation between the gut microbiome composition and cerebral amyloid- β peptide levels or aggregation. While these results are promising, additional studies are required to determine potential causal relationships between gut microbiota alterations and AD pathology.

Experimental Designs and Methods: We propose to longitudinally investigate the relationship between the gut microbiome, the gut metatranscriptome (microbial and host mRNA in the gut, a profile of microbial activity), and the brain metatranscriptome in 3xTg-AD mice, which present with hallmarks of AD pathology including amyloid deposition and neurofibrillary tangles, and wild-type

B6129SF2/J mice. Fecal samples will be collected weekly from mice for a total of 52 weeks. Mice will be sacrificed at 8, 24, and 52 weeks and the frontal cortex and hippocampus will be dissected and prepared for metatranscriptomics and immunohistochemical analysis of amyloid- β plaques tau protein as previously described.

Proposed One-Year and Long-Term Outcomes:

This project may ultimately lead to early markers (detectable through fecal samples) of amyloid- β deposition in pre-Alzheimer’s patients, and to potential approaches to Alzheimer’s prevention through alteration of the gut microbiome. Secondly, this work will allow NAU to develop a framework for conducting AD microbiome research. Collection of brain transcriptome data following sacrifice of mice will allow us to investigate potential microbial activity at the pathological site and the relationship between human AD transcriptome data and 3xTg-AD transgenic mouse transcriptome data in a pooled analysis with the Arizona Alzheimer’s brain transcriptome data allowing us to better understand the 3xTg-AD transgenic mice as a model for human AD. Completion of these studies will provide strong preliminary data toward submission of an NIH R01. We have identified an FOA that is well suited for the proposed research: PAR-15-359 (*Novel Approaches to Diagnosing Alzheimer’s Disease & Predicting Progression*).

Year End Progress Summary.

We have established a colony of 60 wild-type B6129SF2/J and 62 3xTg-AD 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 frontal cortex and metatranscriptomics. We observe a striking difference in the microbiome composition of our wild-type and 3xTg-AD mice between 3-12 weeks, and these differences remain apparent for the duration of our experiment (Figure 1). This is in part to be expected, as the genetic background of mice is known to impact microbiome composition, but the effect was larger than we anticipated. We observe 18 bacterial genera from 4 bacterial phyla that differ in their abundance between the wild-type and 3xTg-AD mice using ANCOM. In subsequent studies, we will have the opportunity to determine whether

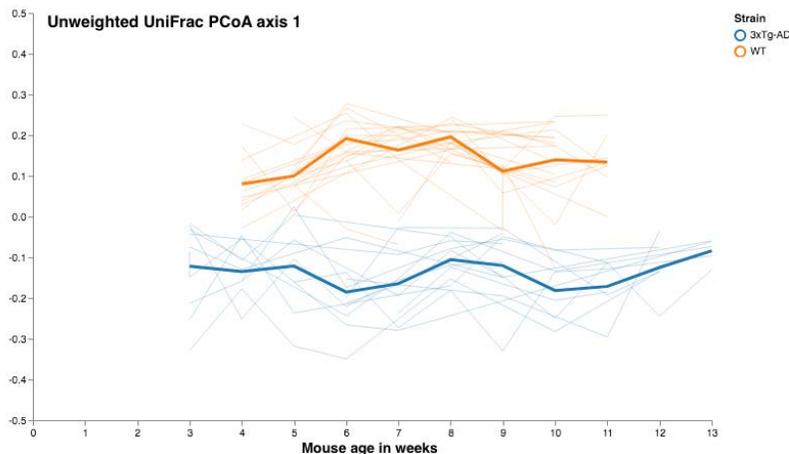


Figure 1: Unweighted UniFrac PCoA axis 1 versus time. Wild type and AD mice differ in the composition of their gut microbiomes, as indicated by the independent grouping of these sample types on PCoA axis 1 (y-axis in this plot). These differences between community compositions are apparent throughout the duration of our experiment. Thin lines track individual mice over time, and dark lines indicate the average across individuals.

these differences in microbiome composition may be causative of AD.

We observe that 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). When we work backwards from this model, we can identify specific taxa that are changing with time, and therefore with progression of 3xTg-AD mice through disease. In some cases we observe bacterial taxa that change in abundance

over time more so 3xTg-AD mice (e.g., Turicibacter in Figure 2a). Other bacterial taxa change

more over time in our wild type mice (e.g., Lachnospiraceae in Figure 2b), and some display similar longitudinal abundance profiles, though differing succession patterns, in both the wild-type and 3xTg-AD mice (e.g., Clostridium in Figure 2c). These differences across our mouse strains point toward certain taxa that may be protective against AD progression (e.g., Lachnospiraceae) or causal of AD progression (e.g., Turicibacter). We are continuing to sequence and analyze longitudinal fecal samples from 3xTg-AD and wild-type mice as they age. Moving forward, we will use a fecal transplantation experiment to assess whether the differing microbiome states illustrated in Figures 1 and 2 have the ability to induce AD-like pathology in wild-type mice or to earlier disease progression in 3xTg-AD mice. If so, this will clearly implicate the gut microbiome in AD.

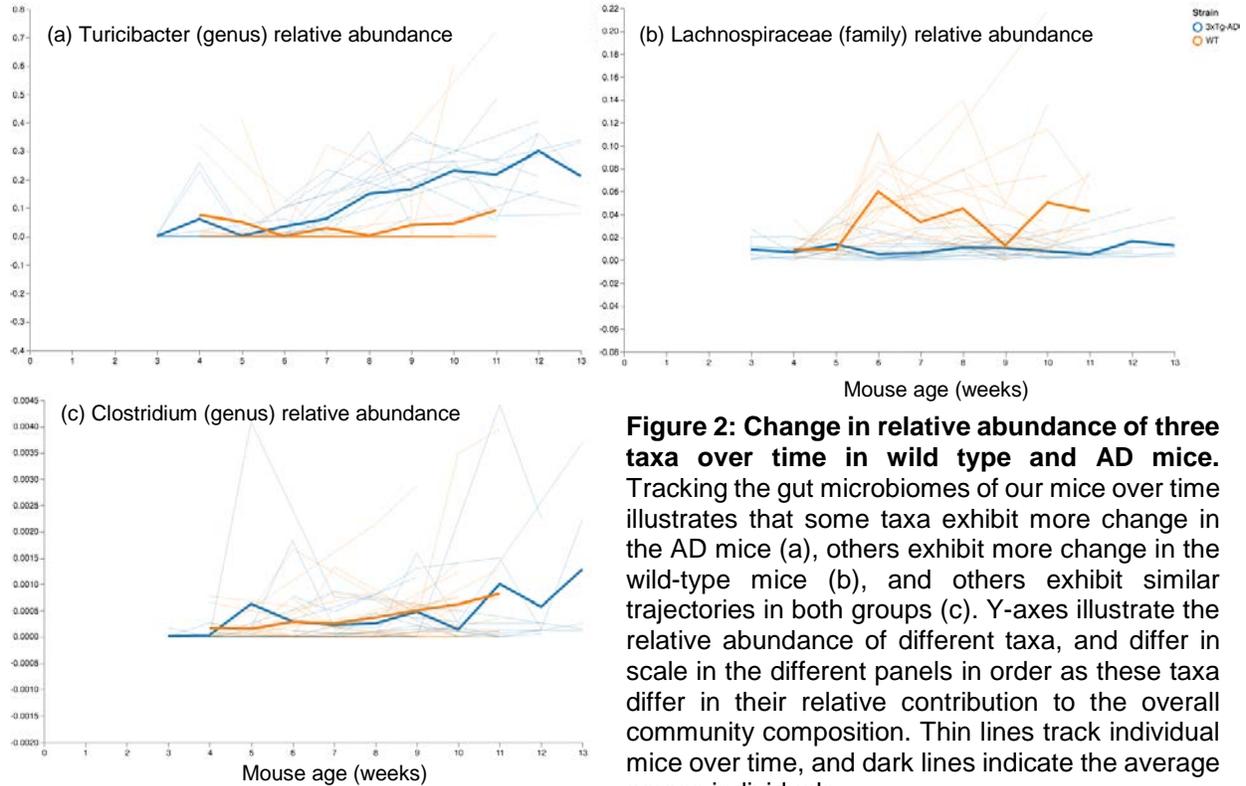


Figure 2: Change in relative abundance of three taxa over time in wild type and AD mice. Tracking the gut microbiomes of our mice over time illustrates that some taxa exhibit more change in the AD mice (a), others exhibit more change in the wild-type mice (b), and others exhibit similar trajectories in both groups (c). Y-axes illustrate the relative abundance of different taxa, and differ in scale in the different panels in order as these taxa differ in their relative contribution to the overall community composition. Thin lines track individual mice over time, and dark lines indicate the average across individuals.

Project Progress Report
Translational Genomics Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

CircRNA regulatory network analysis using multi-modal RNAseq data. Winnie S. Liang, PhD, Shobana Sekar, MS, Lori Cuyugan, MS, Geidy Serrano, PhD, Thomas Beach, PhD. Translational Genomics Research Institute, Arizona Alzheimer's Consortium, Banner Sun Health Research Institute.

Background and significance: Circular RNAs (circRNAs) are an evolutionarily conserved non-coding RNA species that are RNA formed by back-splicing events, presenting as covalently closed loops. These circular molecules were initially regarded as molecular artifacts that did not have any biological significance but with the advent of next generation sequencing (NGS) technologies coupled with efficient computational algorithms, numerous circRNAs have been reported recently. Specifically, these circular molecules have been found to be enriched in the mammalian brain, with well conserved sequences.

In previous work, we performed bioinformatics analyses to detect circRNAs in RNA sequencing (RNAseq) data generated from microdissected posterior cingulate astrocytes (10 Alzheimer's disease [AD] subjects, 10 no-disease [ND] controls) [1]. Following this study and having established and implemented a bioinformatics circRNA detection pipeline, we explored correlation of circRNAs expression in the context of both mRNA and miR expression from the same brain samples provided by Dr's Serrano and Beach at the Banner Sun Health Research Institute's Brain and Body Donation Program.

Year-end progress summary: Fresh frozen brain specimens were provided from four healthy elderly controls and include the inferior parietal lobe (IP), middle temporal gyrus (MTG), occipital cortex (OC), superior frontal gyrus (SFG), and cerebellum (CB). RNAseq analyses encompassed: (1) total RNAseq from total RNA, (2) circRNAseq from RNase R-treated total RNA, and (3) miRseq from small RNAs using total RNA as input. Total RNAseq and circRNAseq libraries were constructed using Illumina's Stranded Total RNA Library Prep Kit and miRseq libraries were constructed using Illumina's Small RNA Library Prep Kit. All libraries were sequenced on the Illumina HiSeq for paired 83bp reads, with the exception to miRseq libraries which were sequenced for single-end 50bp reads.

For integrated analyses, we first identified circRNAs that were detected in all samples, based on brain region, and that were called by six total circRNAs detection algorithms, including find_circ, CIRI, DCC, Mapslice, KNIFE, and CIRCexplorer. Next, we implemented an in silico network prediction workflow which first entails determining expression levels for each data type (SRPBM for circRNAs, RPM for miRs, and FPKM for mRNAs). In the final phase, we evaluated four possibilities: (1) high expression of circRNAs that coincide with high expression of target miRs, (2) high expression of circRNAs that coincide with low expression of target miRs, (3) low, or any, expression of circRNAs that coincide with high expression of target miRs, and (4) low, or any, expression of circRNAs that coincide with low expression of target miRs; where high expression corresponds to those events that are in the top 25% of the expression range and low corresponding to the bottom 25% of the range. The highest number of circRNAs (n=3,625) was identified in the CB with the lowest number (n=64) in the OC. Overall, we observed that for the CB, IP, and SFG, the largest number of circRNAs-miR-mRNA interactions is occurring in more lowly expression RNA species across all brain regions to suggest that circRNAs and miRs are influencing subtle changes in expression. In the MTG, the greatest number of interactions was observed for highly expressed circRNAs, highly expressed miRs, and lowly expressed mRNAs to suggest that elevated transcriptional regulatory activity is occurring in this region. Lastly, for the

OC, the highest number of interactions was observed for highly expressed circRNAs, lowly expressed miRs, and lowly expressed mRNAs, and as well as, lowly expressed circRNAs, highly expressed miRs, and lowly expressed mRNAs to suggest that there may be more active competition in transcriptional regulation between circRNAs and miRs in this region. We are currently reviewing and collating data and plan to submit a manuscript for review in 2019.

Reference: [1] Sekar S, Cuyugan L, Adkins J, Geiger P, Liang WS (2018) Circular RNA expression and regulatory network prediction in posterior cingulate astrocytes in elderly subjects. *BMC Genomics* 19(1): 340, PMID: 29739336.

ARIZONA ALZHEIMER'S CONSORTIUM

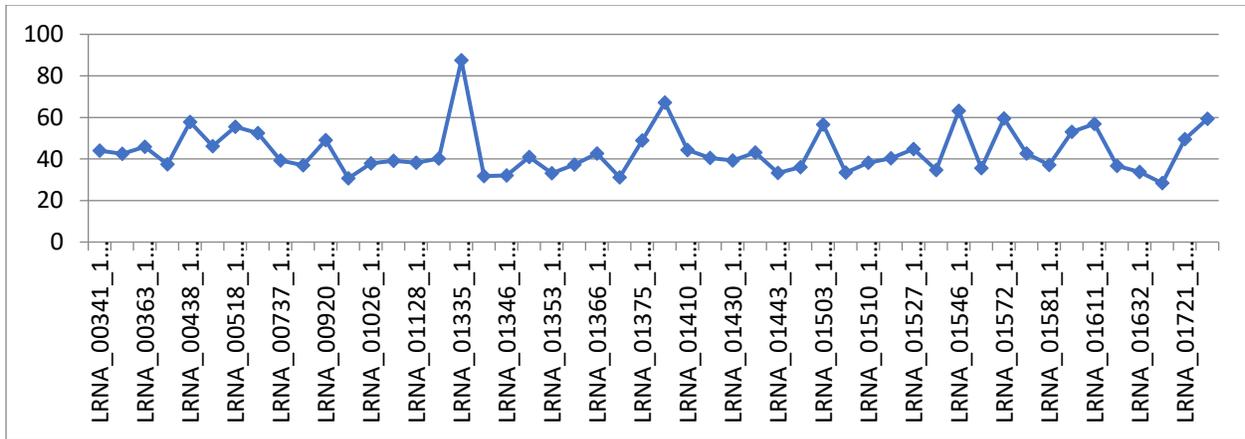
2018-2019 Scientific Progress Report

Whole genome sequencing of the superior frontal gyrus in Alzheimer's disease. Winnie S. Liang, PhD, Jonathan Adkins, BS, Daniel Enriquez, BS, Benjamin Readhead, PhD, Geidy Serrano, PhD, Thomas Beach, PhD, Joel Dudley, PhD, Diego Mastroeni, PhD, Eric M. Reiman, MD. Translational Genomics Research Institute, Arizona State University, Banner Sun Health Research Institute, Icahn School of Medicine at Mount Sinai, New York, Banner Alzheimer's Institute, Arizona Alzheimer's Consortium.

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. While the primary goal of the study is to perform RNA sequencing (RNAseq) of distinct cell populations and cell types across five brain regions, another goal is to evaluate if transcriptomic alterations may be associated with genomic alterations in DNA extracted from the superior frontal gyrus (SFG). This is due to the fact that somatic mosaicism and age-related accumulation of somatic mutations occurs in the human brain, and single nucleotide variants (SNVs) have also been observed in the hippocampus of AD brains [1]. The acquisition of cell-specific RNAseq data and region-specific whole genome sequencing (WGS) data enables quantitative trait analysis and the construction of multi-scale network modeling of AD brains so that we can better understand the genomic and transcriptional alterations that characterize pathogenesis in AD.

Year-end progress summary: TGen received 50 fresh frozen superior frontal gyrus (SFG) specimens from the Banner Brain and Body Donation Program (from 26 AD subjects and 24 healthy elderly control subjects). Processing and analysis of 30 subjects was covered in this project while the remaining 20 subjects were funded by the Nomis study. Approximately 25mg of each sample was used for genomic DNA extractions using the Qiagen DNeasy kit. High quality DNA was extracted from samples with a mean DNA Integrity Number (DIN) of 7.6. Samples were used to generate WGS libraries using 200ng inputs, Roche's Kapa Hyper Prep Kit, and xGEN IDT dual index UMI (unique molecular identifier) adaptors on the Agilent Bravo workstation. Size selection was performed to enrich for library molecules that are approximately 400bp long.

WGS libraries were equimolarly pooled and sequenced on the Illumina NovaSeq 6000 using for 2x150bp reads using the NovaSeq 6000 S4 Reagent Kit (300 cycles). We generated a total of 44,962,289,482 properly paired reads across all samples. Raw BCL files were converted to FASTQs and analyzed through TGen's internal Pegasus pipeline which encompasses alignment of sequencing data against the human reference genome (build hs37d5) and germline variant calling. Overall, we generated an average mapped coverage of 43.7X (see Figure below for distribution of coverages). All FASTQs and VCFs were transferred to ASU for downstream analyses.



Future directions: Analysis of WGS data is ongoing. A key component of analyzing the data is its integration with RNAseq data generated from laser capture microdissected (LCM) cell populations from the SFG of AD and healthy elderly subjects. Cell collections are currently ongoing and we will be generating LCM RNAseq data over the next few years to enable this integrated analysis.

Reference: [1] Parcerisas A, Rubio SE, Muhaisen A, Gomez-Ramos A, Pujadas L, Puiggros M, Rossi D, Urena J, Burgaya F, Pascual M et al: Somatic signature of brain-specific single nucleotide variations in sporadic Alzheimer's disease. *J Alzheimers Dis* 2014, 42(4):1357-1382. doi: 1310.3233/JAD-140891.

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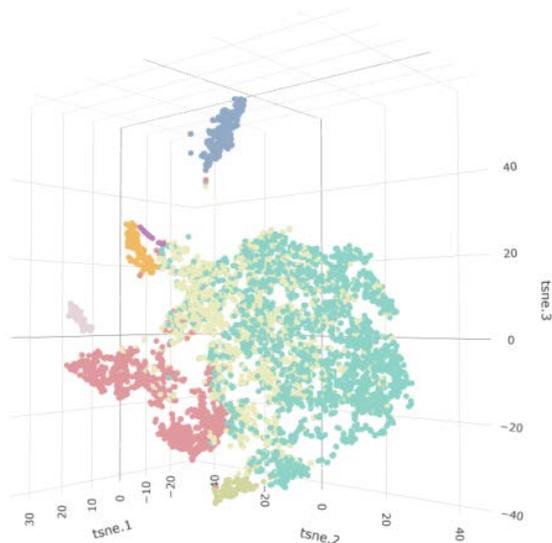
2018-2019 Scientific Progress Report

Single whole cell transcriptomic analysis of Alzheimer's disease. Winnie S. Liang, PhD, Daniel Enriquez, BS, Amir Elyderani, BS, Jerry Antone, BS, Benjamin Readhead, PhD, Jonathan Adkins, BS, Geidy Serrano, PhD, Thomas Beach, PhD, Joel Dudley, PhD, Diego Mastroeni, PhD, Eric M. Reiman, PhD. Translational Genomics Research Institute, Arizona State University, Banner Sun Health Research Institute, Icahn School of Medicine at Mount Sinai, New York, Banner Alzheimer's Institute, Arizona Alzheimer's Consortium.

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. The primary analysis for this proposal is construction of a transcriptomic reference data set generated using laser capture microdissection (LCM) of separate brain cell populations and RNA sequencing (RNAseq). We are complementing this approach using single cell and nuclei strategies (scRNAseq) that has become widely adopted in the community for characterization and assessment of cell sub-populations.

Year-end progress summary: We have tested, optimized, and evaluated single whole cell, as well as single nuclei, approaches on the 10x Genomics platform, which enables the measurement of up to thousands of mRNAs from individual cells or nuclei for up to tens of thousands of cells in a sample using barcoded gel-bead emulsions (GEM). While single nuclei approaches have been most commonly used, evaluation of whole cell approaches is necessary as mRNA transcripts that would not be captured using a single nuclei approach may be biologically meaningful, particularly in the context of disease and AD.

In order to compare whole cell versus nuclei analyses, fresh frozen superior frontal gyrus samples were provided from Dr's Geidy Serrano and Thomas Beach at BSHRI, and which included one no disease control (ND) and one AD subject. For our analyses, we generated quadruplicates using different library preparation kits (3' versus 5' mRNA) and comparing whole cell versus nuclei tissue dissociations. We observed that whole cell approaches did not perform



as well as single nuclei dissociation, likely due to sample quality as specimens were fresh frozen. This observation was reflected by low expression of genes identified in the AD sample; such expression was also lower in the AD sample compared to the ND to suggest that the AD sample was more sensitive to dissociation compared to the ND sample. For both the ND and AD preparations, the 5' mRNA approach demonstrated better performance as reflected by a higher number of genes detected per cell. Further, while single nuclei RNAseq appears to be more feasible when analyzing fresh frozen brain, we were able to identify distinct cell populations in both the ND and AD brains. Cell populations identified in ND and AD nuclei include astrocytes, endothelial cells, neurons (pyramidal, granule, GABAergic), and oligodendrocytes.

Interestingly, in the AD sample (figure to the left), a neuronal stem cell population was also identified, which was not detected in the ND sample.

Future directions: We are currently putting together a manuscript to describe our findings from this pilot study. We have also completed single nuclei libraries from 26 ND and 24 AD SFG samples and will be sequencing these libraries to construct a larger reference data set to complement our LCM study.

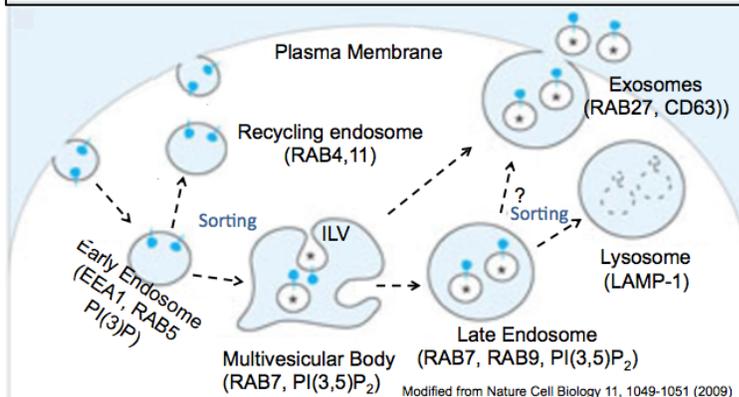
ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Investigating the role extracellular vesicle release in neurodegenerative disease. Kendall Van Keuren-Jensen, PhD, Rita Sattler, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Project description: Disruption of the endosomal-lysosomal pathway is an early hallmark of Alzheimer's disease (Cataldo et al., 1996; Cataldo et al 2000; Ginsberg et al. 2010; Xu et al., 2016). Exosomes are generated as part of the endosomal pathway, and changes in the trafficking of cargo or the biogenesis of vesicles along the pathway will have a direct impact on exosomes

Figure 1. Diagram of the major vesicle populations in the endosomal pathway. There is directional movement and maturation of vesicles through the pathway. Endosomes can act as sorting centers and have specific protein (RAB) and lipid characteristics. There are three potential destinations for proteins entering the cell through the endocytic pathway: recycling to the membrane, degradation in the lysosome, and extracellular release through fusion of Multivesicular Bodies with the plasma membrane.



and their contents. The balance of toxic proteins destined for degradation in the lysosome or for release in exosomes is altered in Alzheimer's disease (AD). Amyloid beta (A β) is the principal protein constituent of extracellular deposits (plaques) in the brains of subjects with AD. Increased A β localization in abnormal endosomes is found to occur simultaneously with early elevations of A β in Alzheimer's disease (Cataldo et al. 2004). Essential endosomal effector proteins, such as rab5 and rab7, are up regulated in subjects with mild cognitive impairment and early AD (Ginsberg et al., 2010). Exosomes contain disease-relevant proteins such as A β , tau, TDP-43, and α -synuclein (Rajendran et al., 2006; Winston et al., 2016; Sproviero et al., 2018; Danzer et al., 2012; Ngolab et

al., 2017).

Figure 1 is a diagram of the endosomal pathway depicting the major vesicle populations. Early endosomes and late endosomes are sorting organelles, from them cellular components are directed to different trafficking routes. Early endosomes traffic materials back to the plasma membrane through recycling endosomes, intraluminal vesicles (ILV) form within endosomes, creating multivesicular bodies (late endosomes) that fuse with the lysosome (for degradation) or the plasma membrane (releasing intraluminal vesicles as exosomes). The balance and function of the endosomal and lysosomal pathway is disrupted with age and in neurodegenerative diseases (Lipinksi et al., 2010; Lopez-Otin et al., 2013; Komatsu et al., 2006; Lee et al., 2007; Filimonenco et al, 2007; Adamec et al., 2000; Gowrishankar et al., 2015; Orr and Oddo, 2013; Wolfe et al., 2013; Maxfield, 2014).

The push and pull between the final sorting decisions in the endosomal pathway, degradation by lysosomes or release via exosomes, may be an early contributor to AD pathogenesis. The promotion of autophagy and the lysosomal pathway induces multivesicular body fusion with lysosomes and reduces exosomal release (Fader et al., 2008). On the other side,

reduced lysosomal function increases exosome release (Alvarez-Erviti et al., 2011) and more inclusion of misfolded seed proteins that are propagated to neighboring cells (Emmanouilidou et al., 2010; Danzer et al., 2012). Early in AD pathogenesis there is increased detection of lysosomal proteins in exosomes (Goetzl et al., 2015). A clearer understanding of how cargo is sorted intracellularly will be critical to understanding the mechanisms that affect trafficking of A β in exosomes in early disease pathogenesis, and as a source of reliable biomarkers for AD. We propose that the disruption of the endosomal pathway, with age and genetic risk factors for disease, alters exosome release and the clearance of A β in AD (Fader et al., 2006, 2008; Alvarez-Erviti et al., 2011, Fujiwara et al., 2013).

Our laboratory has been interested in the extracellular RNA cargo changes associated with neurodegenerative diseases. We have evaluated several biofluids for changes in the expression levels of extracellular RNAs. These data are typically far removed from the source of change (neurons in the central nervous system). Using these cell lines, differentiated into cell types that we can examine in greater detail, provide us with the opportunity to look at how endosomal or lysosomal function might change the cargo we detect in vesicles. We will examine the extracellular RNA cargo released from iPSCs differentiated into cortical neurons from control subjects and subjects that had APP and PSEN mutations. Dr. Brafman, at ASU, generously provided the cells.

Aim: We propose to establish new molecular models to study cargo sorting, as well as for export (exosomes) as potential disease-causing mechanisms as well as potential biomarkers. We will grow neurons and use lysosomal as well as exosomal inhibitors to understand their effects on exosomal cargo. We are also using the tools developed in our previous grant, to assess long read sequencing to examine transcript level changes in the cells and in the cargo. We are currently in the process of growing the cells. We have also been simultaneously using long read sequencing through PacBio and Oxford Nanopore.

Progress Summary: Dr. Brafman has provided the IPS cells and Dr. Sattler is currently growing them and differentiating them into neurons. We will be working closely to collect supernatant and isolate vesicles for characterization.

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The influence of APOE variation on cognitive performance in outlier phenotypes of aging.
Matt Huentelman, PhD, Edward Zamrini, MD, Lee Ryan, PhD, Elizabeth Glisky, PhD.
Translational Genomics Research Institute; Banner Sun Health Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: Specific Aim 1: Investigate the APOE E4 allele frequency in top performing individuals across all ages in the MindCrowd cohort. Individuals who score in the top 1% of their age bracket be recruited electronically to provide a dried blood spot sample via the mail. APOE genotyping will be performed on the DNA isolated from the dried blood and statistically compared to known APOE frequencies in the general population. We hypothesize that the E4 frequency will be lower in the top 1% cohort as a whole and will exhibit a greater selection against E4 in the older ages of MindCrowd.

Specific Aim 2: Explore the APOE E4 allele frequency in the Arizona Longevity Study at Banner Sun Health Research Institute. All individuals enrolled in the Longevity Study will be recruited to provide a dried blood spot sample either via mail or in person during their next visit to the research clinic. APOE genotyping will be performed on the DNA isolated from the dried blood and statistically compared to known APOE frequencies in the general population. We hypothesize that the E4 frequency will be lower in this cohort as a whole.

Background and Significance: The role of the APOE E4 allele is well demonstrated in the area of Alzheimer's disease where it dramatically increases an individual's risk for the disease in a dose dependent fashion. However, much less is known about the effect of E4 in early life as well as its impact on cognitive performance in general in non-demented individuals. In this study we will utilize two cohorts of individuals with top level cognitive performance compared to their matched peers and we will explore the frequency and impact of the APOE E4 allele.

Preliminary Data and Plan: Both experimental cohorts are already in existence and have been followed for 5 years or more. Both cohorts have a demonstrated track record of being very participatory in ancillary studies, therefore, we expect recruitment into our proposed work to be of no issue. The dried blood spot (DBS) collection and APOE genotyping approach has been utilized in the MindCrowd cohort already with success. Individuals will be recruited either electronically or in-person during their regularly scheduled visits. Blood specimens will be collected via finger prick onto Whatman P card filter paper. 1mm punches from a DBS will be used for PCR of the APOE locus followed by HhaI enzyme digest to generate the characteristic APOE banding patterns that may be used to determine APOE allelotypes. Statistical analysis will compare our findings with public databases regarding APOE allele frequencies.

Proposed One-Year and Long-Term Outcomes: By the end of this funding year we expect to have APOE genotype information for approximately 2,000 individuals (half from each study). These individuals are outliers in their cognitive performance related to their age-matched peers. We plan to explore the frequency of the Alzheimer's disease risk associated E4 allele in these individuals. We predict that the E4 allele will be found in lower frequencies in our selected cohorts due to their higher than average cognitive performance. We also expect to apply for federal grant funding to further our efforts in this area.

Year End Progress Summary:

Specific Aim 1: We have been recruiting dried blood spot samples from MindCrowd – focused on the top 1% of performers as well as the 50th percentile group as study-specific controls. Recruitment is still on-going but is expected to be completed by the end of the granting period. Samples already in hand are also being staged for APOE genotyping as they arrive. During this year we have focused on two additional approaches to optimize our dried blood based genotyping approach; (1) the transition from agarose gel to TapeStation analysis of APOE genotypes. This move is important because it improves the test/re-test reliability of the genotyping calling, it simplifies the workflow, it decreases the costs, and it is also more amenable to high through allele calling via the use of image analysis approaches that would dramatically decrease lab personnel time require to report an APOE genotype. We also have developed quality control approaches – via our work with BSHRI – to identify genotypes that are of lower quality and should be annotated with a lower confidence indication with regards to their genotype, and (2) we have been testing automation equipment that would permit the hands-free isolation of DNA from dried blood spot samples thereby further improving the cost-effectiveness of this approach.

Specific Aim 2: This study is a new study and much of our efforts have been focused on: (1) getting the study documentation in place and approved (contracts, protocols, IRB submissions and amendments), (2) pilot testing of dried blood spot collection and analysis approaches – we have now optimized how this will happen as well as the mechanics associated with transfer of samples between teams for analysis, and (3) testing of a small set of samples with known genotypes to determine test/re-test reliability as well as to identify quality assurance and control parameters for dried blood spot APOE analysis. During the remaining months for the grant we will initiate the collection and analysis of samples from the Arizona Longevity Cohort with the goal of completing the analysis of as many samples as possible during the remaining time. We predict that this will be less than the hoped for entire cohort, however, both research teams are committed to continuing this work after the granting period to generate the necessary APOE information for the cohort for future use.

Project Progress Report
University of Arizona

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Modifiable Health & Lifestyle Factors in Brain Aging and Alzheimer's Disease. Gene Alexander, PhD, David Raichlen, PhD, Geoff Ahern, MD, PhD, Thomas Beach, MD, PhD, Richard Caselli, MD, Kewei Chen, PhD, Matt Huentelman, PhD, Yann Klimentidis, PhD, Eric M. Reiman, MD, Lee Ryan, PhD, Ted Trouard, PhD. University of Arizona; Banner Sun Health Research Institute; Mayo Clinic Arizona; Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: This proposal requests support for a cross-institutional, highly collaborative research project, including investigators from the University of Arizona, Banner Sun Health Research Institute, TGen, and Banner Alzheimer's Institute. The project will provide the essential data and methodological developments in support of a multi-disciplinary research program with the goal of advancing our understanding of how common health-related factors and lifestyle characteristics impact brain aging and the risk for Alzheimer's disease (AD). To accomplish this goal, we have established a multi-disciplinary collaborative team of Arizona Alzheimer's Consortium (AAC) investigators, including researchers in the fields of neuropsychology, behavioral neurology, neuroimaging, neuroscience, genetics, statistics and public health, biomedical engineering, and exercise science/sleep behavior. The proposed hypothesis-driven, research program will implement "state-of-the-art" acquisition of physical activity and sleep quality using actigraphy and self-report measures to augment tests of cognition, MRI of brain structure, function, and connectivity, PET imaging of AD pathology, CSF and blood biomarkers, genetics, and post-mortem brain pathology already planned for a unique Arizona-based older adult cognitively-unimpaired cohort. We hypothesize that health-related lifestyle characteristics, including exercise/physical activity and sleep quality, moderate cerebrovascular, genetic, and other health risk factors to influence brain aging and the risk for AD by altering brain networks that depend on frontal and temporal regions and the integrity of connecting white matter.

The proposed project will address the following specific aims: 1) to determine how a) exercise/physical activity and b) sleep quality influence cognitive performance in older adults with differential risk for AD; and 2) to develop, evaluate, and implement novel methods of processing and analysis for physical activity and sleep quality time-series data to identify new behavioral and physiological biomarkers for age-related cognitive decline and the risk for AD.

Additional Goals: This study will provide substantial added value with key pilot data to 1) provide a unique and rich dataset to support cognitive aging and preclinical AD research for aging and AD investigators across Arizona, 2) explore how MRI brain structure, function, and connectivity, and PET AD pathology relate to physical activity and sleep quality differences in older adults; 3) investigate how genetic variation related to the risk for AD and cognitive decline are influenced by physical activity and sleep quality, 4) provide the unique opportunity to evaluate how differences in physical activity and sleep quality ultimately relate to post-mortem brain pathology, 5) support submissions of new external collaborative grant proposals on brain aging and the risk for AD, and 6) enhance efforts for community outreach and recruitment efforts across Arizona.

Background and Significance: The population of older adults is expected to grow rapidly over the next two decades and public health programs, in Arizona and nationally, will need to respond to this escalating growth, including an increase in Alzheimer's dementia and associated cognitive decline. Whereas genetic factors, like apolipoprotein E e4 genotype, and cerebrovascular risk factors, like hypertension, can increase the risk for AD, aerobic exercise can improve cognition

during aging and may reduce the risk of AD, yet the mechanisms underlying these benefits have not been fully elucidated. Studies investigating cognition and brain imaging in older adults are critically needed to determine how increased physical activity and exercise support healthy brain aging, while reducing the risk for AD. In addition, the importance of sleep quality is an emerging and rapidly growing area of research that may reflect a key factor for cognitive aging and the risk for AD, including influencing learning and memory in aging and the clearance of AD pathology.

Preliminary Data: We have previously shown that differences in physical activity in young adults are associated with differences in regional patterns of functional brain connectivity, with endurance athletes showing areas of increased functional connectivity in frontal brain regions (Raichlen et al., *Frontiers in Human Neuroscience*, 2016). Further, we have developed and applied a new analysis method for tracking consistency in daytime physical activity with actigraphy monitors and applied it to a cohort of 11,694 participants 6 to over 85 years of age. Given that current studies do not typically include clinical and cognitive assessments or the potential for evaluating brain at autopsy, the application of our physical activity and sleep measures in the current proposed cohort will provide a unique research opportunity.

Proposed One-Year and Long-Term Outcomes: This work will be leveraged to support planned complementary projects investigating effects of differences in physical activity and sleep quality on cognition and brain structure and function, as well as the relation to genetic risk for AD. Together, these studies reflect collaborations focused on developing externally funded grant proposals, as part of a larger multi-disciplinary, collaborative research program, to investigate how cerebrovascular risk factors, differing levels of physical activity/aerobic fitness, and sleep quality impact brain aging and the preclinical risk for AD. The proposed research will provide novel and rich datasets with which to publish findings that will advance our understanding of the brain changes associated with multiple health-related factors that may either enhance or diminish the risk for dementia and age-related cognitive decline. Importantly, it is expected that this dataset will provide essential pilot data to support new applications during the latter half of the project year for proposals seeking external funding from NIH planned for submission. Specifically, this project will provide key data and methodological developments to support planned grant applications by the project investigators, including NIH applications to investigate the effects of differences in exercise/physical activity and sleep quality on brain aging and cognitive function, including longitudinal prediction of age-related decline and the interactive effects of genetic risk for AD on the trajectories of brain aging.

Year-End Progress Summary: We have made significant progress in our studies on individual differences in health factors and lifestyle characteristics for brain aging and the risk for AD. Data collection for physical activity and self-report measures in this unique Arizona cohort of the Brain Body Donation Program in a collaboration between the University of Arizona, Banner Sun Health Research Institute, TGen, and the Banner Alzheimer's Institute, is fully underway, providing a novel core resource for AD and aging research for use by multiple investigators at the University of Arizona, as well as across Arizona and nationally. It is expected that building 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 effort to support new grant submissions and our developing plans for our NIA center grant renewal. A manuscript applying our novel method of actigraphy pattern analysis has been published showing that less consistent physical activity was associated with increasing age and greater mortality (Raichlen et al., *Journal of Gerontology: Biological Sciences and Medical Sciences*, 2018). We also have two publications showing that a set of novel genetic factors are related to habitual physical activity (Klimentidis et al., *International Journal of Obesity*, 2018a, 2018b). Two additional papers are in submission

showing the relation between physical activity and brain structure (Raichlen et al., submitted), as well as the potential impact of pollution on brain structure in an aging cohort (Furlong et al., submitted).

A new \$3.7M NIA grant has been funded to supplement our Arizona Alzheimer's Disease Center (ADC) to establish a new Brain Imaging and Fluid Biomarkers Core (Core Leader: Alexander; Co-Investigators: Reiman (ADC PI), Beach, Ahern, Kuo, Trouard, Ryan, Su), providing enhanced access and expertise for the use of MRI, PET, CSF, and blood biomarkers in collaborative AD and aging research across Arizona. We plan to further incorporate our physical activity lifestyle measures as additional technology-based biomarkers into this new core to provide expanded cutting-edge markers for preclinical AD risk. In addition, a \$120K collaborative pilot study between the University of Arizona and University of Florida, Gainesville has been funded by the McKnight Brain Research Foundation to test a novel approach to reduce brain aging using near infrared light stimulation (MPIs: Alexander, Bowers, Woods). A new \$3.8M collaborative NIA grant has also been submitted to further evaluate the use of near-infrared stimulation to reduce the risk of AD (MPIs: Alexander, Bowers, Woods). Initial NIA R56 grant funding of \$300K for a collaborative research project was awarded to evaluate the neuroimaging and cognitive effects of a novel cognitive decision-making task in older adults (PI: Wilson; Co-Investigators: Alexander, Ekstrom, Chou, Andrews-Hanna) and a follow up complementary \$1.3M NIA grant was submitted to expand this research effort. In addition, a new \$3.8M NIA grant is planned for submission in spring, 2019 to investigate factors influencing brain aging and the risk for AD (MPIs: Alexander, Raichlen).

Work from this AAC project also supports ongoing studies of physical activity 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 is currently 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 to vigorous activity is associated with greater brain volume in regions of frontal cortex. An abstract of this work was presented at the McKnight Reception of the Society for Neuroscience in San Diego, CA in November, 2018. In additional abstracts presented at the same SFN meeting, we also showed that 1) high levels of self-reported physical sport activity were related to less volumes of white matter hyperintensity (WMH) lesions in healthy older adults (Franchetti et al., SFN, November, 2018), 2) that hippocampal volume mediates the relation between age and self-reported memory complaints among those with hypertension (Van Etten et al., SFN, November, 2018), and 3) that healthy aging is associated with an increasing relation between WMH lesion load and regional cortical thickness that is distinct from common vascular risk factors of aging (Bharadwaj et al., SFN, November, 2018). In addition, Drs. Alexander and Raichlen have been invited to give a special symposium on their collaborative work on physical activity and the aging brain at the May, 2019 meeting of the American College of Sports Medicine in Orlando, FL.

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Neuronal pentraxin receptor 2 (NPTX2): A promising target for preserving memory circuits in normative aging and in Alzheimer's disease. Carol A. Barnes, PhD, Alejandro Terrazas, PhD, Monica K. Chawla, PhD, Theodore P. Trouard, PhD, Paul F. Worley, MD. University of Arizona; Johns Hopkins University; Arizona Alzheimer's Consortium.

Specific Aims: Recent findings from Worley's group (Xiao et al., 2017, eLife) have shown that NPTX2 is markedly depleted in brains and in CSF of individuals with AD diagnosis at autopsy. Levels of cognition and hippocampal volume were positively correlated with CSF levels of NPTX2 in these patients. By contrast, human subjects with neuropathological findings of AD who were cognitively normal at death (asymptomatic AD) exhibited normal levels of brain NPTX2. In fact, low CSF levels of NPTX2 may well be an excellent biomarker for measuring defects in neural circuits observed in patients with AD. Taken together, these findings support the premise that NPTX2 may represent an age-related resilience factor. We will begin to test this hypothesis in the three Aims listed below:

Aim 1: Hypothesis: Regardless of age, rats with the highest levels of cognition within their age group will have correspondingly higher brain levels of NPTX2.

Aim 2: Hypothesis: NPTX2 knockout rats (NPTX2 KO) will exhibit accelerated normative brain aging that results in cognitive deficits and changes in hippocampal volume and connectivity.

Aim 3: Hypothesis: Circuits critical for memory will be disrupted in NPTX2 KO rats, as assessed by high-density ensemble recordings of single units and local field potentials.

Background and Significance: One of the most pressing unanswered questions in the biology of aging is why chronological age is a major risk factor for neurodegenerative disease. During normative aging the brain undergoes minimal neuron loss. We know, however, that there are age-related changes in synaptic connectivity and function. This can range from reduced plasticity at functional synapses in old brains (e.g., less durable LTP, overactive LTD), to synapse-specific loss of function (e.g., silent synapses) or reduction of actual synaptic contacts. NPTX2 is critical for normal synaptic function, is secreted by axon terminals, and participates in strengthening of synaptic connections. Because *in vitro* brain slice recordings of NPTX2 KO mice have suggested that there is hyperexcitability in hippocampal CA1 circuits, we propose to examine this synaptic dysfunction and behavior in awake freely behaving NPTX2 KO rats.

Preliminary Data: Worley's laboratory has recently created the NPTX2 KO rat, and is making them available to the Barnes laboratory. We currently have 12 animals, 4 of whom have cleared quarantine. We have begun to test these animals (2 wildtype and 2 knockout) on a battery of tasks that tap into hippocampal, perirhinal, entorhinal and prefrontal cortical function. We have set up two other tasks that examine motor function (the rotarod) and anxiety (elevated zero maze) that we will use to further test these animals. While we do not have the ability to make a statement about cognition without full analysis of the data, and more rats in each group, we did notice two unusual features expressed by the two NPTX2 KO rats. The first was the tendency of the KO rats to vocalize more than the wildtype. There are normally individual differences in vocalization in any group of rats – but this was particularly noticeable in these animals. Another finding was the tendency for the KO rats to intermittently cease behavior (for example, in the Morris water

maze) and then ‘restart’ the behavior. We are curious to determine whether this is correlated with any abnormal electrographic events when these animals are implanted, and we record from the hippocampus.

Proposed one-year and long-term outcomes: We will submit an RO1 proposal to NIA using the preliminary data from this rat NPTX2 KO model, and will propose to also conduct behavior testing and recordings from NPTX2 KO rats who are crossed with APP transgenic rats. The prediction here is that low levels of NPTX2 will result in accelerated plaque accumulation in these APP crosses. For the RO1 we will also reach out to the Brain and Body Donation program that is directed by Tom Beach, and other datasets that would be helpful to establish links between NPTX2 levels and genetics such as David Bennett’s the Religious Orders study, and Emily Rogalowski’s SuperAger population.

Year-End Progress Summary: We did submit an RO1 proposal to NIA, using the preliminary data that we collected for the Worley NPTX2 KO rat model and we obtained permission to include in the grant brain tissue from three different human data banks: Tom Beach from the Brain and Body Donation program to assess NPTX2 in temporal lobe regions of cognitively normal versus those with a diagnosis of AD dementia, brain tissue from Rogalowski’s Super Ager population (with unusually good cognition for their age) and brain tissue from Kawas’s 90+ study (with a range of cognitive status in very old individuals). This grant was scored but did not make the payline, and we are planning to resubmit it for the July 5, 2019 deadline. We did obtain some very unexpected results, however, with respect to hippocampus-dependent behavior in our NPTX2 KO rats – instead of accelerating cognitive decline in middle aged rats, germline deletion of NPTX2 appears to confer a cognitive advantage. Specifically, the behavior data suggest that the KO rats learn the spatial version of the Morris watermaze task more rapidly than do the wild type animals. We were expecting greater excitability and network dysfunction from our ensemble recordings in the KOs, but the hippocampal firing rates were not increased in the knockout animals, and while we have more analysis to do, the place fields appear reasonably normal. This is not to say that these KOs are ‘normal’, they do exhibit odd behavioral stereotypies, but their hippocampus-dependent memory is not worse (nor are the circuit properties that we have thus far examined). Paradoxically with respect to our original predictions, Worley also has preliminary data suggesting a similar pattern in mice in which the NPTX2 KO is crossed with APP transgenics - this cross seems to protect against accelerated cognitive decline compared with APP^{swe} transgenic mice alone. These findings are fascinating because they may be pointing to alternative pathways that arise because of the developmental deletion that are strongly “pro-cognitive”. Paul is working now on producing a conditional NPTX2 KO rat, so that we can directly test these predictions.

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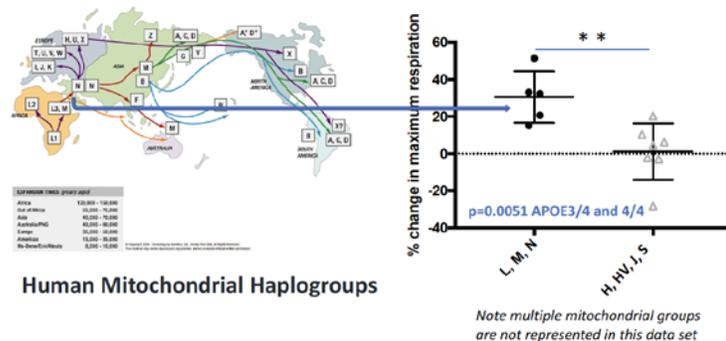
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Convergence of Maternal History of AD, Mitochondrial Haplotype, ApoE Genotype and Ethnic Heritage: Relationship to Alzheimer's Disease. Roberta Diaz Brinton, PhD, Thomas Beach, PhD, Fei Yin, PhD, Rui Chang PhD. University of Arizona; Banner Sun Health Research Center; Arizona Alzheimer's Consortium.

Background and Significance: The mitochondrial genome is unique in that this source of DNA is exclusively inherited from the mother, is distributed throughout the cell and DNA copy numbers in the thousands. The maternal lineage is also associated with increased risk of AD. Together, maternal inheritance of the mitochondrial genome, the increased risk for AD in persons with a mother with AD and the emergence of bioenergetic decline early in the prodromal phase of AD suggests convergence of factors linking maternally inherited mitochondrial DNA and AD risk. Mitochondrial DNA encodes catalytic subunits required for oxidative phosphorylation and ATP generation. Despite being just 2% of body weight, high ATP demand accounts for brain consumption of 25% of total body glucose, 15% of the cardiac output and 20% of total body oxygen. Functionally, synaptic transmission consumes 75% of all ATP generated in brain.

Substantial progress in determining nuclear genes that cause familial AD, increase the risk of early onset AD and increase risk of late onset AD has been achieved. In contrast, contributions of the mitochondrial genome remain unresolved. Although, an association between mitochondrial dysfunction and AD has been proposed for decades, a simple causal relationship between mitochondria and AD remains unresolved suggesting that multiple factors in addition to mitochondrial dysfunction drive risk of AD. *Thus we will test the hypothesis that persons with a mitochondrial haplotype associated with a low respiratory endophenotype coupled with APOEε4 genotype will have a maternal history of AD.* If this hypothesis is correct, then persons disproportionately at risk for AD should exhibit the mitochondrial haplotype / APOE genotype association. Women and African-Americans have a 2-fold greater lifetime risk whereas Hispanics are 1.5 times more likely to develop AD. *Thus, we hypothesize that the low respiratory mitochondrial endophenotype and maternal history of AD will disproportionately localize to women and persons of Hispanic or African origin.*

Impact of Mitochondrial Haplogroup on Respiratory Response in Human Neural Stem Cells Derived from APOE 3/4 & 4/4 Carriers



Our approach will investigate the association between 4 contributing factors and their impact on risk of AD: 1) maternal history of AD; 2) mitochondrial haplotype; 3) APOE genotype and 4) ethnic heritage.

Preliminary Data: An initial test of the mitochondrial haplotype impact on mitochondrial respiration was conducted using iPSC-derived neuron stem cells (NSC) from participants diagnosed with AD. Outcomes indicated that NSCs derived from APOE3/4 and 4/4 participants with mitochondrial haplogroups L, M, or N had a significantly greater mitochondrial respiratory

response to allopregnanolone in comparison to APOE3/4 and 4/4 participants with H,HV,J or S mitochondrial haplogroups.

Proposed One-Year and Long-Term Outcomes: Sample acquisition and mitochondrial haplotyping will be completed during the first 6 months followed by association analysis between maternal history of AD, mitochondrial haplotype, APOE genotype and ethnicity, clinical indicators of disease onset and severity. In total we anticipate completion of the project within the funding period. Plan for Grant Submission: Outcomes of these analyses will form the basis for an R01 proposal to investigate convergence of mitochondrial genomic risk factors driving AD progression in diverse populations. Translationally, outcomes of this pilot study will form the basis of mitochondrial targeted therapeutic development.

Year-End Progress Summary:

Participants

A total of 46 participants with complete hot flash diaries were included in the response analysis. Participants' ages ranged from 47 to 60 years old, with an average of 54.2 +/- 3.3 SD years old. Participants had on average 17.3 +/- 3.2 SD years of education. 4 participants were Asians, 2 were black or African Americans, 35 were Caucasians, and 5 were unknown.

Mitochondrial Haplotyping

Of the 40 participants for which mitochondrial haplotyping was possible, Haplogroup H had the greatest representation in this cohort (see treatment by mitochondrial haplogroup in 1). Because haplogroup H was the most common mitochondrial variant among European descendants and the most represented in the study, the limited number of participants from other haplogroups, data by haplogroup H (N=11) and non-H (N=29).

Table 1. Participants by treatment groups and mitochondrial haplogroups.

	Placebo	PS50	PS100	Total
A	1	3	0	4
B	0	1	1	2
C	0	0	1	1
D	0	1	0	1
H	5	5	1	11
K	2	1	1	4
L	0	1	0	1
M	0	1	1	2
T	3	0	3	6
U	1	2	2	5
V	1	1	0	2
W	1	0	0	1
Total	14	16	10	40

APOE Genotype

Thirty-two participants were APOE 3/3 carriers (67%) and 14 were APOE 3/4 carriers (33%), which is consistent with prevalence in the general population (Table 2). There were no APOE 4/4 carriers in this analysis. See Table for treatment by APOE genotype.

Table 2. Participants by treatment and APOE genotype.

	Placebo	PS50	PS100	Total
APOE 3/3	12	14	6	32
APOE 3/4	4	4	6	14

Effect of PhytoSERM on hot flash frequency

Daily average hot flash frequency at week 1 was used as baseline for each participant. Change in hot flash frequency was calculated as the difference between week 12 and week 1 hot flash frequency. No difference in baseline hot flash frequency was observed among the three treatment

groups, or between different mitochondrial haplogroups or APOE genotypes. Nor was there significant difference among different age groups.

When stratified by mitochondrial haplogroup, those belonging to mitochondrial haplogroup H had significantly decreased hot flash frequency when treated with 50mg of PhytoSERM per day compared to the placebo group ($p=0.039$). Only one haplogroup H participant was assigned to the PS100 group and no statistical analysis was conducted. Non-H participants on PS50 demonstrated a comparable magnitude of reduction in hot flash frequency. Due to the large variation within the P50-nonH haplogroup, the change in frequency was not statistically different. Haplogroup H on placebo had significantly decreased ability to learn the trial throughout the clinical study compared to non-H haplogroups ($p=0.007$), whereas treatment of 50mg of PhytoSERM per day successfully prevented such decline ($p=0.0476$). No such preventative effect was observed in non-H haplogroups due to the invariant performance of the non-H placebo group.

While this study was not powered for efficacy analysis, a responder analysis indicates that participants on 50mg of daily PhytoSERM for 12 weeks had significantly reduced hot flash frequency compared to their baseline and to the placebo group. Participants on 50mg of daily PhytoSERM also had improved performance on verbal learning and cognitive flexibility. We further identified that participants of a mitochondrial haplogroup H and APOE genotype were more responsive to PhytoSERM treatment.

Ongoing analyses are underway to determine the convergence of maternal history of AD, mitochondrial haplotype, ApoE genotype and ethnic heritage and relationship to Alzheimer's Disease.

ARIZONA ALZHEIMER'S CONSORTIUM

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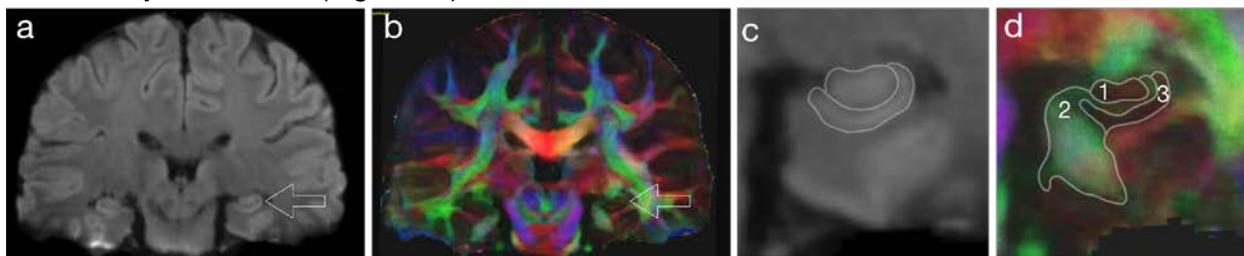
High-resolution MR imaging technologies for mapping neuronal connectivity network to subfields of hippocampus and amygdala: Application to studies of Alzheimer's disease.
Nan-kuei Chen, PhD, Ted Trouard, PhD, Ying-hui Chou, ScD, Lee Ryan, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

- Aim 1: Developing high-resolution functional MRI (fMRI) and diffusion-tensor imaging (DTI) pulse sequences capable of measuring the connectivity networks to subfields of hippocampus and amygdala, which are implicated in Alzheimer's disease (e.g., alteration in various aspects of memory including emotional memory).
- Aim 2: Evaluating the performance of our developed high-resolution MRI methods in measuring 1) functional activity in subfields of hippocampus and amygdala that are involved in verbal encoding of neutral and emotional stimuli and 2) the association between functional connectivity (measured with high-resolution fMRI) and structural connectivity (measured with high-resolution DTI) in healthy controls and patients with Alzheimer's disease.

Background and Significance: The hippocampus is among the earliest and most severely affected structures in Alzheimer's disease. The hippocampal formation consists of a number of distinct subfields that are involved in different aspects of memory function and exhibit different brain network topologies. The capability of measuring both functional and structural connectivity networks to subfields of the hippocampus and its connected structures, such as the amygdala (implicated in emotional memory), not only can help better stage disease progression in individual patients but may also potentially lead to identification of improved imaging biomarkers of Alzheimer's disease.

Preliminary Data: Our lab has been developing a series of high-resolution DTI and fMRI protocols, achieving 0.85mm^3 isotropic resolution in mapping the connectivity networks of human brains in vivo (using a 3 Tesla clinical MRI scanner) [1-10]. Figures 1a and b show the mean diffusion-weighted image and fractional anisotropic map derived from our high-resolution DTI scan (with hippocampus indicated by arrows). The zoom-in view (Figures 1c and d) further demonstrates that the color-coded connectivity map (Figure 1d) can better delineate dentate gyrus (region 1), fibers (region 2) that connect hippocampus and entorhinal cortex to other brain areas, and hippocampal CA1, CA2, and CA3 (region 3), as compared with images without connectivity information (Figure 1c).



Proposed One-Year and Long-Term Outcomes:

- At the end of year 1, the optimized high-resolution MRI pulse sequence will be shared with and made available to our imaging community.
- The preliminary data will be used for submission of new grant proposals (to NIH and other funding agencies).
- The capability of more precisely imaging hippocampal subfields is expected to largely benefit both research and clinical studies of Alzheimer's disease in the long term.

Year-End Progress Summary: First, our research team has created an addendum to the master research agreement between the University of Arizona and Siemens Medical Solutions USA, for us to acquire the source codes of the MRI pulse sequence for implementing the proposed high-resolution MRI technologies. Second, our research team has been implementing the proposed "super-resolution MRI" pulse sequences, enabling fMRI and DTI scans at significantly improved spatial-and-temporal resolution. Third, we have designed super-resolution reconstruction algorithms and MRI denoising procedures, based on which the acquired data could be processed to produce high-quality images. The developed algorithms have been shared in github.com. Fourth, we have started to collect pilot data (from human volunteers) using the developed procedures. Sixth, one of the developed multi-band high-resolution diffusion-tensor imaging protocols has been thoroughly and quantitatively evaluated (in terms of the signal-to-noise ratio, fidelity), and the initial findings were submitted to a scientific journal, Magnetic Resonance in Medicine, for publication.

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Developing an Image-Guided Magnetic Brain Stimulation Protocol for Mild Cognitive Impairment: A Pilot Study. Ying-hui Chou, ScD, Steven Rapcsak, MD, Nan-kuei Chen, PhD, Lee Ryan, PhD, Roberta Brinton, PhD, Carol Barnes, PhD, Phillip Kuo, MD, PhD. University of Arizona; Arizona Alzheimer's Consortium.

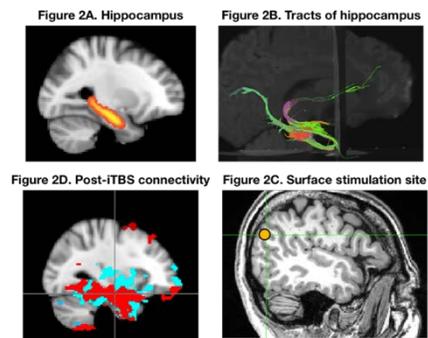
We propose to develop a hippocampal-rTMS protocol and evaluate the dose-response relations of the rTMS effects in amnesic MCI (aMCI). Specifically, we will utilize high-resolution MRI map of brain wiring (i.e., structural and functional connectivity data) as a guide to accurately transmit the surface magnetic field strength to the hippocampus. The feasibility of this proposal is supported by previous research¹ and our pilot data in healthy adults demonstrating that applying rTMS over a surface region that is connected to the hippocampus modulated hippocampal activity and enhanced associative memory. In this application, we propose three specific aims:

Specific Aims: The **first aim** of this project is to develop a personalized hippocampal-rTMS protocol for aMCI. The **second aim** is to verify the deliverability of rTMS to the hippocampus. The **third aim** is to determine dose-response relations of the rTMS effects on memory function and hippocampal connectivity. For Aims 1 and 2, we propose a randomized, double-blind study testing the effect of 1-session excitatory rTMS effect on hippocampal connectivity in aMCI patients compared to aMCI patients receiving 1-session inhibitory rTMS. For Aim 3, we propose a randomized, double-blind Phase I study testing the dose-response relations of the 4-week (20-day) administration of daily excitatory iTBS intervention on memory and brain function in aMCI patients.

Background and Significance: rTMS is a non-invasive brain modulation technique frequently used for the treatment of medication-refractory depression. Recently, rTMS has been investigated as a treatment tool for an array of neurodegenerative diseases including Alzheimer's Disease (AD). Animal models of AD have demonstrated that rTMS promotes hippocampal synaptic plasticity, improves learning and memory abilities, and increases brain-derived neurotrophic factor (BDNF)²⁻⁶. Although a few human studies have investigated the therapeutic effects of rTMS in patients MCI^{7,8}, none of the human MCI studies have targeted the hippocampus due to its deep location inside the brain. The biggest **barrier** to targeting the hippocampus is the lack of a method to guide the placement of an rTMS coil to modulate hippocampal activity and modify its communication with other brain regions.

We propose to develop an image-guided rTMS protocol that uses high-resolution brain imaging data, including white matter tractography and functional connectivity, as a guide to target the hippocampus in individuals with early-stage aMCI. We will also evaluate the dose-efficacy relations of this protocol on memory function and hippocampal connectivity. This project represents a critical step in developing a platform for non-invasive hippocampal brain stimulation that can be **shared across multiple projects in Arizona**. This method of image-guided target selection and fMRI-informed target verification could be generalized to deep targets for other neurodegenerative disorders. Moreover, the current line of research will provide a new approach for a profound impact on therapeutic strategies grounded in precision medicine.

A MagVenture MagPro X100 stimulator (MagVenture Inc. Denmark) connected with a figure-of-eight magnetic coil will be used for the iTBS protocol. We will co-register patient's head, patient's individual structural T1 image, and TMS coil in the same space using a TMS 3D Neuronavigation System (Localite TMS Navigator, Germany). Once they are co-registered, the Neuronavigation system will provide real-time feedback of the coil location/orientation and record the coil position/orientation to ensure consistency across treatment sessions. We will follow up-to-date safety guidelines to minimize side effects⁹. Earplugs will be worn to protect hearing.



Preliminary Data: Our research team has expertise in rTMS, high-resolution diffusion weighted imaging¹²⁻¹⁵, resting-state functional MRI¹⁶⁻²¹, Alzheimer's disease, and molecular brain imaging (e.g., PET amyloid imaging) for clinical trials. Our pilot data demonstrated the feasibility of generating white matter fiber tracts of the hippocampus (Figure 2B), identifying the surface brain region (i.e., the inferior parietal lobule) that is connected to the hippocampus (Figure 2C), and modulating hippocampal functional connectivity with iTBS (Figure 2D) in healthy volunteers. We are confident that our research experience and expertise will make us a suitable team for this proposed project.

Proposed One-Year and Long-Term Outcomes:

We plan to complete Aims 1 and 2 of this pilot project within one year. The first two months of the project will be devoted primarily to additional experimental design and preparation, recruitment, and pilot testing, and the last month will be devoted primarily to data analyses and manuscript completion. During the intervening months, the research will proceed at the rate of approximately 2-3 completed participants per month. This proposal is developed to collect pilot data for the submission of an NIH R01 proposal in responding to the funding opportunity: Pilot Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01 Clinical Trial Optional, PAR-18-175, NIA and NINR). The NIH proposal we are planning to submit will involve implementing a double-blind, randomized, sham-controlled crossover trial to 1) evaluate the efficacy of the image-guided iTBS protocol on memory function, 2) elucidate mechanisms of the iTBS effects, and 3) address heterogeneity of response to optimize the iTBS intervention.

Year-End Progress Summary:

Eight individuals with aMCI have been recruited for this pilot study. As planned, we submitted an R01 proposal "Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation" in response to the PAR-18-175. The proposal is scored with a percentile of #45. We will address reviewers' comments and resubmit the R01 proposal in July 2019. We also submitted two manuscripts to "*Journal of Alzheimer's Disease*" and "*Brain Stimulation*" and presented posters in the *International Brain Stimulation Conference*, and *Alzheimer's Association International Conference*.

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Sleep's Role in Age-Related Changes in Memory and Cognition: A Pilot Study. Jamie Edgin, PhD, Jessica Andrews-Hanna, PhD, Elizabeth Glisky, PhD, Matthew Grilli, PhD, Steven Rapcsak, MD, Lee Ryan, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

We aim to add sleep assessment and a test of sleep-dependent memory retention to a collaborative project on aging at the University of Arizona. With this Project, we will complete the following aims:

Specific Aims:

Aim 1: To add to our understanding aging processes by including a multi-method assessment of sleep to a University of Arizona based study of aging – the “ACHIEVE” Study. We expect that older adults will have impaired sleep efficiency and sleep quality (lower percentage of slow wave sleep), replicating the findings from previous work. We will assess sleep and daily rhythms through objective (actigraphy, polysomnography) and subjective approaches (a series of questionnaires of sleep quantity and quality). As in previous work, sleep disturbances will correlate with measures of neuropsychological function (specifically episodic recall) and functional connectivity.

Aim 2: To design a new study determining the ways that coarse and fine-grained spatial representations may be remembered by older adults before and after a 12-hour period of sleep and wake, and how sleep-dependent change may correlate with variation in sleep parameters. We expect that better sleep quality, and particularly slow-wave sleep duration, will allow for additional refinement of fine spatial discriminations, and this should be evident in recall and eye movement parameters. Sleep-dependent memory benefits should be reduced in older adults, relating to their levels of sleep impairment. **NOTE: We modified this aim to examine Self-referential memory processing across sleep intervals this year.**

Aim 3: Preliminary studies suggest sleep physiology may differ across aging individuals with varying levels of neurological risk. Therefore, in an additional exploratory aim, we will examine how sleep and sleep-dependent learning may differ in individuals identified as carrying one or two vs. no APOE e4 alleles. Paradoxically, recent data suggest *increases* in slow wave sleep in e4 carriers. Therefore, in this study, we will seek to determine if any sleep parameters differ in e4 carriers vs. non-carriers and how those parameters may influence sleep-dependent learning.

Background and Significance: There is a burgeoning set of findings that suggest a mechanistic relationship between sleep alterations, aging, and cognitive decline. While current data suggests individuals at high risk for AD-related decline have alterations in sleep architecture and quality, the impact of these alterations on memory retention is relatively unexplored. To address these questions, we propose to establish a *Sleep Assessment Core* (SAC) as part of a multi-disciplinary, collaborative aging project among members of the Psychology Department at the University of Arizona. The SAC will help to support a collaborative study – the “ACHIEVE Study” (Aging, Cognition, and Health: An Interdisciplinary Ecologically-Valid Experiment) and broader efforts within the Arizona Alzheimer's Consortium.

Edgin and collaborators have been devising sleep-dependent learning paradigms in patients with Down syndrome and hippocampal impairments, and now hope to conduct new studies to determine which sleep-dependent memory processes may be most impacted by aging. This work will add to the literature by further examining the nature of specific cognitive deficits in aging, and how these deficits may impact long-term memory consolidation across time intervals

containing sleep and wake. The SAC will provide a unique data set of pilot data that we believe will be well-placed to contribute to grant applications suitable for a number of funding mechanisms.

Preliminary Data: Preliminary data from the Edgin laboratory suggest correlations between sleep and learning outcomes in individuals with Down syndrome (who are at increased risk for Alzheimer's disease). In more recent work, we have demonstrated sleep-dependent learning deficits (Spano et al., 2018; *PNAS*) in this population and patients with hippocampal damage.

Proposed One-Year and Long-Term Outcomes: We anticipate that these data will provide pilot data that can be used for foundation and federal grant proposals in 2020. Our goal is to publish a study examining the self-reference effect across sleep in the coming year, thus establishing our group's collaboration in the area of sleep and aging. These data, alongside the Edgin lab's high-impact paper on sleep-dependent learning (Spano et al., 2018, *PNAS*) and a recently funded grant on sleep and memory from the NIH (Edgin, RO1) place our group in an excellent position to submit joint proposals on sleep, memory, and aging.

Year-End Progress Summary: **Aim #1:** Part of the ACHIEVE sample has received sleep assessment (actigraphy) and in the upcoming year we plan on expanding data collection with that cohort. This year we focused our efforts on piloting sleep-dependent memory protocols for use in older adults (**Aim #2**) based on previous memory interventions from ACHIEVE investigators. In particular, given Glisky and Grilli's results of self-referential memory benefits in aging (Hou, Grilli, & Glisky, 2019), we aimed to test if these effects persist across sleep periods. We expected that these effects would be evident immediately and across delays but would not be enhanced by sleep, given the measured independence of the self-reference effect and hippocampal-based memory.

For the pilot study (**Aim #2**), we recruited ten undergraduate students, four males and six females. The mean age was 21.5 years with a range of 20-24 years. One older adult, a female aged 75 years, was also tested. Participants completed four sessions, with two 12 hour delays that spanned either from morning to night or night to morning and contained sleep. During the learning sessions, participants were shown a list of 64 person-location-object triplets, with half of the sets being learned in reference to themselves ("Self" condition), and the other half in reference to George Clooney ("Other" condition). After a brief interval of neuropsychological testing, a short recall test was given, followed by a 12-hour delayed recall test. Participants completed this protocol again after one week, alternating the time of the learning phase. Participants wore an Actiwatch to track their sleep, and completed a variety of questionnaires assessing sleep and lifestyle habits. The study replicated the self-reference effect in undergraduates and showed a trend toward sleep effects on both conditions (self and other).

The older adult was near floor on the task, suggesting we need to revise the protocol for difficulty. Once these protocols are effectively modified and are suitable for older adults, we can then pursue **Aim #3** to determine any differences between those at greater genetic risk for AD and apply these protocols to the ACHIEVE study at large (**Aim #1**).

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Chemical Proteomic Approach to Discover Novel Neuroinflammation Targets. Kevin Gaffney, PhD, Paul Langlais, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: In Specific Aim 1, we will first optimize a workflow for identifying the target of SPMs through a chemical proteomic approach using lipoxin A₄ (LXA₄) and its receptor FPR2 as a model system. In Specific Aim 2, this workflow will be repeated with human neutrophils to further optimize this process and produce a general workflow capable of identifying the targets of lipoxin B₄ (LXB₄) and neuroprotectin D1 (NPD1).

Background and Significance: With the repeated failures of anti-A β antibodies and beta-secretase 1 inhibitors, the identification of novel therapeutic targets for Alzheimer's disease (AD) beyond the Amyloid hypothesis is of the utmost importance. Neuroinflammation is a target of growing interest due to its potential role in both initiating and potentiating neurodegeneration. While acute inflammation is crucial for healing injury and clearing infections, persistent inflammation can lead to tissue damage. To prevent the inflammatory process from reaching a chronic/persistent state, the body locally synthesizes a number of short-lived, highly potent specialized pro-resolving mediators (SPMs) from membrane bound polyunsaturated fatty acids. Unfortunately, with age, the capacity to produce these lipid mediators is decreased. A number of recent works have shown that supplementation with these SPMs decreases neuroinflammation and increases neuroprotection. DHA-derived NPD1 (**Fig. 1A**) was shown to promote neuronal survival and decrease the A β 42-induced inflammatory process in *in vitro* and *in vivo* models of AD. Further, LXB₄ (**Fig. 1A**) was recently identified as an important neuroprotective factor secreted by astrocytes capable of promoting retinal ganglion cell survival in a mouse model of glaucoma.⁴

LXA₄ and its receptor FPR2 (**Fig. 1B**) make up the most widely studied components of the SPM pathway and our lab is currently focused on developing blood-brain barrier penetrant mimetics of LXA₄ for the treatment of neurodegenerative diseases. However, based on their preliminary pharmacology, NPD1 and LXB₄ hold great potential as treatments for AD. Despite their structural similarities to lipoxin A₄, the biological actions of SPMs are not mediated through FPR2, but different, unknown receptors. Therefore, **the goal of this proposal is to develop a workflow for identifying the target of these orphan SPMs through a chemical proteomic approach using clickable photoaffinity SPM analogs.** While we are seeking to identify the receptors of

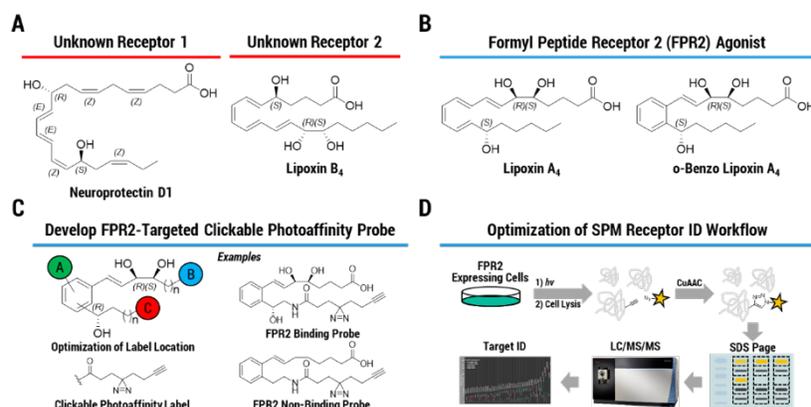


Figure 1. (A) The chemical structures of neuroprotectin D1 (NPD1) and LXB₄. (B) The chemical structures of FPR2 agonists LXA₄ and benzo-LXA₄. Despite their structural similarities to lipoxin A₄, the biological actions of LXA₄ and NPD1 are not mediated through FPR2. (C) The design of FPR2-targeting clickable probes is based on the benzo-LXA₄ to allow the facile synthesis of clickable photoaffinity labeled analogs. Additionally, to help control for non-specific and off-target binding, an FPR2 non-binding probe lacking the triol of LXA₄. (D) The SPM-directed workflow starts with the incubation of HEK293 cells overexpressing FPR2 with 1) FPR2-BP, 2) FPR-NBP, and 3) FPR2-BP + LXA₄ followed by *hv* irradiation to bind the photoaffinity tag to its proximal target and lysis of the cells. Through CuAAC, the probe-bound protein will be "clicked" with biotin-azide. Following purification, the tagged proteins will be identified by LC/MS/MS.

NPD1 and LXB₄, we will first optimize our workflow using LXA₄ and FPR2 as a model system.

The FPR2-targeted clickable photoaffinity probes will be based on benzo-LXA₄ as it provides a synthetically advantageous scaffold on which varied positioning of the clickable photoaffinity label can be explored (**Fig. 1C**). Additionally, to help control for non-specific and off-target binding, a negative control FPR2 non-binding probe lacking the triol required for LXA₄ affinity will be used. The FPR2 activity of the chemical probes will be verified in HEK293 cells overexpressing FPR2 using an NF-κB luciferase reporter system. Following the selection of the FPR2 binding probe (FPR2-BP), a corresponding non-triol containing FPR2 non-binding probe (FPR2-NBP) will be synthesized. The SPM-directed chemical proteomic workflow will be optimized following the steps outlined in **Figure 1D**. Step 1: HEK293 cells overexpressing FPR2 will be incubated with i) FPR2-BP, ii) FPR2-NBP, or iii) FPR2-BP + LXA₄. Step 2: The cells will be irradiated to bind the photoactivatable diazirine group to its proximal target and the cells lysed. Step 3: Probe-bound protein will be “clicked” with biotin-azide by copper-catalyzed azide-alkyne cycloaddition (CuAAC). Step 4: The biotin-tagged proteins will be streptavidin-enriched and the purified proteins will be separated by SDS-PAGE. Step 5: Using a “GEL-C-MS” approach, the proteins will be processed for LC/MS/MS-based analysis and identification. Following successful identification of FPR2 in the FPR2-BP pull down experiments in the HEK293 cells, this workflow will be repeated with human neutrophils, cells that respond to LXA₄, LXB₄, and NPD1, finalizing a general work flow capable of identifying the targets of LXB₄ and NPD1.

Preliminary Data: We have no preliminary data to date.

Proposed One-Year and Long-Term Outcomes: Data and findings from this proposed project will be submitted for presentation at relevant scientific conferences and in peer-reviewed manuscripts. In addition, the results set the stage for the discovery of novel neuroinflammatory targets for the treatment of AD. This work to optimize a SPM-directed chemical proteomic workflow will provide the preliminary data necessary to pursue NIH and/or DoD funding and industry and investor support.

Year-End Progress Summary: In order to meet the goals outlined in our proposal, we have begun in parallel several task that will converge to assist in identifying novel receptors for AD-relevant bioactive lipids. We have started the synthesis of the clickable photoaffinity probes. Additionally, we have begun the culture of THP-1 cells and will soon start optimizing the NF-κB luciferase reporter system.

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Memory and Executive Function in Normally-Aging Older Adults: Completion, Analyses and Publication of Two Projects. Elizabeth L. Glisky, PhD, Lee Ryan, PhD, Gene Alexander, PhD, Matt Grilli, PhD, AJ Figueredo, PhD, Matt Huentelman, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Project Description: This proposal will support the completion, analyses, and publication of two projects that are still in progress but nearing completion, as well as data-sharing of the longitudinal dataset with other collaborators in the consortium. The first project is a longitudinal study that has tracked changes in memory and executive function over several years and several time points in normally-aging older adults. The well-characterized participants from the longitudinal study have served and continue to serve as participants in numerous other experimental studies past and present, and as a baseline against which to assess levels of neurocognitive function in other older adults. The database now comprises data from over 800 adults aged 65 and over, and includes demographics, health-related variables, a comprehensive set of neuropsychological test measures and questionnaire data, as well as neuroimaging and genetic data on a subset of participants. Ongoing analyses of these data focus on identifying the variables associated with normal aging, abnormal aging and exceptional aging, and include regressions, factor analyses, structural equation models, hierarchical growth curve analyses, and others to be determined. Recently, we have received requests to share our longitudinal database with other consortium researchers, and we are working with the Institutional Review Board to facilitate this. The second project compares older to younger adults with respect to various sub-components of executive function. Based on reviews of a paper submitted last year, we are currently testing additional participants to strengthen our claims.

Specific Aim 1: To document changes over time in episodic memory and executive function in normally-aging older adults, and identify specific demographic, health, genetic and neurocognitive variables that are associated with differential change trajectories.

Specific Aim 2: To validate an executive function test battery in older adults looking at three sub-components of executive function—shifting, updating, and inhibition—that have been identified in young adults.

Background and Significance:

Specific Aim 1: Although episodic memory has traditionally been associated with the medial temporal lobes, particularly the hippocampus, it has become evident in recent years that the prefrontal cortex also contributes significantly to memory performance. Several studies have suggested that prefrontal cortex shows earliest declines in normal aging, although medial temporal regions are also implicated. Over the past 20+ years, we have been collecting neuropsychological test data associated with two independent factors: one reflecting fundamental episodic memory processes associated with MTL function, and the other reflecting executive control functions associated with prefrontal function. We now have longitudinal data on composite measures of these two functions, along with numerous other demographic and health-related variables that may mediate or moderate changes in these functions with age. Preliminary analyses suggest that memory and executive function change differentially over time and are differently affected by several of the other variables. Identifying those variables that are

associated with greater or lesser declines within the normal range, may inform early intervention strategies that might slow cognitive decline and enhance successful aging.

Specific Aim 2: Although much of the past literature has treated executive function as if it was a unitary construct or could be identified by a single task, more recent literature has suggested that executive function consists of multiple control processes that depend on different regions of prefrontal cortex. Miyake et al. (2000) identified three independent but correlated factors in young adults—shifting, updating, and inhibition. Attempts to replicate these findings in older adults have been inconsistent. However, no studies have compared young to older adults on the same set of executive function measures. We completed a study directly comparing young and older adults but failed to completely replicate Miyake’s findings in young adults. Further, we found differences between young and older adults. Reviewers of our submitted paper suggested additional analyses and increased sample size to strengthen our findings. We have almost completed the additional data collection and are beginning a series of confirmatory factor analyses. We also plan to combine these data with the executive function tests in our longitudinal database to get a better understanding of the nature of the sub-components of executive function. Creating a battery of executive function tests for older adults that measures three separate functions may enable better assessment and characterization of age-related declines, potentially leading to more targeted interventions.

Preliminary Data: In the longitudinal study, we have data on 306 older adults with at least two time points and 172 older adults with data from three or more time points for a total of 912 observations on each of the composite measure of memory and executive function. For the executive function battery we have increased our older adult sample from 150 older adults (aged 60 or older) to 247 older adults, with 121 young-old (60-74) and 126 old-old (75+). We are in the process of adding 25 participants to our young group to create a sample of 125 young people.

Proposed One-Year and Long-Term Outcomes: The one-year outcome is expected to be two peer-reviewed publications. However, the databases will continue to support other studies, including the microbiome project (Barnes), effects of genetic risk for AD on memory and emotion (Grilli). Data from these projects have supported current grant applications (Grilli) and are expected to support future grant applications (Barnes, Ryan, Huentelman).

Year-End Progress Summary: We have completed data collection for the executive function battery paper and have been working on a series of analyses to best conceptualize our findings. The general paper is written, but we are still trying to select the analyses and account for them in a way that best meets the objections of the previous reviewers. We expect to submit this paper within the next month. For the longitudinal study, we have several preliminary analyses completed, but are still working out what exactly to include in this paper. We continue to collaborate with Carol Barnes on the microbiome project and make our data available to other researchers.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

The status of personal semantic memory among cognitively normal older adults and individuals with mild cognitive impairment. Matthew Grilli, PhD, Jessica Andrews-Hanna, PhD, Jamie Edgin, PhD, Elizabeth Glisky, PhD, Steven Rapcsak, MD, Lee Ryan, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Project Description:

Specific Aim 1: To identify patterns of spared versus impaired personal semantic memory (PSM) among cognitively normal older adults relative to young adults, as well as in comparison to individuals with mild cognitive impairment (MCI).

Hypothesis 1: PSM will be impaired among cognitively normal older adults relative to young adults, but more so for spatiotemporal dependent knowledge relative to spatiotemporal free knowledge. A viable alternative hypothesis is that PSM impairments are only detectable among cognitively normal older adults who exhibit subtle cognitive decline, as determined through a data-driven neuropsychological approach.

Hypothesis 2: Among cognitively normal older adults, PSM impairment will mirror deficits in the general semantic domain, and both will be less severe in comparison to episodic memory.

Hypothesis 3: Individuals with MCI will have more severe PSM impairment relative to healthy older adults.

Specific Aim 2: To reveal that PSM status is related to neural markers of the integrity of the medial temporal and ventrolateral temporal lobes, as measured with MRI methods.

Hypothesis 1: Spatiotemporal PSM will be associated with volume, white matter structural integrity, and intrinsic functional connectivity of the medial temporal lobe (MTL) to other default mode network regions, as measured with structural, diffusion, and resting state fMRI methods.

Hypothesis 2: Similar neural markers of integrity of the anterior ventrolateral temporal lobe are expected to be associated with integrity of spatiotemporal free autobiographical facts.

Hypothesis 3: Personal trait knowledge will correlate with neural integrity of medial prefrontal cortex.

Background and Significance: PSM is knowledge of about the self, including autobiographical facts and personal trait knowledge. Disrupted PSM is associated with a degraded personal identity and an impaired ability to remember the past or imagine the future. In individuals with episodic memory impairment, PSM is essential for these reflective and future-oriented functions. Despite the importance of such knowledge, the extent to which PSM is spared in cognitively normal older adults is poorly understood, as is the degree to which it is impaired in individuals with MCI. Yet, accumulating evidence indicates that the retrieval of PSM relies on some neural regions that are vulnerable to structural and functional changes with healthy and abnormal aging, but also regions that are relatively spared in cognitively normal older adults, and to a lesser extent, in MCI.

In this pilot project, we will study the integrity of the cognitive and neural mechanisms of PSM in cognitively normal older adults and individuals with MCI. We will use established and novel behavioral tasks that have been developed in the PI's laboratory, coupled with magnetic resonance imaging (MRI) methods. The expected contribution of this research includes a) a better understanding of whether subtypes of PSM are uniquely spared among cognitively normal older adults relative to individuals with mild cognitive impairment and b) the neural correlates of different

types of PSM. This will be the first project to comprehensively study the status of PSM and its neural correlates in cognitively normal older adults and individuals with MCI.

Proposed One-Year and Long-Term Outcomes:

1. In one year, we anticipate that we will have developed a comprehensive battery of PSM that can be applied to young and older adults, including individuals with memory disorders.
2. In one year, we also expect to have a clearer picture of the extent to which PSM is spared in cognitively normal older adults, and whether there are any aspects of PSM that are selectively affected by MCI.
3. This pilot project will support an R01 proposal to NIA focused on autobiographical memory, normal cognitive aging, and preclinical signs of Alzheimer's disease.

Year-End Progress Summary: We have developed, piloted, and begun to implement a comprehensive battery of semantic memory tests. As part of our cognitive test development, we created a manual for administration and scoring of this battery. We complemented this battery with measures of episodic autobiographical memory and standard neuropsychological tests. As of February 21, 2019, we have administered our new battery to over 50 participants (~20 younger and ~30 older adults). A subset of these participants have undergone MRI as part of our involvement in the ACHIEVE (Aging, Cognition, and Health: An Interdisciplinary, Ecologically-Valid Experiment) project. Other participants in ACHIEVE have been administered additional tests of PSM and episodic autobiographical memory, which also will be used for Aim 2 of the present proposal.

For our one-year outcomes, we have successfully completed our first goal and have collected the data necessary to evaluate our second goal. We are in the process of scoring the data and are on-track to be done by our one-year deadline. We anticipate that these pilot data will be valuable for a future grant proposal to NIA focused on autobiographical memory and AD risk.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

MRI and automated segmentation of thalamic nuclei for Alzheimer's disease. Gloria J. Guzmán and Manojkumar Saranathan, University of Arizona

Specific Aims:

1. To validate automatic segmentation of thalamic nuclei at 3T

We hypothesize that our method for thalamic nuclear segmentation which has been developed and tested at 7T will perform comparably well at 3T and will outperform diffusion tensor imaging (DTI) based methods.

2. To improve the quality of hippocampal subfield segmentation using multi-modality data

We hypothesize that the addition of white-matter-nulled MPRAGE will improve the estimation of hippocampal subfields compared to using just CSF-nulled MPRAGE and will be comparable to T2 based methods which are slow and motion susceptible.

3. To perform volumetry of thalamic nuclei and hippocampal subfields on a cohort of normal age-matched subjects and patients with mild cognitive impairment (MCI)

We hypothesize that, in addition to whole volume, there will be specific differences at a thalamic nuclear and hippocampal subfield level between normal subjects and patients with MCI.

Background and Significance: Due to its close links to memory loss, hippocampal volumetry has been significant in Alzheimer's disease (AD). Almost all MRI studies of AD are volumetric analyses documenting temporal changes in total hippocampal volumes. The role of the thalamus in AD has been ignored despite initial reports from Braak and Braak that structures like the antero-dorsal nucleus are affected, due to the difficulties in direct visualization of thalamic nuclei using MRI.

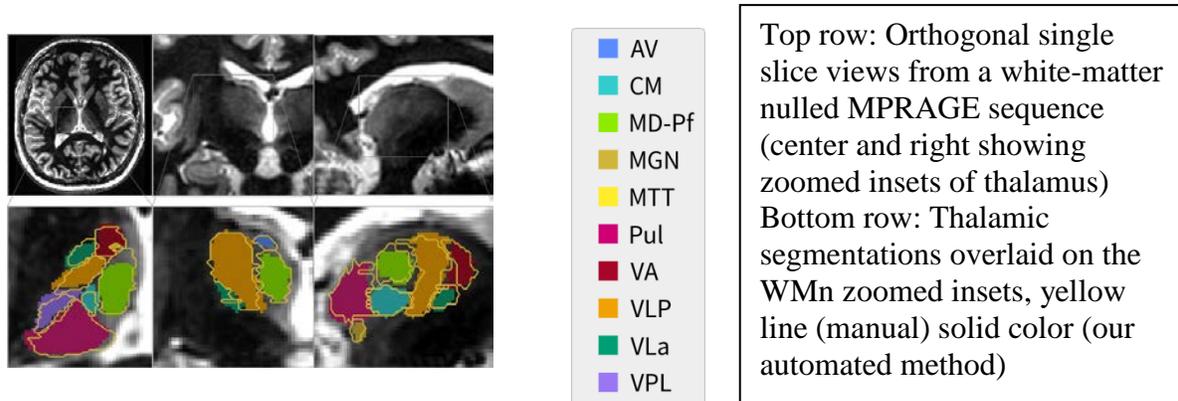
We have been developing new strategies for visualization and segmentation of thalamic nuclei for 7T and, more recently, 3T MRI. Specifically, we have developed and optimized for 3T MRI³, a white-matter nulled (WMN) MPRAGE² sequence which provides excellent delineation of the whole thalamus as well as improved contrast between the thalamic nuclei. This sequence is also motion robust, making it ideal for imaging patients with dementia. We have also developed a fast, automatic segmentation algorithm for delineation of thalamic nuclei⁴ reducing the manual processing time of several hours to ten minutes. Manual delineation also requires an expert neuroradiologist with domain knowledge. Note that conventional MPRAGE sequence nulls cerebro-spinal fluid (CSF) and lacks intra-thalamic nuclear contrast and is also sensitive to subject motion.

There is increasing evidence that AD might affect deep brain structures in a more targeted fashion (e.g. CA1 or SRLM thickness specifically) and investigating volume changes in hippocampal subfields might be more sensitive to the disease process.. Almost serendipitously, we have discovered that this same white-matter nulled MPRAGE sequence can also help improve the characterization of hippocampal subfields due to its "T2 like" contrast whilst retaining motion robustness.

Volumetry of thalamic nuclei and hippocampal subfields would provide a more detailed picture of disease progression and improve sensitivity specificity compared to whole volumes where specificity to nuclei or subfields are lost.

Preliminary Data: We have developed a white matter nulled MP-RAGE sequence and successfully segmented the thalamic nuclei from data acquired at 7T. This sequence has been optimized for 3T as well. We have also developed a fast automatic method for segmentation of

7T WMN MPRAGE images and validated it against manual delineation. The figure below shows an example of a 7T WMN MPRAGE segmentation. The boundaries of the thalamus and the intra-nuclear contrast are excellent using the new MPRAGE sequence. The automatic segmentation (solid) matches well to the manual segmentation (yellow borders) for almost all the nuclei.



Proposed One-Year and Long-Term Outcomes: At the end of one year, we hope to have a robust segmentation method for 3T WM-nulled MPRAGE as well as an improved hippocampal subfield segmentation strategy. We will also have preliminary data from 30 subjects (15 normal and 15 MCI) from which we can derive high quality thalamic and hippocampal parcellation and quantify differences at subfield and nuclear level (as opposed to whole volumes which are presumably less sensitive and specific to the disease process)

We have started a collaboration with Dr. Eric M. Reiman and Dr Kewei Chen to transfer our sequences to Banner Alzheimer’s Institute and collect thalamus and hippocampal data from MCI and AD patients on their 3T scanner. This will further increase the number of subjects and help investigate if there are changes happening at thalamic nuclear level during the disease progression, esp. since those scans will be longitudinal studies.

We are awaiting the publication of the thalamic segmentation paper (based on 7T analysis) and once we have some data validating this method for 3T data and demonstrate the ability to perform accurate fast segmentation of thalamus and hippocampus at 3T which this funding would help achieve, we plan to submit an R01. Both of us are first time investigators per NIH rules and will be given priority in the review process and it will have a high chance of getting funded, especially given the importance of AD. We are hoping to be ready to submit the R01 within a year after starting this pilot project (if we start the pilot this June, we hope to submit the R01 for the Jun 2019 submission).

Year-End Progress Summary: Since receiving this grant, we have developed two new thalamic segmentation schemes- one that is atlas based that will enable retrospective analysis of existing AD image databases to investigate the role of thalamic nuclear volumetry in disease progression and another method that uses a deep learning framework to achieve robust segmentation at 3T, leveraging our manual segmentation 7T atlases. These have been accepted as digital posters in the upcoming ISMRM conference in Montreal (May 2019). The basic segmentation method is in the last stage of revisions in the journal *Neuroimage*. We have also, in conjunction with Dr Nan-kuei Chen, created an imaging protocol that includes structural, diffusion and resting state functional imaging to provide comprehensive information. We have also transferred the optimized thalamic MRI protocol to Banner Alzheimer’s Institute (Phoenix) for prospective acquisition on patients. The IRB for collection of data on MCI patients and age-matched controls from Banner Tucson campus was approved on Jan 24th 2019 and we are getting ready to scan patients from

the Behavioral Neuroscience and Alzheimer's Clinic. Lastly, we have started preparing an R01 grant proposal to be submitted to NIA.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Identify small molecule inhibitors to block Protein-Protein interactions from AMP-AD targets. May Khanna, PhD, University of Arizona; Arizona Alzheimer's Consortium.

The goal of this grant is to identify and validate the minimal binding domain(s) between proteins predicted to be functionally interacting with CSF1. For this grant proposal, we will focus on CSF1R and IL10R.

Specific Aims:

Aim 1: Define the physical interaction of CSF1R with functionally linked protein partner IL10R using peptide arrays.

Aim 2: Validate interactions of peptides-proteins and PPI using microscale thermophoresis (MST) and Surface Plasmon Resonance (SPR).

Aim 3: *In silico* docking of the regions that interface between the proteins (guided by protein-peptide mapping).

Background and Significance:

Given 29 top protein targets from AMP-AD curated by Sage Bionetworks, our first step was a search for protein-protein interactions. This was done using the STRING database (<https://string-db.org/>) to predict protein-protein (PPI) interactions. Figure 1 highlights the output from STRING. These are a combination of predicted functional connection and physical interactions. There is one major network that connects with most proteins with CSF1R at the center of the network.

Preliminary Data:

Figure 1 highlights the output from STRING. These are a combination of predicted functional connection and physical interactions. We used this network analysis to design the experiments highlighted below.

Proposed One-Year and Long-Term Outcomes: Includes Plans to obtain additional, external, non-state funding. Following data obtained from this grant, we intend on applying for NIH funding on targeting protein-protein interactions for AD therapeutics.

Year-End Progress Summary: We have printed a peptide array on CSF1R and have tried purifying IL10R without much success in *E. Coli*. Our next step is to purify IL10R in insect cells. This is more challenging, but we are currently working on optimizing this protocol for several proteins.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Defining the mechanism of *T. gondii* induced plaque clearance. Kathryn McGovern, PhD, Anita Koshy, MD, Roberta Brinton, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aim: Define how strain-specific *T. gondii* infection leads to differences in A β clearance by immune cell populations. This aim will test if infection with *T. gondii* changes the priming and differentiation of the initial immune response against A β , which populations subsequently infiltrate the brain, and what the effector populations against A β actually are.

Background:

Alzheimer's Disease (AD) and Neuroinflammation: Neuroinflammation is generally considered harmful to the brain and data suggest it plays a role in AD progression. This view has restricted most research to ways to diminish immune infiltration to the CNS, but thus far this strategy has been unsuccessful and can lead to fatal reactivation of latent disease. Interestingly, very recent studies suggest that the "right" immune response can, in fact, be protective against AD. Therefore, to harness the immune response to affect AD, we must develop a more nuanced understanding of how brain immune responses are controlled. One way to accomplish this goal is to utilize an existing model system of CNS inflammation to study chronic and tightly regulated brain immune responses and then determine what impact those responses have on AD pathology, such as A β deposition.

***Toxoplasma* Biology:** *Toxoplasma gondii* is a common neurotropic parasite of warm-blooded animals. In humans and mice, *T. gondii* establishes a chronic, life-long CNS infection. Control of parasite replication relies on the continuous influx of immune cells to the brain. Unlike most CNS infections or inflammatory processes, *T. gondii* infection is largely asymptomatic with an estimated 2-3 billion people harboring this parasite without their knowledge. Thus, *T. gondii* infection drives a brain immune response that is robust enough to control the parasite yet controlled to avoid immune-mediated pathology. *T. gondii* has three canonical, well-studied strains that are genetically diverse and have phenotypic differences in mice. These features make *T. gondii* infection a unique model for understanding what drives and dampens the CNS immune response. The Koshy lab, which studies strain-specific CNS- *T. gondii* interactions, is the first to show that not all *T. gondii* infections protect against A β deposition, creating an effective tool to determine which *T. gondii*-induced CNS changes are linked to A β protection versus simply with infection.

***Toxoplasma* and Alzheimer's disease:** Three groups have reported that infection with *T. gondii* leads to a striking decrease in A β plaques in the brains of human amyloid precursor (hAPP) model mice, a common model of AD. The first group attributed the phenotype to the production of the anti-inflammatory cytokines IL-10 and TGF- β , while the second group suggested that this protection was secondary to an increase in phagocytosis of soluble A β by infiltrating monocytes. A flaw common to both of these studies is that they used a single parasite strain (type II) and compared infected mice to uninfected mice. This experimental set up makes it difficult to determine if A β protection was due to the parasite specifically or merely due to a persistent immune response in the brain. To answer this question, we infected a third hAPP mouse model with all three canonical parasite strains (including an attenuated type I strain that only causes an acute infection then is cleared, and at 6 months post infection (mpi) assessed A β deposition. We found that protection against plaque formation is restricted to infection with a type II strain, which reduces both the number and size of A β plaques. Now, we can compare the CNS changes occurring in "protective" (type II) versus "non-protective" (type III) infection to determine which CNS changes are linked to protection against A β and which ones are simply secondary to CNS

infection. Further, these results inspired a subsequent experiment where J20 mice were aged to 9 months (plaque accumulation begins at 5-7 months) and infected with type II parasites to test if *T. gondii*'s "protective" effect could also rescue mice from plaques that had already formed. Preliminary results indicate that type II infection significantly reduces the size of established plaques while plaque number remained similar.

Macrophage Immunology: Recently there has been a remarkable increase in our understanding of how myeloid lineage cells respond to various insults. The traditional view that entire populations of cells are classically (M1, differentiated under the influence of IFN- γ) or alternatively (M2, differentiated under the influence of IL-4 and/or IL-13) activated is enhanced by the nuanced plasticity these cells display in response to local stimuli. While the role of classically activated macrophages is well-defined in *T. gondii* infection, the role of alternative activation is beginning to be characterized. Data from the Koshy lab indicates that despite a strong Th1 (IFN- γ mediated) response induced by both type II and type III strains, a larger population of alternatively activated macrophages is generated during infection with type II parasites early in the chronic stage of infection. These cells may be a key component of the mechanism that leads to plaque protection in hAPP model mice.

Significance:

The study proposed here drives the science behind *T. gondii* mediated A β protection from mere description to mechanism. By using *T. gondii* strain differences as a tool we can now distinguish the specific changes in the immune-CNS environment that mediate plaque clearance from the vast number of changes that occur in the brain due to a general infection. These experiments will provide critical information about how a devastating neurodegenerative disease can be controlled through manipulating the CNS immune response. Additionally, the findings from this proposal may have implications other neurodegenerative diseases (e.g. Parkinson's Disease or Amyotrophic Lateral Sclerosis) that also have protein deposition pathology.

Proposed One-Year and Long-Term Outcomes:

With the completion of this proposal, we will have determined how strain-specific immune modulation by *T. gondii* affect the responding immune cells and how these changes can lead to clearance of A β in the case of a type II infection. Importantly, the training I receive here at the University of Arizona will allow me to build the skills required to establish a career studying how neuroinflammation can be beneficially targeted in AD and other neuroinflammatory conditions. Finally, data generated from this application will provide the basis for a mechanistic future K99/R00 or K22 "pathway to independence" application, with a particular focus of how effector populations may be generated in the absence of the parasite to keep A β burden in the brain as low as possible.

Progress Summary:

With the awarding of this grant we have been able to breed our AD model mice to sufficient numbers that we were able to age and infect two individual cohorts with both the protective and non-protective strains of *T. gondii*. Mice are being monitored throughout the infection and once they reach the appropriate time point, brain-infiltrating immune cells will be phenotyped using flow cytometry, and plaque burden will be determined using immunohistochemistry. We have a further cohort aging in order to be able to determine the cell populations that are actively phagocytosing A β .

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Mechanisms of Neuroprotection by Mas Agonists. Kathleen Rodgers, PhD, Joanne Berghout, PhD, Roberta Diaz Brinton, PhD, Kevin Gaffney, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: In a study evaluating the effects of orally available Mas agonists on heart function and cognition in a model of arterial hypertension (transaortic constriction), we showed that the surgical model reduced diastolic heart function and cognition as measured by the Novel Object Recognition test. In this model, one Mas agonist improved both heart and cognitive function, but the other only improved cognition. Therefore, in this proposal, we will evaluate

- 1) possible cellular mechanisms by which the Mas agonists could improve cognition including changes in oxidative stress (OS; nitrotyrosine labeling and MitoSox), inflammation (cytokine and chemokine levels as well as microglial activation) and regenerative markers;
- 2) changes in RNA transcript levels by RNA Seq in the brain tissues to allow hypothesis generation for novel pathways that might distinguish the actions of these two molecules.

Background and Significance: Dysfunctions of the microvascular system that occur in Alzheimer's Disease (AD), such as neurovascular uncoupling and disruption of the blood brain barrier (BBB), detrimentally effect the ability of the brain to clear degraded and misfolded proteins, including amyloid β ($A\beta$), leading to their accumulation.¹ In fact, cardiovascular disease has a strong, positive correlation with neurodegenerative diseases.² The central nervous system utilizes approximately 20% of cardiac output and hypertension during midlife increases the risk of AD later in life. Studies show that anti-hypertension intervention correlates with a decreased risk in AD with angiotensin receptor blockers (ARBs) being the most efficacious.

ARBs impart their therapeutic effect by blocking the pathological arm of the renin-angiotensin system (RAS), specifically by antagonizing activation of the angiotensin II type 1 receptor (AT_1R) by the hypertensive peptide angiotensin II (A-II).- AT_1R is localized in brain stem and forebrain which accounts for its well-characterized effects regulating central sympathetic and hormonal systems as well as the limbic system and in the endothelial layer of cerebral microvessels.^{7,8,9,10} Persistent activation of the A-II/ AT_1R axis results in extensive cerebrovascular remodeling, inflammation, and OS leading to neurovascular uncoupling and disruption of the blood brain barrier (BBB).^{11,12} While the results on ARBs in AD are compelling, the protective arm of RAS, comprised of the Mas receptor and its ligand A(1-7), holds even greater potential to treat AD. A(1-7), through Mas, counter regulates the pathological actions of A-II and AT_1R such as decreasing inflammation and OS and increasing cerebral blood flow reactivity, but also activates regenerative processes. These include increase in mesenchymal stem cells (MSCs), a cell therapy currently in Phase II in AD patients.

Preliminary Data: A number of labs have begun to investigate the role of the ACE2/A(1-7)/Mas axis in AD. Interestingly, in AD patients, serum and brain ACE2—the main A(1-7)-producing enzyme—levels are reduced compared to control subjects. In these brains, ACE2 was inversely correlated to $A\beta$ levels and phosphorylated tau pathology. These trends were mirrored in animal mouse models of AD. In senescence-associated mouse prone 8 (SAMP8) mouse model of sporadic AD, brain levels of A(1-7) were found to be low while brain tau hyperphosphorylation levels were elevated, a trend also seen in in P301S mice, a model of pure tauopathy. The effects of Ang-(1-7) treatment on AD was tested in the 5xFAD mouse which develops amyloid deposition

and cognitive deficits at as early as 2 months of age. Intracerebroventricular (ICV) infusion of A(1-7) ameliorated cognitive impairment and increased cerebral blood flow reactivity in these mice. Additionally, ICV treatment of stroke prone spontaneously hypertensive rats with A(1-7) increased neuronal survival, neurological status, neuronal survival, and overall survival while decreasing the incidence of hemorrhages, indicating a reversal of microvessel dysfunction.²¹

While these results are impressive, ICV administration of a Mas agonist is not commercially feasible route of administration for AD. Therefore, over the past three years we have developed orally bioavailable Mas agonists, small molecules RASRx1902 and RASRx1911. Funding from the AAC from 2017 allowed us to test the ability of RASRx1902 and -1911 to treat cognitive impairment in a mouse model of arterial hypertension induced by transverse aortic constriction (TAC) which induces cerebral hypoperfusion, amyloid deposition and neuroinflammation. In this model, treatment was started after TAC was established and both small molecules improved cognition (Figure 1). However, only RASRx 1902 improved heart function.

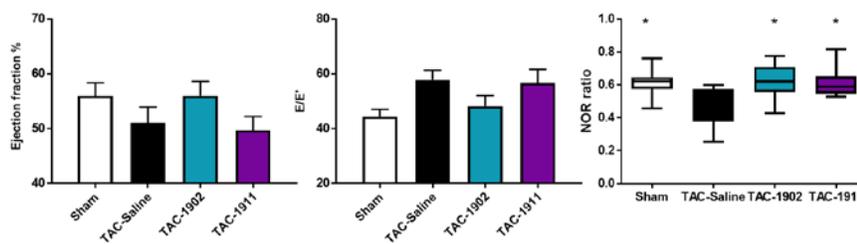


Figure 1. Treatment with Mas Agonists after TAC improved cognition in NOR assay.

In other models, we have seen subtle differences in the pharmacology of these two agents. Therefore, for this current proposal, we would like to further probe the responses of these two Mas agonists to see if their cognitive effects result from the same or different mechanism using tissues collected from this study (brain, heart and blood). Measures will include OS (nitrotyrosine labeling and MitoSox), inflammation (cytokine and chemokine levels as well as microglial activation) and regenerative markers. Further, we will conduct RNA Seq on a subset of the brain tissues to allow hypothesis generation for novel pathways that might distinguish the actions of these two molecules.

Proposed One-Year and Long-Term Outcomes: Data and findings from this proposed project will be submitted for presentation at relevant scientific conferences and in peer-reviewed manuscripts. In addition, the results will be used to inform further research into the neuroregenerative mechanisms of Mas agonism. We will seek external, non-state funding from NIH, industry and investors to support our efforts to develop novel therapeutics for AD.

Year-End Progress Summary: Studies were conducted to evaluate the effects of RASRx1902 and 1911 on OS, inflammation and regenerative markers. TAC surgery increased the number of cells in the brain with mitochondrial OS 2-3 fold. Treatment with Mas agonist reduced the levels of microglial and neuronal mitochondrial OS to levels comparable to sham controls. In the TAC model, surgery resulted in decreased MSC colonies, which was reversed by Mas agonist treatment. Treatment with RASRx1902 and 1911 also increased circulating EPC levels. RASRx 1902 also reduced cytokine levels in the hippocampus and periphery. In the periphery, the levels of interleukin 2 (IL-2) and IL-5 were reduced. In the brain, IL-2, IL-5, IL-12, interferon γ , IL-1 β , IL-4, IL-6, KC/GRO and tumor necrosis factor were reduced. RNA seq analysis is ongoing, but predicted the increased mitochondrial dysfunction.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Establishing pipelines for biomarker collection and data sharing for cognitively healthy older adults at the University of Arizona. Lee Ryan, PhD, Gene Alexander, PhD, Carol Barnes, PhD, Ted Trouard, PhD, Roberta Brinton, PhD, Matt Huentelman, PhD, Tom Beach, MD, PhD. University of Arizona; Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: To establish and implement standardized procedures for collecting and bank biomarker specimens, including blood and CSF, from cognitive healthy older adults.

Specific Aim 2: To establish a database for sharing data from a cohort of cognitively healthy older adults, including neuropsychological testing, neuroimaging, and biomarker data.

Background and Significance: Understanding the variability of cognitive trajectories in normal and pathological aging requires data from large numbers of participants who are well characterized. Many of the most promising approaches to early detection and predicting cognitive decline in otherwise healthy older adults involves biomarkers from blood, CSF, and neuroimaging, among others. The complexity and high cost of collecting large-scale datasets with these types of measurements highlights the importance of sharing data across laboratories.

The funds for this project will be used to begin establishing and implementing standardized protocols for collection of biomarkers including blood, CSF, and neuroimaging data from cognitively well-characterized older adults without a diagnosis of dementia. Drawing on expertise at UA and our partner institutions within the AAC, will explore the most efficient way to collect and bank specimens, and build a database for sharing standardized measurements that will be made available to all AAC researchers.

Proposed One-Year and Long-Term Outcomes: Establishment of standardized data collection and data management systems will allow us to consider funding mechanisms that will support a large-scale and longitudinal cohort of cognitively normal older adults at UA.

Year-End Progress Summary: Standardized protocols for CSF and blood collection, pre-processing, and sample storage have been written consistent with best practices. We anticipate that we will collect 5-8 samples by June 30th to establish feasibility. With the help of Dr. Nan-kuei Chen, we have obtained centralized storage space and high priority nodes for neuroimaging analysis at the University of Arizona's HPC facility. Dr. Chen's laboratory is creating the database and analysis pipeline for standardized image analysis. In addition, a front-end database is being created to share basic demographics and data types available in various samples. We expect that both databases will be completed by the end of the year and we have identified several large existing samples to load into the system for testing. In early June, a workshop on the use of the system will be provided to researchers in the AAC.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

A Novel Model of Medial Temporal Lobe Functions: Implications for Aging and Memory.
Lee Ryan, PhD, Matt Huentelman PhD, Matthew Grilli, PhD, Jamie Edgin, PhD, Jessica Andrews-Hanna, PhD, Elizabeth Glisky, PhD, Steven Rapcsak, MD, Manoj Saranathan, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: Aim 1. To determine whether differential patterns of performance exist between object discrimination, pattern separation, and context-specific recognition in older adults with and without genetic and cognitive risk for AD. Aim 2. To obtain measurements of PRC and PHC volumes, fMRI activation, and resting state connectivity in the same participants, and to correlate those measures with performance on memory tasks.

Background and Significance: The perirhinal cortex (PRC) plays an important role in identifying and recognizing objects, two important processes that allow animals to function within, and navigate through, their world. Although few studies of the impact of aging on PRC exist, they suggest that across species – rats, monkeys, and humans – PRC functions decline with age. However, we know little about the impact of declines in PRC integrity and object identification/recognition on hippocampally-mediated memory such as pattern separation, associative memory, or autobiographical memory. In contrast, parahippocampal cortex (PHC) may remain relatively intact in older adults, suggesting that context may be utilized by older adults to a similar degree to older adults, or may even compensate for impaired object processing.

Recently, my colleagues and I published a theoretical paper presenting a novel view of the interactive functions of the PRC and PHC in memory, and how these two structures may change differentially during normal aging and in the preclinical stages of Alzheimer's disease. We posit that there are two parallel but relatively independent pathways, both relying upon contributions from PRC and PHC. The "coarse" pathway creates a global representation of the environment that includes gist-like information on object forms and spatial relations among them. The second pathway, the "detail" pathway, provides information on the combinations of specific features of objects and space, and is utilized whenever there is ambiguity in the environment. That is, when objects or space are unfamiliar, or whenever identification errors are detected, the detail pathway takes precedence and provides additional feature information that disambiguates experience. Based on data from animal models and human studies, we hypothesize 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.

Preliminary Data: Our laboratory has recently published data consistent with the model. Relative to young individuals, we have preliminary evidence that older adults are impaired on visual "pattern separation" tasks that rely on the ability to differentiate between previously experienced items and items that are similar to, but not identical to items that have been previously experienced. Because these tasks almost always include sets of complex objects that are similar to one another – that is, objects with multiple overlapping features – it is possible that the memory impairment occurs because of the inability of the detail pathway to differentiate between these similar representations. In addition, new data from our laboratory suggests that older adults utilize context to the same degree as older adults in order to support object recognition and associative memory, consistent with the hypothesis that the coarse pathway remains intact in older adults. Based on these data, my collaborators and I are well-positioned to

submit a RO1 grant to NIA to test the predictions of our new model. In this pilot project, we will obtain the additional data necessary to support an RO1 testing the predictions of the model with object discrimination, pattern separation, and context-specific recognition tasks in older adults with and without significant risk for AD. Based on the model, we expect that older adults with genetic and cognitive risk for AD will be more severely impaired on object discrimination and pattern separation. Importantly, while low risk older adults will be equally sensitive to contextual shifts as young adults, older adults with high risk will not utilize context to the same degree and older adults without significant risk for AD. Additionally, pattern separation and context-specific recognition performance among older adults will be related to structural and functional MRI measures in the PRC and PHC, respectively.

This will be the first project to compare PRC- and PHC- dependent memory measures in older adults with and without significant risk for AD. Our recently published model of medial temporal lobe function provides novel hypotheses regarding the components of memory and how they change with age, and the types of memory tests that may provide early markers of preclinical Alzheimer's disease.

Research team. We have formed the **Ageing, Cognition, and Health Study: Investigating Brain Versatility (ACHIEVE study)**, which brings together five labs in the Department of Psychology (Andrews-Hanna, Glisky, Grilli, Edgin, and Ryan) that study cognitive and brain aging using neuropsychological and experimental behavioral tasks, neuroimaging, and naturalistic assessment methodologies. Our team includes experts in sleep and cognition (Edgin) and mild cognitive impairment and the dementias (Rapcsak). The ACHIEVE study shares data, resources, and staff through three cores: the Cognitive Assessment Core (Director: Grilli), the Neuroimaging Core (Director: Ryan), and the Naturalistic Assessment Core (Director: Andrews-Hanna). Although the PIs of these cores are submitting separate pilot projects with non-overlapping aims, our collaborative model has the advantages of reducing costs, developing rich datasets, and enabling more ambitious projects leading to extramural funding opportunities. Notably, Grilli and Ryan have implemented this same collaborative model since spring 2016.

Proposed One-Year and Long-Term Outcomes: This pilot project will support an R01 proposal to NIA focused on testing the predictions of the PRC-PHC model in older adults with and without cognitive and genetic risk profiles for AD. We will propose obtaining positron emission tomography scans to determine the regional distribution of tau in participants who are cognitive normal older adults with and without risk for AD, as well as those with Mild Cognitive Impairment. We anticipate this grant to be submitted in fall, 2019.

Year-End Progress Summary: We have made significant progress on this project. Pilot testing for new paradigms is complete, and we have been recruiting and testing participants for the study. As we proposed, data collection is being shared across the four laboratories. We anticipate complete testing of 60 to 80 older adults by June 30th on neuropsychological and neuroimaging protocols. In May, the research team will begin drafting an RO1 grant supported by the results of the study.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Project Description

Ultra-sensitive and label-free detection of Alzheimer's disease proteins. Judith Su, PhD, Gene Alexander, PhD, Tom Beach, MD, PhD. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Project Description: We have recently developed a technique known as FLOWER (frequency locked optical whispering evanescent resonator) (Figure 3) that can detect low concentrations of molecules down to the single molecule limit without requiring the use of labels such as fluorescent

or radioactive tags. We plan to evaluate the ability of FLOWER to test for the Alzheimer's disease (AD) biomarker tau in both cerebrospinal fluid (CSF) and serum/plasma. There are potential benefits for applying FLOWER to both types of samples. For CSF, FLOWER offers greater sensitivity that could be more reliable and robust, cheaper, and easier to reproduce across labs. Furthermore, because of its particularly high sensitivity, FLOWER offers the potential to detect Alzheimer's disease biomarkers in serum and/or plasma, which can be more easily collected from participants with lower risk than the collection of CSF. This is especially conducive for repeated measurements. The serum/plasma detection

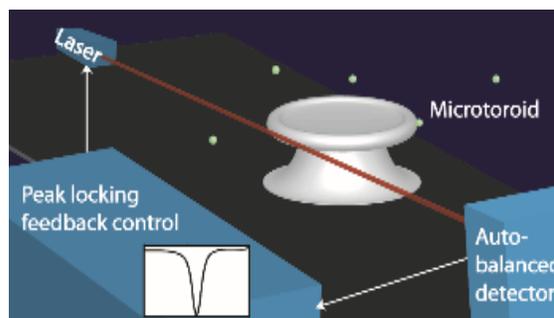


Figure 3. FLOWER schematic. In the FLOWER detection scheme, microtoroid optical resonators are used in conjunction with frequency-locking feedback control and balanced detection to improve the signal-to-noise ratio of the system. As a result, single-macromolecule detection becomes possible.

can be directly assessed against the CSF markers to help validate the measures with established markers that reflect deposition in brain. **The objective of this one year pilot project is to obtain the necessary preliminary data that demonstrates the feasibility of our approach and will form the basis for an R01 proposal, as well as for publications to further support this research plan.** In a previous pilot project, we focused on detecting amyloid beta, which was related to an R03 (PI: Su; R03AG055020) we were awarded. In the current pilot project proposal, we will focus on detecting the AD protein, tau.

Specific Aims:

Aim 1: *Fabricate devices and establish surface chemistry protocols.* The first aim of this pilot study is to fabricate the sensor devices needed for this project. The devices will be imaged using scanning electron microscopy (SEM) to ensure that they are defect-free. We will covalently bind anti-tau uniformly to the surface of the microtoroid in order to serve as capture agent. We will use confocal microscopy with fluorescently tagged tau to confirm that uniform binding has occurred.

Aim 2: *Evaluate the sensitivity of FLOWER for detecting different levels of tau fragments in spiked control saline.* We will demonstrate that amyloid beta fragments can be detected by FLOWER in spiked saline solutions. Specifically, we will attempt to detect tau. We will functionalize the surface of the resonator with antibodies for amyloid beta fragments and flow solutions containing varying concentrations of amyloid beta fragments over the surface of the microtoroid resonator. For each of these experiments, we will record the change in the resonance frequency of the microtoroid as binding occurs. Using controlled samples in saline, we will generate a dose response curve to establish a limit of detection for our system. In addition to these experiments, we will perform

control experiments to quantify the degree of non-specific binding. This will be done by attempting to bind interleukin-2 to anti-tau bound to the surface of the toroid as well as by attempting to bind tau to anti-interleukin-2 bound to the surface of the microtoroid. Interleukin-2 was chosen as it should not bind to tau. Sensor response time, stability, and reversibility will be assessed as well.

Background and Significance: 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.

Preliminary Data: FLOWER has already been used to detect a wide variety of particles and biological molecules and is in demonstrated agreement with established theoretical predictions. Figure 2 summarizes the wide range of particles, both in size and composition, that have been detected to date in aqueous solution with FLOWER.

Proposed One-Year and Long-Term Outcomes: Our proposed one-year outcome is to demonstrate the feasibility of detecting tau using a microtoroid optical resonator and provide the data needed to estimate the limit of detection. Our desired long-term outcome is to do this for patient samples. We plan to leverage the CSF and blood samples of the new Brain Imaging and Fluid Biomarkers Core (Core Leader: Alexander), as part of the Arizona Alzheimer's Disease Center, which is expected to start enrollment this coming year to help support our external grant submission plans. At the end of the proposed pilot project, we plan to submit an NIH R01 proposal. It is expected that this data will support new publications to aid detection of AD pathology in CSF and potentially plasma.

Year-End Progress Summary: We have successfully detected 2.7 fM of tau protein in phosphate buffered saline (Figure 3) and demonstrated a detection limit 1000x better than what was obtained using a commercial ELISA kit.

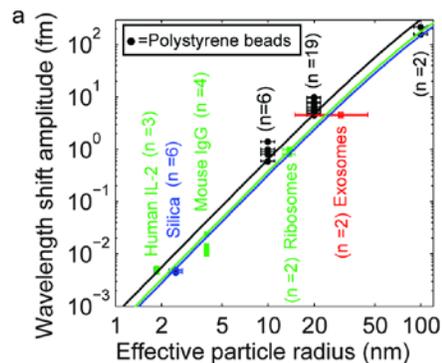


Figure 2. Summary of particle detection data using FLOWER. A wide range of particle sizes with radii from 2-100 nm were detected. The solid lines are theoretical predictions based on the different dielectric constants of the particles being detected.

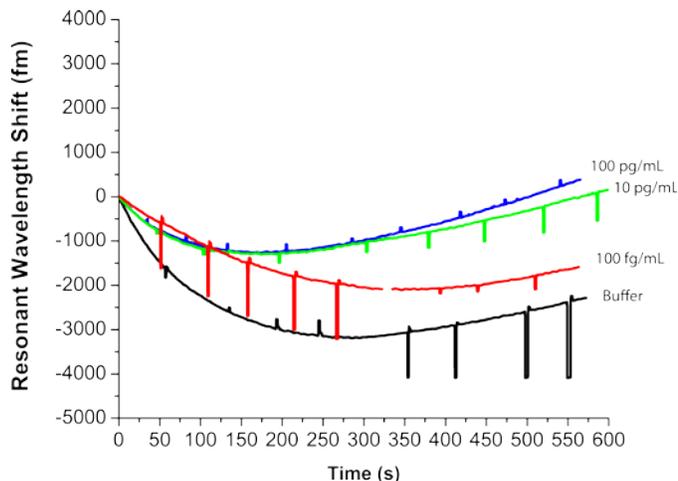


Figure 3. Detection of tau protein in phosphate buffered saline. We were able to detect 100 fg/mL of tau which corresponds to 2.7 fM.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Reports

Evaluation of amyloid in the blood and brain of Alzheimer's mice before and after treatment with focused ultrasound: A therapeutic and biomarkers study. Ted Trouard, PhD, Salvatore Oddo, PhD, Matthew Huentelman, PhD. University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: In this project, we propose to evaluate Magnetic Resonance Imaging guided focused ultrasound (MRgFUS) to facilitate the *release* of amyloid beta (Ab) from the brains of 5X transgenic Alzheimer's disease (AD) mice. The enhanced release of Ab from the brain can function as both a therapeutic approach as well as provide biomarkers of disease.

Background and Significance: MRgFUS is a relatively new technology that uses focused ultrasound in conjunction with microbubble (μ B) contrast agents to temporarily allow molecules to cross the blood brain barrier (BBB). MRgFUS is currently being evaluated for delivering antibody therapeutics to the brain in mouse models of neurological disease.

Preliminary Data: We have demonstrated the MRgFUS technique for temporarily opening the BBB in mice. All of the procedures have been developed and the equipment procured to carry out the proposed experiments in the 5X transgenic AD mouse model of Alzheimer's.

Proposed One-Year and Long-Term Outcomes: We aim to collect the data necessary within the first 6 months of the project to submit a manuscript describing the experiments and results. The results will also provide needed preliminary data that will support the submission of an R21 or R01 grant in February 2019. The NIH grant will include the addition of treatment studies to investigate the extent of A β removal with MRgFUS alone and in combination with the administration of antibodies to different forms of A β .

Year-End Progress Summary: A new 7T small animal MRI system, purchased through support of a \$600,000 NIH Shared Instrument Grant (S10 OOD025016; PI: Ted Trouard) was recently installed in the new Translational Bioluminescence Resource (TBIR) within a Bioscience Research Laboratory (BSRL) building at the University of Arizona. The focused ultrasound (FUS) system has also been moved into the TBIR and now resides adjacent to the 7T MRI system. We have re-established all of the MRI and FUS protocols needed for BBB opening in mice and have successfully carried out MRgFUS experiments in control mice. While establishing a new MRI system and moving into new space has been a tremendous amount of work and has delayed progress on this project in the short term, the new state-of-the-art facilities and equipment will enable us to carry out experiments more efficiently and reliably and provides major long term benefit to the project. Arrangements are currently being made to transfer 5X transgenic mice from Dr. Oddo's laboratory at ASU to the TBIR at the University of Arizona. We expect that the MRgFUS experiments will be finalized by the end of April and that analysis of the blood and brain tissue will be carried out by the end of the funding period.

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Mitochondrial Genome Stability and Late Onset Alzheimer's Disease. Fei Yin, PhD, Rui Chang, PhD, Roberta Brinton, PhD, Tian Wang, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: Aim 1: To generate the forebrain neuron-specific Tfam^{-/-} knockout mouse line. Aim 2: To generate the forebrain neuron-specific Tfam^{-/-} mouse carrying either hAPOE4 or hAPOE3 alleles. Aim 3: To initiate the characterization of the young hAPOE-Tfam^{-/-} mice.

Background and Significance: Brain aging and late-onset Alzheimer's disease (LOAD) both have a multifactorial nature and their progressions are associated with a preceding hypometabolic state, as manifested by the impairment of glucose metabolism and mitochondrial function. Moreover, maternal – but not paternal – history has been found associated with increased AD risk and decreased cognitive performance, further linking deficits in mitochondrial respiratory capacity to AD, as the mitochondrial genome (mtDNA) is exclusively maternally inherited. Cognitively normal subjects with a maternal history of AD also exhibit an early hypometabolic phenotype similar to those who carry the APOE4 allele, the biggest AD genetic risk factor.

This proposal is aimed to *develop a novel mouse model combining mtDNA-induced mitochondrial dysfunction and the APOE4 load, for investigating the impact of mtDNA quantity and stability on brain bioenergetic function and AD risks via the mitochondrion-APOE interaction.* To disrupt mtDNA stability and reduce its copy number, we will generate the conditional knockout mouse of the mitochondrial transcription factor A (Tfam^{-/-}) in the forebrain neurons on either a humanized APOE4 (hAPOE4) or hAPOE3 background. The development of this animal model is rationalized by: 1) mtDNA variations elicit profound effects on nuclear gene expression, cellular physiology and individual aging (12, 13); 2) mtDNA copy number is reduced significantly in aging brain and exaggerated in AD patients and animal models; 3) as the major regulator of mtDNA replication, Tfam levels correlate with mtDNA copy numbers and decrease in aging brain and AD; 4) Tfam bends and packages mtDNA into mitochondrial nucleoids and is therefore critical for mtDNA stability against mutations; 5) APOE4 has been connected with compromised mitochondrial function, but the underlying mechanism is still elusive.

Investigation of the role of mtDNA stability and copy number in normal brain aging and LOAD progression could potentially lead to early identification of those at greatest AD risk and development of interventions targeting mitochondria and energy metabolism to prevent the disease or to maintain a health brain aging.

Preliminary Data: Our pathway-centric bioinformatic analysis of the hippocampal transcriptomes of the hAPOE mice indicated that APOE4 genotype elicited significant impact on the expression of mitochondrial genes encoded by both the nuclear- (nDNA) and mitochondrial genomes in both sexes. The Gene Set Enrichment Analysis (GSEA) ranked Oxidative Phosphorylation (OXPHOS) geneset the most suppressed Hallmark geneset (22) in both male- and female 16-month-old APOE4 mouse hippocampi relative to age- and sex-matched hAPOE3 mice. Moreover, when analyzed separately, both nDNA- and mtDNA-encoded OXPHOS genes were significantly suppressed in APOE4 groups, suggesting interactions between APOE genotype and mtDNA replication/transcription. Decline in hippocampal mitochondrial gene expression is also in parallel with the significantly lowered plasma levels of glucose in the hAPOE4 mice.

Proposed One-Year and Long-Term Outcomes: We expect to generate the conditional Tfam^{-/-} line (Aim 1) in ~4 months, and to generate the hAPOE^{3/3}-Tfam^{-/-} and hAPOE^{4/4}-Tfam^{-/-} lines (Aim 2) in ~8 months. We will be characterizing the newly generated models (Aim 3) during the last 4 months of the funding period.

Upon the end of this funding period, the hAPOE^{3/3}-Tfam^{-/-} and hAPOE^{4/4}-Tfam^{-/-} lines will be expanded for a pilot aging study to delineate the impact of mtDNA decline in combination with age and different APOE genotype on brain bioenergetic function and Alzheimer's risks. Results from that study will be used to seek external, non-state funding from NIH or private agencies to support our hypothesis of mitochondrial dysfunction as one of the initiating mechanisms for LOAD.

Year-End Progress Summary: We have generated and confirmed the genotype of the forebrain neuron-specific Neuro-Tfam^{-/-} (Tfam^{fl/fl}-CaMK2a-Cre) and Neuro-Tfam^{+/-} (Tfam^{+fl}-CaMK2a-Cre) mice. We are actively expanding these colonies for age- and sex-specific characterizations. The hAPOE3-Neuro-Tfam^{-/-} (hAPOE^{3/3}-Tfam^{fl/fl}-CaMK2a-Cre) and hAPOE4-Neuro-Tfam^{-/-} (hAPOE^{4/4}-Tfam^{fl/fl}-CaMK2a-Cre) lines have also been generated and breeding pairs set up for initial phenotyping. Characterization of these lines are focused on mitochondrial bioenergetic capacity and morphological changes, nucleus genome-encoding bioenergetic gene expression during aging and their interactions with APOE genotype.

Our *in vitro* studies in hAPOE3 and hAPOE4 mice suggested that brain mitochondrial phenotype and fuel preference interact with APOE genotype in a cell type dependent manner. While both APOE3 and APOE4 neuronal mitochondria relied primarily on glucose, astrocytes could metabolize more fatty acids than neurons. Our results further revealed that APOE4 astrocytes exhibited higher basal mitochondrial respiration, but lower maximum-to-basal respiration ratio compared to APOE3 astrocytes. Across energy fuels, APOE4 astrocytes had higher capacity metabolizing glucose than fatty acids upon high energetic demand while such a fuel preference was much less significant in APOE3 astrocytes. Outcomes from the hAPOE3-Neuro-Tfam^{-/-} and hAPOE4-Neuro-Tfam^{-/-} mice will provide further insights into the interactions between mitochondrial phenotype and APOE genotype and the communications among the heterogeneous brain cell types in late-onset AD.

Project Progress Report
University of Arizona
College of Medicine – Phoenix

ARIZONA ALZHEIMER'S CONSORTIUM

2018-2019 Scientific Progress Report

Neuroinflammation and neuroplasticity in traumatic brain injury (TBI) disease; cognition assessment in mouse and influence of blood transfusion in man. Maha Saber, PhD, L. Matthew Law, PhD, M. Luisa Rojas, MS, Jonathan Lifshitz, PhD. University of Arizona College of Medicine – Phoenix; Barrow Neurological Institute; Phoenix Children's Hospital; Phoenix Veterans Administration Health Care System; Arizona Alzheimer's Consortium.

Background and Significance: According to the NIH, approximately 7 million people suffer from some type of neurodegenerative disease, and if left unchecked this number will rise to 12 million in 30 years. Alzheimer's disease (AD) is by far the most common neurodegenerative disease affecting over 5.4 million Americans with costs estimated at \$203 billion dollars in 2013 alone (Alzheimer's Association). There is currently no way to prevent, stop, or reverse Alzheimer's disease. Although there is no cure for AD, attenuating risk factors for the eventual expression of the disease could reduce the incidence of Alzheimer's disease. One risk factor for AD and many other neurodegenerative diseases is traumatic brain injury (TBI), and it affects approximately 3.8 million people worldwide every year. Like Alzheimer's disease, the natural progression of TBI leads to age-related cognitive impairments, without specific therapeutic interventions to prevent, stop, or reverse neurological symptoms. Our group investigates the efficacy and mechanisms of action for practical therapies that can become daily routine in the battle against neurological symptoms. For now, we pursue remote ischemic conditioning (RIC) as a therapeutic intervention. RIC is the repeated, transient restriction of blood flow to a non-vital organ in order to generate reparative and restorative molecules that circulate in the systemic and central vasculature. By extension, it becomes plausible that blood transfusion from young donors may harbor regenerative molecules to improve cognitive function. And, either of these approaches may work through the development or reinforcement of synapses within memory circuits of the brain. To this end, we propose to develop a quantitative approach for synaptic profiling and a cognitive task to evaluate cognitive performance in rodents. Our translational approaches advance our understanding of aging, injury, synaptic function, and the potential of practical therapies.

Specific Aims:

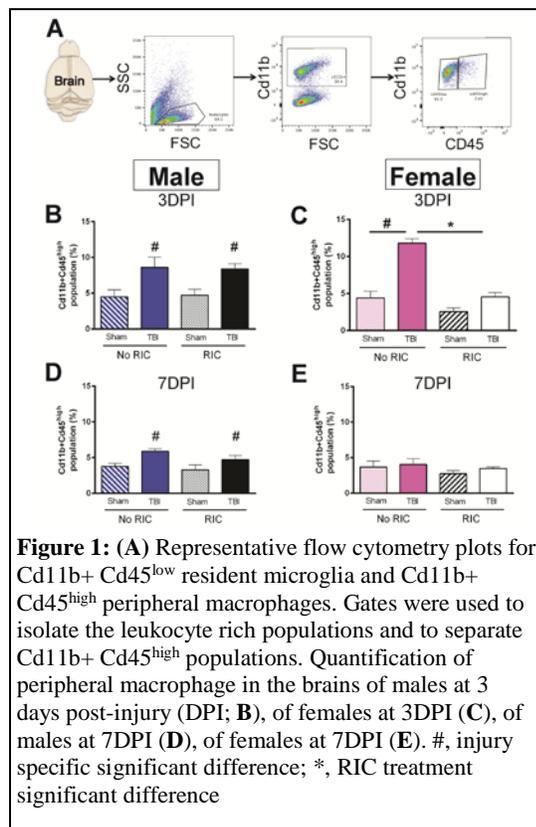
Specific Aim 1: To determine the therapeutic efficacy of remote ischemic conditioning (RIC) to treat TBI-induced cognitive impairments. RIC can prevent physiological and neurological consequences of experimental brain injury in the mouse, but symptom treatment remains unknown. Mixed sex mice (2 month old) will receive diffuse TBI by midline fluid percussion injury (mFPI) or a sham injury. At 1-month post-injury, cognitive performance will be evaluated by novel object testing and Y-maze. Half of the mice will receive RIC (4x5 min) three times over the next week, followed by cognitive assessment. At 2 months post-injury half of the mice will receive an immune challenge (LPS, i.p.), followed by (1) collection of cardiac blood, spleens, and brain for flow cytometry of monocytes (n=6 per group) or perfused with aldehydes for immunohistochemistry (n=4 per group). Outcome analyses are (A) RIC influence on cognitive performance within and between animals, (B) RIC influence on LPS stimulated monocyte numbers in the presence and absence of TBI, (C) sex differences in injury, RIC, and LPS stimulation, (D) histological damage and inflammation in the hippocampal circuit.

Specific Aim 2: To develop flow cytometry and sorting protocols to quantify synapses during development and cognitive rehabilitation. Development, disease, and recovery depend on synaptic organization and reorganization. Traditional microscopic approaches are limited in spatial area, whereas a measure of whole brain regions is necessary to quantify disease

and therapeutic impact. Synaptosome flow cytometry and sorting holds promise to quantify and profile synapse type in dissected brain regions, initially during known phases of development. To develop the quantitative protocol for synaptic profiling, antibodies will be conjugated for fluorescent detection of total (PSD95, SNAP25), excitatory (NR1-4, GluR1-3), and inhibitory (GABAA, GABAB) synapses. Synaptosomes are isolated from whole brains and dissected regions (7.27%, 10%, 20% percoll gradient). Antibody-stained synaptosomes undergo fluorescence activated cell sorting (FACS). Collected synaptosomes samples will be analyzed by electron microscopy to confirm the synaptosome structure and differences between profiles.

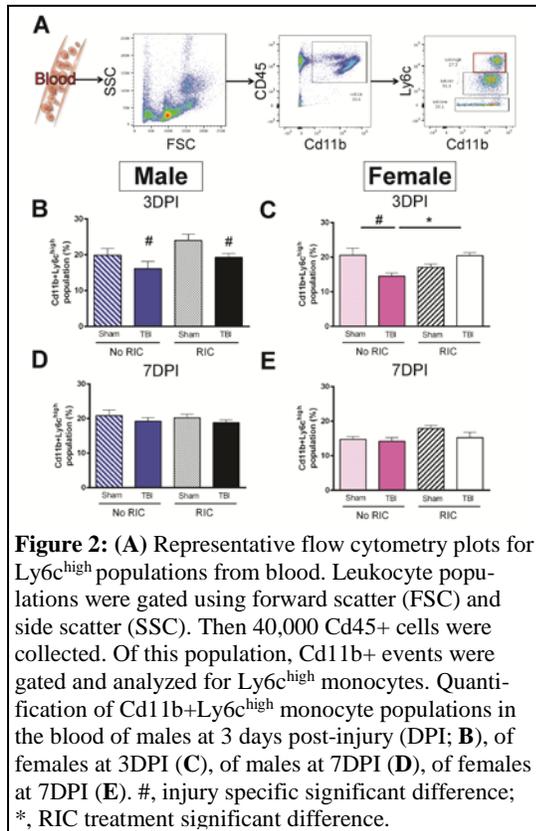
Specific Aim 3: Adaptation of the Peg Forest Arena into a hippocampal-dependent cognitive test. Our group designed an arena (70x70x46 cm) that can accommodate 576 (24x24) 10cm vertical pegs in 9×10^{154} novel arrangements of 92 pegs. To date, we have implemented the Peg Forest Arena as a spatial navigation tool for cognitive rehabilitation after experimental TBI. Now, we propose to develop a cognitive task to measure global and/or local contextual feature discrimination. In rats with and without chemical lesion or inactivation of the hippocampus, the local features (a cluster of pegs) or global features (a quadrant of 23 pegs) will be rotated, removed, added, or textured (e.g. sandpaper, felt) to determine whether animals spend more time investigating the novel context among distractors.

Specific Aim 4: Influence of blood transfusion on age-related cognitive function. In mice, blood transfusion from younger donors can reverse pathology and reduce neurological impairment. In a translational framework, we propose to plan a retrospective clinical investigation on cognitive performance before and after a blood transfusion. We will take advantage of ongoing, longitudinal studies at Banner Alzheimer's Institute, where subjects have taken multiple cognitive tests. We will identify subject that have received blood transfusion between consecutive tests to determine changes in cognitive performance.



Preliminary Data:

The peripheral immune response in systemic circulation that arises from an isolated diffuse TBI can be attenuated by practical interventions. Wild-type male and female mice were subjected to diffuse TBI by midline fluid percussion, an established model of clinical TBI. In the first week post-injury, brain and blood were collected to quantify the fractional population of immune cells by flow cytometry. Resident microglia (Cd11b+ Cd45^{low}) can be distinguished from peripheral macrophages (Cd11b+ Cd45^{high}) in the leukocyte rich populations of the brain (Figure 1A). Over time and between sexes, peripheral macrophages in the brain show sex-specific, injury-specific, and treatment-specific responses (Figure 1B-E). Further, monocytes in the blood were identified using a flow cytometry protocol that detected Ly6c^{high} populations after gating on forward scatter, side scatter, and Cd45+ (Figure 2A). Over time and between sexes, monocyte populations in the blood show sex-specific, injury-specific, and treatment-specific (Figure 2B-E). These protocols are



now well established and under implementation in ongoing and future studies of central and peripheral inflammation after experimental TBI.

Synaptosome flow cytometry has been postponed while the immunology flow cytometry protocols were verified and applied, as indicated above. The established immunology protocols have been taught to the research group as an introduction to the methodology, as relevant published protocols have been acquired to develop the synaptosome flow cytometry. To the same extent, the Peg Forest devices that we manufactured in-house are over used. We have worked with local manufacturers to produce a series of new devices (plastic peg board with 1000+ holes and pegs) to advance our studies of cognition. The new devices have been received and initially tested for utility with wild-type rats and mice. Ongoing studies are preparing for unbiased assessment of pre-frontal cortex blood flow (fluorescent dextran, i.v.) using miniature microscopes, while juvenile rats explore local and global features of the Peg Forest.

Through the consortium, cohorts of aged 3xTg and wild-type female mice were made available to our group. These mice were subjected to combinations of

TBI and RIC to evaluate the acute effects of TBI and treatment in an Alzheimer's mouse model. Data were collected before the mice died naturally, but analysis has not begun.

The plan for clinical analysis of blood transfusion stalled in the funding period due to the need for Banner University Hospital to establish an honest broker data warehouse. As of March 2019, an honest broker system for the extraction, formatting, and sharing of data is now possible. With standard procedures in place, it is possible to identify whether individuals with subsequent cognitive tests also received a blood transfusion.

Impact: The percentage of peripheral macrophages increased in response to diffuse TBI at 3 days post-injury (DPI) in both males and females. However, females showed a significant reduction of these peripheral macrophages with RIC treatment. At 7DPI, peripheral macrophage populations remained increased in the brain of brain-injured males, regardless of treatment. This was not seen in females. There was an injury-induced decrease in Cd11b+Ly6c^{high} monocyte populations in males regardless of treatment at 3DPI. There was an injury-induced decrease in Cd11b+Ly6c^{high} monocyte populations in females, however this was not seen with RIC treatment in brain-injured females at 3DPI. Neither injury or treatment affected Cd11b+Ly6c^{high} monocyte populations at 7DPI in males and females.

The primary impact of this current work relates to the chronic conditions of TBI, one of the leading causes of death and disability worldwide and is a risk factor for multiple neurodegenerative and age-related diseases. There are currently no treatments that are known to prevent neurological disorders, neurodegeneration, or age-related TBI pathologies. These studies propose not only a mechanism for how brain injury can lead to neurodegeneration (central to peripheral inflammation), but a potential treatment to reduce neuroinflammation, peripheral inflammation, and behavioral deficits. With these funded projects, new projects have emerged to

refine the role of RIC treatment on inflammation and TBI-induced pathologies and behaviors. Further, as cellular and behavioral assessments are developed, we will be equipped to investigate the injured and diseased brain in new ways.

Remainder of proposed work: The Arizona Alzheimer's Consortium support for the UA College of Medicine – Phoenix has allowed the program to expand on TBI induced inflammation, chronic outcomes, and rehabilitation. Data analysis of RIC and TBI flow cytometry and neurological behavior continue, with plans for direct comparisons and multiple linear regression modeling. The intention is to determine clinically relevant diagnostics (peripheral immune cells) that can predict neurological impairment and/or recovery. We remain flexible to detect specific changes in the presence or absence of an inflammatory challenge (LPS). Protocol development continues for the synaptosome flow cytometry and cognitive evaluations.

Proposed One-Year and Long-Term Outcomes: The Translational Neurotrauma Research Program is now equipped with protocols to assess central and peripheral inflammation in injury and disease states. These protocols have broadened the impact of a range of studies underway by various investigators. We plan for the synaptosome and cognition protocols to similarly impact the quantitative assessment of function and mechanism. We foresee evaluating unique blood flow signatures of cognitive exploration and the effect on synaptosome profiles in the limbic circuitry. Further, we continue to evaluate the feasibility of a human data blood transfusion study.

A) **RIC as an intervention for TBI and AD induced peripheral inflammation in aged mice**
RIC may reduce peripheral inflammation that occurs in the first few days after TBI. Alzheimer's disease shares a similar inflammatory response to TBI, and RIC is effective in reducing cognitive deficits associated with vascular dementia. Hence, we propose a comparison of peripheral inflammation between TBI and AD aged mouse models to determine the extent to which RIC has therapeutic efficacy.

B) **Peg Forest as a novel spatial navigation cognitive evaluation**
Other funded projects have brought fluorescent miniscope technology to our program. Intravenous fluorescent dextrans label the cerebral vasculature to measure blood flow and vasoconstriction. We will observe cerebral vascular function while animals navigate the peg forest to determine physiological manifestations of cognitive function. Future studies will evaluate cognitive load in the presence and absence of TBI.

C) **Sleep, inflammation, and sex differences**
In response to sex differences found in the current work, we propose an extensive inflammatory profile of males and females after TBI, including characterizing sleep differences. We hypothesize that males will show a more robust change in inflammation and sleep compared to females. These studies will provide rationale for personalized medicine approaches that account for sex differences.

Year End Progress Summary:

Specific Aim 1: The acute time points for this aim have been completed. All flow cytometry data for 3 and 7 DPI have been analyzed and a manuscript is currently being written based on the findings. Cohorts needed for the chronic studies (120DPI) have also been completed. Analysis for the chronic study is still ongoing.

Specific Aim 2: Antibodies to quantify synaptosomes with flow cytometry are currently in the process of conjugation and verification. Supplies have been identified and ordered. Permission and training for the flow cytometry and cell sorter have been obtained.

Specific Aim 3: To date, 10 rats have been run in a first attempt of using the peg forest for cognitive assessment. The peg forest was divided into 4 quadrants, each with the same peg arrangement. After exposure to normal pegs, every peg in one quadrant was covered with a sand paper. After a 10-minute delay, rats are reintroduced to the setup except the quadrant with the sand paper pegs has moved to a novel quadrant. Results showed that rats explored the novel quadrant with sandpaper pegs 28 seconds more the previous sandpaper quadrant. When comparing total exploration time of the 4 quadrants, rats spent 52% more of their time in the novel sandpaper quadrant compared to the other 3 quadrants combined.

Specific Aim 4: The program has been at the forefront of establishing a data warehouse and honest broker system. To this end, a new human IRB can be prepared, while aligning collaborators for the project.

2018 – 2019

Publications, Manuscripts, & Grants

2018 Publications and Manuscripts

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Current and Pending Grants

Current Grants

Eric M. Reiman (PI) 5P30AG019610 NIH/NIA Arizona Alzheimer's Disease Core Center	09/30/01-06/30/19 \$1,628,650
Eric M. Reiman (PI) 5P30AG019610-19S1A1 NIH/NIA Arizona Alzheimer's Disease Core Center – Brain Imaging and Fluid Biomarker Core	09/15/18-06/30/21 \$1,242,362
Eric M. Reiman (PI) 5R01AG031581 NIH/NIA Brain Imaging, APOE, & the Preclinical Course of Alzheimer's disease	05/01/08-03/31/19 \$1,350,755
Eric M. Reiman (PI) 5R01AG055444 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/17-03/31/22 \$1,582,894
Eric M. Reiman (PI) Alzheimer's Association/GHR/FBRI (Reiman/Tariot/Langbaum) Alzheimer's Prevention Initiative APOE4 Trial	01/01/16-12/31/20 \$10,000,000 Total Costs
Eric M. Reiman (PI) 1R01AG058468 (Reiman/Tariot/Langbaum/Aisen/Sperling/ Johnson) NIA/NIA Aducanumab Alzheimer's Prevention Trial	09/01/18-08/31/23 \$4,085,182
Eric M. Reiman (PI) 5U01NS093334 (Cummings/Reiman/Shenton/Stern) NIH/NINDS/Boston University via Mayo Clinic Arizona Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course and Risk Factors	12/15/15-11/30/22 \$1,969,873 Total Project DC
Eric M. Reiman (PI) 3OT2OD026549 (Ojo/Reiman/Theodorou) NIH/NIA via University of Arizona University of Arizona-Banner Health All of Us Research Program	04/01/18-03/31/23 \$958,240
Eric M. Reiman (PI) NOMIS Foundation NOMIS Foundation via Banner Alzheimer's Foundation	09/01/07-08/31/21 \$1,240,381

Eric M. Reiman (PI) TGEN TGen Professional Services Agreement Translational Genomics Research Institute	07/01/08-12/31/19 \$30,330
Eric M. Reiman (Site PI) P01AG052350 (Zlokovic/Toga) NIH/NIA via USC Vascular contributions to dementia and genetic risk factors for Alzheimer's disease	09/30/16-05/31/21 \$74,670
Eric M. Reiman (Site PI) SAGA-17-415540 (Rasgon) Alzheimer's Association/Leland Stanford Jr University Sex Specific Interactions of Modifiable and non-Modifiable Risk Factor	12/01/17-05/31/19 \$36,263
Eric M. Reiman (Site PI) 5R01AG054671 (Quiroz) NIA/NIA via Harvard University Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease	09/01/17-05/31/22 \$33,040
Eric M. Reiman (OSC) RF1AG054617 (Pa) NIH via USC Gender and APOE4 effects on brain morphometry, cognition, and clinical progression to Alzheimer's Disease	09/01/17 - 08/31/22 \$11,318
Eric M. Reiman (Site PI) U19AG024904 (Weiner) NIA/Northern California Institute Res & Educ. Alzheimer's Disease Neuroimaging Initiative	09/30/17-07/31/21 \$43,809
Eric M. Reiman (Site PI) 2U54MD000507 (Manson) NIH/NIA via University of Colorado Denver American Indian and Alaska Native Health Disparities	09/01/17-08/31/22 \$50,000
Yi Su (Project PI) Arizona Alzheimer's Research Consortium (Reiman) State of Arizona Advanced Image Analysis Techniques for the Detection and Tracking of Alzheimer's disease and its prevention	07/01/18-6/30/19 \$150,000
Yi Su (Project PI) Arizona Alzheimer's Research Consortium (Reiman) State of Arizona Statistical and Neuroimaging Core Resources Serving	07/01/18-6/30/19 \$50,000

the Consortium members for the Alzheimer's disease and prevention related studies

Yi Su (Project PI) Arizona Alzheimer's Research Consortium (Reiman) State of Arizona Application of Deep Learning Methods to Develop Computer Aided Diagnostic Tools for the Early Detection, Tracking and Diagnosis of Alzheimer's Disease	07/01/18-6/30/19 \$40,000
Yi Su (PI) R21EB024366 (Wang/Goyal/Su) NIH/NBIB via Cornell University Feasibility of challenge-free QSM based quantitative mapping of cerebral metabolic rate of oxygen	04/01/17-01/31/20 \$17,000
Yi Su (PI) ADR A2017272S BrightFocus Foundation Blood Brain Barrier and Metabolism in Aging and Alzheimer Disease	07/01/17-06/30/20 \$300,000 Total Project Costs
Yi Su (PI) AARG17532945 Alzheimer's Association Amyloid PET as a biomarker for white matter integrity in Alzheimer Disease	10/01/17-09/30/20 \$150,000 Total Project Costs
Yi Su (Site PI) SAGA-17-415540 (Rasgon) Alzheimer's Association/Leland Stanford Jr University Sex Specific Interactions of Modifiable and non-Modifiable Risk Factor	12/01/17-05/31/19 \$36,263
Yi Su (Site Co-PI) 0 U19AG024904 (Weiner) NIA/Northern California Institute Res & Educ. Alzheimer's Disease Neuroimaging Initiative	9/30/17-07/31/21 \$43,809
Yi Su (Co-Investigator) 5R01AG055444 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/17-03/31/22 \$1,582,894
Yi Su (Co-Investigator) 1R01AG058468 (Reiman/Tariot/Langbaum/Aisen/Sperling/ Johnson) NIA/NIA Aducanumab Alzheimer's Prevention Trial	09/01/18-08/31/23 \$4,085,182
Jessica Langbaum (Co-Investigator) 5R01AG055444 (Reiman/Tariot/Lopera) NIH/NIA	04/01/17-03/31/22 \$1,582,894

Alzheimer's Prevention Initiative ADAD Colombia Trial	
Jessica Langbaum (Project PI) Arizona Alzheimer's Research Consortium (Reiman) State of Arizona Arizona Alzheimer's Registry	07/01/11-06/30/19 \$30,000
Jessica Langbaum (Co-I) 2 R01 AG031581 NIH/NIA Brain Imaging, APOE, & the Preclinical Course of Alzheimer's disease	05/01/08-03/31/19 \$1,110,690
Jessica Langbaum (Co-PI) Alzheimer's Association/GHR/FBRI (Reiman/Tariot/Langbaum) Alzheimer's Prevention Initiative APOE4 Trial	01/01/16-12/31/20 \$10,000,000 Total Costs
Jessica Langbaum (Co-PI) 1R01AG058468 (Reiman/Tariot/Langbaum/Aisen/Sperling/ Johnson) NIA/NIA Aducanumab Alzheimer's Prevention Trial	09/01/18-08/31/23 \$4,085,182
Don Saner (Project PI) Arizona Alzheimer's Research Consortium (Reiman) State of Arizona Enhancements to a Centralized Data Management System For the Arizona Alzheimer's Disease Core Center (ADCC), Brain and Body Donation Program (BBDP), and Apolipoprotein E4 (APOE4) Gene Dose Program	07/01/11-06/30/19 \$100,000
Don Saner (Core Leader) 5P30AG019610 NIH/NIA Arizona Alzheimer's Disease Core Center	09/30/01-06/30/19 \$1,628,650
Don Saner (Data Science Sr. Director) 3OT2OD026549 (Ojo/Reiman/Theodorou) NIH/NIA via University of Arizona University of Arizona-Banner Health All of Us Research Program	04/01/18-03/31/23 \$958,240
Yalin Wang (PI) ASU-Mayo Seed Grant Integrating genomic and imaging biomarkers for early detection of Alzheimer's disease	1/1/2019-12/31/2019 \$25,000
Yalin Wang (PI) Children's Hospital Los Angeles Predicting the early childhood outcomes of preterm brain shape abnormalities	9/22/2018 – 6/30/2019 \$96,884
Yalin Wang (PI)	8/1/2014 – 7/31/2019

National Science Foundation III: Small: Multi-modal Neuroimaging Data Fusion and Analysis with Harmonic Maps Under Designed Riemannian Metric	\$418,114
Yalin Wang (PI) University of Michigan Multi-Source Sparse Learning to Identify MCI and Predict Decline	6/1/2016-5/31/2020 \$792,315
Yalin Wang (PI) University of Pittsburgh Modeling Multi-modal Neuroimaging Biomarkers in the SVRIII Cohort in Relationship	9/15/2018-4/30/2019 \$59,874
Yalin Wang (PI) University of Southern California ENIGMA Center for Worldwide Medicine Imaging Genomics	6/1/2015-9/30/2019 \$178,224
Yalin Wang (Co-PI) Arizona Alzheimer's Consortium FY19 Arizona Alzheimer's Disease Consortium	7/1/2018-6/30/2019 \$30,000
Velazquez, Ramon AARFD-16-442710 ASUF 30007328 Arizona State University Foundation (ASUF) Pim1 inhibition as a therapeutic strategy for Alzheimer's disease	10/1/2016-9/30/2019 \$62,256.00
Caccamo, Antonella AARG-17-503765 ASUF 30007546 Arizona State University Foundation (ASUF) Molecular mechanisms of cognitive decline in Alzheimer's disease	3/1/2017-2/28/2020 \$45,454.00
Oddo, Salvatore R01 AG037637 HHS: National Institutes of Health (NIH) Molecular interplay between A tau and mTOR: Mechanisms of neurodegeneration	6/1/2016-5/31/2021 \$275,756.00
Oddo, Salvatore R21 NS096375 HHS: National Institutes of Health (NIH) Tau conditional knockout mice to elucidate the function of tau in the adult brain	7/15/2016-6/30/2019 \$150,000.00
Oddo, Salvatore R01 AG057596 HHS: National Institutes of Health (NIH) Necroptosis as a novel mechanism of neurodegeneration in Alzheimer's disease	9/1/2018-5/31/2023 \$632,046.00
Caccamo, Antonella R01 AG059627 HHS: National Institutes of Health (NIH)	9/15/2018-5/31/2023 \$346,948.00

Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome

Oddo, Salvatore 6/14/2017-4/30/2019
425243 \$41,383.00
University of Arizona
U of A NRSA Postdoctoral Training Grant

Oddo, Salvatore 6/1/2016-5/31/2021
R01 AG037637 \$275,756.00
HHS: National Institutes of Health (NIH)
Molecular interplay between A tau and mTOR: Mechanisms of neurodegeneration

Oddo, Salvatore 7/15/2016-6/30/2019
R21 NS096375 \$150,000.00
HHS: National Institutes of Health (NIH)
Tau conditional knockout mice to elucidate the function of tau in the adult brain

Oddo, Salvatore 9/1/2018-5/31/2023
R01 AG057596 \$632,046.00
HHS: National Institutes of Health (NIH)
Necroptosis as a novel mechanism of neurodegeneration in Alzheimer's disease

Caccamo, Antonella 9/15/2018-5/31/2023
R01 AG059627 \$346,948.00
HHS: National Institutes of Health (NIH)
Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome

Oddo, Salvatore 6/14/2017-4/30/2019
425243 \$41,383.00
University of Arizona
U of A NRSA Postdoctoral Training Grant

Omar Khdour (PI) 12/30/2017-12/31/2019
Sidney Hecht (Co-PI) \$300,000
Optimization of Methylene Blue Derivatives as Mitochondrial Therapeutic Agents for the Treatment of Friedreich's Ataxia

Cassandra Gipson-Reichardt (PI) 09/2018 - 08/2020
R03 DA045881 \$100,000
National Institute on Drug Abuse.
Glutamatergic mechanisms underlying nicotine addiction and relapse following nicotine reduction

Foster Olive (PI) 09/2018 - 07/2022
Cassandra Gipson-Reichardt (Co-I) \$1,250,000
R01 DA043172
National Institute on Drug Abuse.
Characterization and reversal of neurocognitive dysfunction produced by long-term synthetic cathinone use

Cassandra Gipson-Reichardt (PI) R00 DA036569 National Institute on Drug Abuse. Contributions of Glial Glutamate Transport and NMDA Receptors in Nicotine Relapse	01/2016 - 12/2019 \$249,000
Robert Zaczek (PI) Cassandra Gipson-Reichardt (Subcontract PI) Foster Olive (Subcontract PI) R41 Grant National Institute on Drug Abuse. Preclinical assessment of the GluN2B inhibitor clinical candidate NP10679 as a medication to prevent opiate abuse	07/2018 - 06/2019 \$70,000
Cassandra Gipson-Reichardt (PI) R21 DA044479 National Institute on Drug Abuse. Cholinergic modulation of glutamatergic signaling in nicotine addiction and relapse	07/2018 - 06/2020 \$400,000
Cassandra Gipson-Reichardt (PI) R21 DA044479-S1 Diversity Supplement National Institute on Drug Abuse. Cholinergic modulation of glutamatergic signaling in nicotine addiction and relapse	01/2019 - 06/2020 \$60,000
David Coon (Co-PI) Barrow Neurological Foundation Parkinson's Partners in Care	7/1/2018-3/31/2020 ASU Budget: \$100,000
David Coon (PI) Phoenix Symphony ASU Budget: Music and Memory III	8/1/18-7/31/19 \$100,000
David Coon (PI & Project Director) Alzheimer's Disease Initiative-Specialized Supportive Services (ADI-SSS) Arizona Dementia Capable System Expansion	9/01/17-8/31/20 ASU Budget: \$999,903
David Coon (PI & Project Director) Valley of the Sun United Way Health and Human Services Promotores II	1/1/18 – 12/31/18 \$50,000 Total Costs
David Coon (PI) National Institute on Aging EPIC: A Group-based Intervention for Early-stage AD Dyads in Diverse Communities	5/15/16-6/30/21 ASU Budget: \$3.6M
David Coon (Core Leader) National Institute on Aging Outreach & Recruitment Core - Arizona Alzheimer's Disease Core Center ORE Core Leader for the Arizona Alzheimer's Disease Center fostering education, outreach and recruitment, particularly of diverse participants into the clinical core. ORE Core Leader Total Award: \$459,230	07/01/16 – 06/30/21 \$8.8M Total Award

David Coon (Co-PI) HHS-HRSA -University of Arizona Center on Aging Empowering Caregiver Self-Care	07/01/15 – 06/30/19 ASU Budget: \$420,000
Caccamo, Antonella AARG-17-503765 ASUF 30007546 Arizona State University Foundation (ASUF) Molecular mechanisms of cognitive decline in Alzheimer's disease	3/1/2017-2/28/2020 \$45,454.00
Oddo, Salvatore R01 AG057596 HHS: National Institutes of Health (NIH) Necroptosis as a novel mechanism of neurodegeneration in Alzheimer's disease	9/1/2018-5/31/2023 \$632,046.00
Caccamo, Antonella R01 AG059627 HHS: National Institutes of Health (NIH) Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome	9/15/2018-5/31/2023 \$346,948.00
Heather Bimonte-Nelson (PI) R01 AG028084 National Institute on Aging Variations in hormones during menopause: Effects on cognitive and brain aging	10/2007 - 8/2023
Heather Bimonte-Nelson (PI) R01 AG028084-09S1 R01 Grant, Diversity Supplement Variations in hormones during menopause: Effects on cognitive and brain aging	5/2017 - 4/2019
Eric M. Reiman (PI) Co-Directors of the Research Education Component: Heather Bimonte-Nelson and Yonas Geda (Mayo) NIH 2P30AG19610 Alzheimer's Disease Core Center Grant (Arizona) Arizona Alzheimer's Disease Core Center	7/1/2001 - 6/30/2021
Jason Newbern (PI) Heather Bimonte-Nelson (Co-I) R01 NS097537 Functions of ERK/MAPK Signaling in GABAergic Circuit Development	7/1/2016 - 5/31/2021
Foster Olive (PI) Heather Bimonte-Nelson (Co-I) R01 DA043172 Characterization and reversal of neurocognitive dysfunction produced by long-term synthetic cathinone use	9/26/2017 - 8/31/2022
Carol Barnes (PI) Paul Coleman (Co-I)	5/01/2016 - 4/30/2021

Eric M. Reiman (Co-I)
Heather Bimonte-Nelson (Associate Director)
Matthew Huentelman (Associate Director)
NIA (NIH) T32AG044402
Postdoctoral T32 Training Grant
Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease

Juliana Kling (PI) 1/1/2017 - 6/31/2019
Heather Bimonte-Nelson (Co-I)
Virginia Miller (Co-I)
Cynthia Stonnington (Co-I)
Leslie Baxter (Co-I)
Anita Mayer (Co-I)
Paru David (Co-I)
Julia Files (Co-I)
Dona Locke (Co-I)
Yonas Geda (Co-I)
Hamy Temkit (Co-I)
Mayo MEGA Award
Cognitive effects of ovarian hormones in menopause

Heather Bimonte-Nelson (Co-PI) 2/1/2017 - 1/31/2018
Julia Files (Co-PI)
Anita Mayer (Co-PI)
Marcia Ko (Co-PI)
Rosy Krajmalnik-Brown (Co-PI)
Mayo Ken and Linda Morris Weight and Wellness Solutions Program Awards
Obesity in menopause: The role of estrogen therapy on the gut microbiome and host energy balance after surgically-induced menopause

Andrew A. George (PI) 10/31/14 - 6/31/18
Heather Bimonte-Nelson, Paul Whiteaker (Faculty Mentors)
Arizona Biomedical Research Commission (ABRC) Early Investigator Award (Mentor)
Amyloid beta-induced homeostatic neuronal instability in basal forebrain cholinergic neurons

David Brafman (PI) 04/1/2019-3/31/2021
T0042-C \$1,387,138 Total Costs
Department of Defense
Biomanufacturing of Cells in the Neuroectoderm Fate Space

David Brafman (PI) 04/1/2019-3/31/2021
T0138 \$800,000 Total Costs
Department of Defense
Adaptable Multi-Modality Nanoprobes for Non-Invasive Real-Time Monitoring of Engineered Cells and Tissues

David Brafman (PI) 07/1/2018-12/31/2019
Arizona Board of Regents \$400,000 Total Costs
Statewide Collaborative Regenerative Medicine Research and Training Facility

David Brafman (PI) R21 AG056706 NIH-NIA Generation and characterization of isogenic hiPSC lines with various APOE genotypes	09/15/2017-4/30/2019 \$409,034 Total Costs
David Brafman (PI) R01 GM121698 NIH-NIGMS Investigating the mechanisms of a multi-state model of Wnt signaling	04/01/2017-03/31/2022 \$1,518,984 Total Costs
David Brafman (PI) ADHS16-162401 Using human induced pluripotent stem cells to investigate the contribution of aging to the onset and progression of Alzheimer's disease	04/01/2017-03/31/2020 \$225,000 Total Costs
Andrew George (PI) The Barrow Neurological Foundation Award The Effects of Maternal Choline Supplementation on Basal Forebrain Cholinergic Neuronal Excitability and the Role of $\alpha 7$ Nicotinic Acetylcholine Receptors (nAChRs)	06/1/17-6/1/19
Elliott J. Mufson (PI) P01 AG014449 NIH-NIA Neurobiology of mild cognitive impairment in the elderly Role: Collaborator	09/01/1997-01/31/2019
Elliott J. Mufson (PI) R01 AG043375 NIH-NIA TCellular and molecular medial temporal lobe pathology in elderly preMCI subjects Role: Collaborator	09/15/2013- 05/31/2019
Elliott J. Mufson (PI) W81XWH-13-2-0095 Department of Defense Tau pathology post traumatic brain injury Role: Collaborator	09/01/2014-09/30/2018
Andrew Ducruet (Co-I) Dignity Health/ Arizona State University Collaborative Strategic Initiatives Program Multi-institutional program to translate liquid embolic to the clinic	
Daniela Zarnescu (PI) Department of Defense Small molecules targeting TDP43-RNA interaction in ALS	07/01/18 – 06/30/20
Ashley Stokes (PI) AARC at BNI Pilot Project Grant Multimodal Biomarkers of Alzheimer's Disease: Combining advanced MRI biomarkers with clinical, genetic, and structural imaging biomarkers	07/01/2018-06/31/2019 \$50,000 Total Direct Costs

Ashley Stokes (PI) Arizona Biomedical Research Commission New Investigator Award Multi-parametric MR imaging signatures of brain tumor burden	03/01/2017-02/29/2020 \$204,546 Total Direct Costs
Ashley Stokes (PI) Barrow Neurological Foundation Multiscale MR Perfusion Imaging of Multiple Sclerosis	\$85,000 Total Direct Costs
5U18 FD005320 Critical Path Public Private Partnerships	9/1/14-8/31/19
Richard Casell (PI) National Institute on Aging (2P30 AG019610). Core B: ADCC Clinical Core in: Alzheimer's Disease Core Center, Cores A, B and C.	08/15/2011 - 06/30/2019
Richard Caselli (PI) National Institute on Aging (2P30 AG019610) Core C: ADCC Data Management Statistical Core in: Alzheimer's Disease Core Center, Cores A, B and C.	08/15/2011 - 06/30/2019
Richard Caselli (PI) Core A: ADCC Admin Core in: Alzheimer's Disease Core Center, Cores A, B and C. Funded by National Institute on Aging (2P30 AG019610)	08/15/2011 - 06/30/2019
Richard Caselli (PI) National Institute of Neurological Disorders and Stroke (2R01 AG031581-15A1) PET, APOE, & the Preclinical Course of Alzheimer Disease.	05/01/2014 - 04/30/2019
Richard Caselli (PI) (ADHS12-010553) Arizona Department of Health Services Normal and Pathological Aging (Preclinical Alzheimer's Disease) in: Normal and Pathological Aging (Preclinical Alzheimer's Disease).	07/01/2011 - 06/30/2019
Richard Caselli (PI) Merck & Co., Inc. (Protocol No. MK-8931-017) A Randomized, Placebo Controlled, Parallel-Group, Double Blind Efficacy and Safety Trial of MK- 8931 in Subjects with Mild to Moderate Alzheimer's Disease.	11/01/2013 - 10/31/2020
Layla Al-Nakkash (PI) Arizona Alzheimer's Consortium through the Midwestern University Alzheimer's Advisory Committee (MAAC) Diabetic obesity results in cognitive impairment: evaluation of the gut, brain and bone effects in response to exercise and genistein treatment.	07/01/17 - 06/30/18 \$25,598
Layla Al-Nakkash (PI) Arizona Alzheimer's Consortium through the Midwestern University Alzheimer's Advisory Committee (MAAC) Diabetic obesity results in cognitive impairment: evaluation of the gut, brain and bone effects in response to exercise and genistein treatment-Part II.	07/01/18 - 06/30/19 \$15,000

Layla Al-Nakkash (PI) Diabetes Action and Research Foundation Genistein: Understanding its ability to ameliorate intestinal dysfunction in diabetes.	01/01/17 - 12/31/18 \$18,182
Layla Al-Nakkash (PI) Diabetes Action and Research Foundation High fat diet-induced diabetes is abolished by combined genistein and exercise treatment: identifying the mechanisms.	01/01/19 - 12/31/19 \$9,091
Layla Al-Nakkash (Consultant) NIH-R15 Physical activity as a therapeutic intervention in endometriosis.	04/01/18-03/31/21 \$470,124
Layla Al-Nakkash (PI) Midwestern University Intramural Grant Program The DF508-CF mouse: influence of genistein on the intestinal epithelial barrier and bile acids.	07/01/18 - 06/30/19 \$5,000
Nancy Bae (Co-PI) and Mark Swanson (Co-PI) Arizona Alzheimer's Consortium through the Midwestern University Alzheimer's Advisory Committee (MAAC) Investigating the differences between ape and human GFAP proteins involved in neurodegeneration.	07/01/17-06/30/18 \$9,300
Tom Broderick (PI) Midwestern University Intramural Grant Program Effects of the Diabetic State on Hepoatic Biosynthesis and Renal Handling of Carnitine	07/01/18-06/30/19 \$5,000
Delrae Eckman (PI) and T.B. Jones (Co-PI), Johana Vallejo-Elias (Co-PI), Carleton Jones (Co-PI), Jessica Powell (Co-PI) Arizona Biomedical Research Commission RFGA ADHS 17-00007401 Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4 Targeted-Replacement Mice.	04/01/18-03/31/21 \$225,000
Delrae Eckman (PI) Arizona Alzheimer's Consortium through the Midwestern University Alzheimer's Advisory Committee (MAAC) Cerebrovascular Function in APOE3 and APOE4 Targeted-Replacement Mice	07/01/17-06/30/18 \$9,078
Delrae Eckman (PI) Midwestern University, College of Health Sciences Research Grant Cardiovascular and Cerebrovascular Function in APOE3 and APOE4 Targeted-Replacement Mice.	10/25/17-06/30/18 \$7,000
Delrae Eckman (PI) Midwestern University Intramural Grant Program Cerebral Artery Function in 3-month and 9-month-old 3xTg-AD Mice	07/01/18-06/30/19 \$5,000
Delrae Eckman (Co-PI) Midwestern University, MSRA,	07/01/17-06/30/18 \$20,000

Multidisciplinary Stimulus Research Award

Can laser therapy in the dental office heal cold sores better than anything else?

Mitra Esfandiarei (PI) 01/01/17-12/31/19
Marfan Foundation, Subaward from Stanford University \$30,484
Children and Adolescents with Marfan Syndrome – 10,000 Healthy Steps and Beyond

Mitra Esfandiarei (PI) 01/15/19-12/31/21
NIH R15 AREA Grant \$303,864
Targeting Endothelial Dysfunction in a Genetic Mouse Model of Aortic Aneurysm: Implications for Prevention and Therapy

Fernando Gonzalez (PI) 07/01/18-06/30/19
Midwestern University Intramural Grant Program \$5,000
Role of Oral Microbiota in Fungal Viability.

Michael Griffin (PI) 07/01/18-06/30/19
Midwestern University Intramural Grant Program \$6,000
Transcriptional Regulation of Adipocyte Inflammation by Early-B Cell-Factor-1 (Ebf1).

Jose Hernandez (Co-PI) 07/01/17-06/30/18
Midwestern University, One Health Stimulus Research Award \$10,000
Elucidating the role of *R. sanguineus* as a vector for RMSF transmission in Arizona.

Garilyn Jentarra (PI) and Bucky Jones (Co-PI) 07/01/17-06/30/18
Arizona Alzheimer's Consortium through the \$33,000
Midwestern University Alzheimer's Advisory Committee (MAAC)
The Role of Infection in the Development and Pathological Features of Alzheimer's Disease.

Garilyn Jentarra (Co-PI) and Bucky Jones (Co-PI) 07/01/18-06/30/19
Arizona Alzheimer's Consortium through the \$78,998
Midwestern University Alzheimer's Advisory Committee (MAAC)
Continuing investigations into the role of microbes in the development of Alzheimer's disease.

Bucky Jones (Co-I) 10/03/17-06/30/18
NIH: NINDS R01NS082463 Subcontract to MWU \$5,294
Motoneuron pool plasticity following spinal cord injury

Carleton Jones (PI) 10/25/17-06/30/18
Midwestern University, College of Health Sciences \$6,000
Research Grant
Effects of Losartan and Exercise on Aortic Inflammation in Marfan syndrome Mice.

Kathy Lawson (PI) 07/01/17-06/30/18
Midwestern University Intramural Grant Program \$4,500
The Role of P-cadherin in Tumor Progression

Kathy Lawson (PI) 07/01/17-06/30/18
Midwestern University Intramural Grant Program \$5,000
The Role of P-cadherin in Breast Cancer Chemoresistance

Ashlesh Murthy (PI) NIH R15 AREA Grant Mechanism(s) of CD8 T Cell-mediated Chlamydia-induced Reproductive Pathology	07/01/16-6/30/19 \$300,000
Ashlesh Murthy (PI) USDA NIFA Capacity Grant USDA Animal Health and Disease Research Grant	10/01/18-9/30/19 \$25,604
Ashlesh Murthy (PI) Boehringer Ingelheim Boehringer Ingelheim Veterinary Scholars Program	06/01/18-09/30/18 \$20,000
Ashlesh Murthy (PI) PetSmart Charities, Inc. Title: MWU-PSC Student Summer Fellowship	06/01/18-09/30/18 \$5,000
Mark Olsen (Co-I) Winn Feline Foundation Subaward from University of California-Davis Developing a Safe and Effective Combined Anticoronaviral Therapy (CACT) for Cats with FIP	12/01/17-05/31/19 \$6,000
Pamela Potter (PI) Midwestern University Intramural Grant Program Beta Arrestin in Transgenic Mice	07/01/18-06/30/19 \$4,400
Pamela Potter (PI), Doug Jones (Co-I) Arizona Alzheimer's Consortium through the Midwestern University Alzheimer's Advisory Committee (MAAC) Effects of Norclozapine on beta Amyloid in Transgenic Mice- a potential new treatment option for Alzheimer's Disease?	07/01/18-06/30/19 \$6,002
Charles Veltri (Co-PI) Midwestern University, College of Veterinary Medicine – Academic Research Enhancement Awards Establishing pharmacokinetics of fluoxetine in horses	07/01/17-06/30/18 \$7,480
Charles Veltri (Co-PI) Midwestern University, College of Pharmacy Intramural Grant Stability of Cefovecin Sodium (Convenia) Stored Off-Label in Veterinary Clinical Practice	07/01/17-06/30/18 \$9,687
Charles Veltri (Collaborator) Grants for Laboratory Animal Sciences Alternative Delivery Methods for Post-Operative Analgesia Using Meloxicam in Mice	07/01/17-06/30/18 \$7,500
J Gregory Caporaso (PI) 1565100 National Science Foundation Extensible, reproducible and documentation-driven microbiome data science.	05/01/2016 – 04/30/2020 \$525,795
J Gregory Caporaso (Co-Investigator) APP1085372	03/01/2015 – 01/31/2020 \$530,000

National Health and Medical Research Council (Huttley)
Robust bioinformatics for predicting bacterial pathogens from microbiome sequencing

Emily Cope 07/01/2017 - 06/30/2019
TRIF-SPA 2.0 \$160,000
NSF-CLP
Postdoctoral scholar award: Upper and lower airway microbiota in asthma

Paul Keim (MPI) 01/01/2016 - 12/30/2019
Flinn Foundation Research Grant (Keim/Lal/LaBaer) \$1,200,000
Flinn Foundation
Characterization of the Chronic Rhinosinusitis (CRS) Microbiome-Host Interaction for
Microbiota-Directed Probiotic Therapy

Emily Cope (Co-I) 02/01/2018 - 01/31/2020
1U54MD012388-01 (Baldwin/Stearns-MPI) \$59,892
SHERC Pilot grants program (Pilot: Koppisch, Co-I: Cope)
NIH/NIMHD
Novel Ionic Liquid Formulations to Combat Diabetic Foot Ulcer Infections

Emily Cope 02/01/2018 - 01/31/2020
1U54MD012388-01 (Baldwin/Stearns-MPI) \$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 (MPI) 01/01/2019 - 12/30/2021
Flinn Foundation Research Grant (Cope/Rank MPI) \$100,000
Project #2188
Precision Treatment of Asthma Through Targeted Manipulation of the Gut Microbiome Lung
Axis

Matthew Huentelman (Multi-PI) 08/01/2013 - 07/31/2019
UH2/UH3TR0000891 (Huentelman) \$242,183
NIH/Trans-NIH Research
exRNA signatures predict outcomes after brain injury

Matthew Huentelman (Multi-PI) 09/15/2014 – 05/31/2019
R0AG048907 (Huentelman/Barnes) \$245,145
NIH/NIA
CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox

Matthew Huentelman (Co-I) 08/01/2014 – 03/31/2019
RO1 AG049465 (Barnes) \$162,203
NIH/NIA
Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging

Matthew Huentelman (Co-I) 08/01/2014 – 05/31/2019
1 RO1 AG049464 (Coleman/Barnes/Alexander) \$178,013
NIH/NIA

Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain

Matthew Huentelman (Co-I) Grant (Sabbagh) Alzheimer's Association Treatment for AD in individuals with Down's Syndrome	04/01/2016 – 03/31/2019 \$37,829
Matthew Huentelman (Co-I) P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center	07/01/2016 - 06/30/2021 \$12,190
Matthew Huentelman (Co-I) UG30D023313 (Deoni) NIH The Developing Brain: Influences and Outcomes	09/21/2016 – 08/31/2021 \$70,000
Matthew Huentelman (Co-I) R01AG054180 (Kaczorowski) NIH Systems Genetics of Cognitive Aging and Alzheimer's Disease	05/01/2017 – 04/30/2022 \$10,028
Matthew Huentelman (Co-PI) Grant#20170715 Aging Mind Foundation Ealry Onset Alzheimer's Disease Genomic Study	11/08/2017 – 11/07/2019 \$32,441
Matthew Huentelman (Co-I) R01AG031581 (Reiman) NIH Brain Imaging, APOE & Preclinical Course of Alzheimer's Disease	05/01/2018 – 03/31/2019 \$78,465
Matthew Huentelman (Co-I) R56HL141165 (Hale) NIH Identifying a Pathogenic Fibroblast Subpopulation to Target for Protection Against Cardiac Fibrosis	09/20/2018 - 08/31/2023 \$48,416
Matthew Huentelman (PI) AAC - DHS (Huentelman) Investigator (Reiman) State of Arizona, DHS AARC FY 19: Alzheimer's Projects	07/01/2018 – 06/30/2019 \$100,000
Matthew Huentelman (Co-I) FA8650-11-C-6159 (Broderick) Wright State Applied Research Corporation RFP WSARC-17-00751 Revolutionary Intelligence	07/01/2018 – 08/01/2019 \$85,055
Kendall Van Keuren-Jensen (PI) Grant ID: 17491	02/14/2019 – 02/13/2020 \$19,029

Michael J Fox Foundation for Parkinson's Research
Collaboration and Advisory role for the Industry LRRK2 Detection Consortium: CSFExosome Study

Kendall Van Keuren-Jensen (Co-I) 05/24/2018 – 05/23/2020
Grant 15065 (PI: Singleton-NIH) \$158,726
Michael J Fox Foundation for Parkinson's Research
The Foundational Data Initiative

Kendall Van Keuren-Jensen (Co-I) 06/08/2018 – 06/04/2020
Grant 14539 (PI: Cookson-NIH) \$80,000
Michael J Fox Foundation for Parkinson's Research
LRRK2 Biology Consortium Program

Kendall Van Keuren-Jensen (Subaward Co-PI) 10/30/2018 – 08/14/2019
FA8650-11-C-6159 (Subaward contract: 11142.002) \$85,055
(PI: Broderick)
OFC of Naval Research
WSARC-17-00751 Revolutionary Intelligence and Influence Technologies (RIIT)

Kendall Van Keuren-Jensen (Multi-PI) 08/01/2013 - 07/31/2019
4UH3TR000891 (Van Keuren-Jensen/Huentelman/Adelson/
Kalani) \$336,309
NIH/Trans-NIH Research
exRNA signatures predict outcomes after brain injury

Kendall Van Keuren-Jensen (PI) 08/01/2015 – 07/31/2019
Grant ID: 16-IIP-255 \$80,000
ALS Association Grant
Assessment of extracellular vesicle contents in patients with ALS

Kendall Van Keuren- Jensen (Co-I) 07/01/2017 - 06/30/2019
Arizona Department of Health Services Grant \$100,000
(PI: Eric M. Reiman)
TGen Arizona Alzheimer's Consortium Projects
Identification of RNA modifications altered in Alzheimer's disease

Kendall Van Keuren- Jensen (PI) 04/01/2017 – 3/31/2019
Grant ID: 12749.01 \$90,568
Michael J Fox Foundation for Parkinson's Research
RNAseq and miRNAseq in PPMI whole blood samples (2nd)

Kendall Van Keuren- Jensen (PI) 08/31/2017 – 08/30/2019
Grant ID: 14696 \$48,599
Michael J Fox Foundation for Parkinson's Research
RNAseq and miRNAseq in PPMI whole blood samples-Phase 2

Kendall Van Keuren- Jensen (PI) 06/01/2017 – 05/31/2019
Grant 977871 \$150,000
Sidell-Kagan Foundation

Advancing prevention of Alzheimer's disease: Extracellular RNAs as candidates for monitoring Alzheimer's patients

Winnie Liang (Co-I) Contract (Jonathan Keats) MMRF Longitudinal, Observation Study in Newly Diagnosed Multiple Myeloma (MM) Patients to Assess the Relationship between Patient Outcomes, Treatment Regimens and Molecular Profiles (The MMRF Longitudinal Study)	09/01/2011 -08/31/2019 \$1,364,526
Winnie Liang (Co-I) W81XWH-16-TSCR-IDA (Vinodh Narayanan) DoD TS160074:Phenotypic Variability in Tuberous Sclerosis Complex (TSC)	12/01/2016 – 11/30/19 \$150,000
Winnie Liang (Co-I) R01GM121698 (David Brafman) Investigating the mechanisms of a multi-state model of Wnt signaling	02/01/2017 – 03/31/2019 \$11,144
Winnie Liang (Co-I) Grant (Eric M. Reiman) NOMIS Foundation	07/01/2017 – 06/30/2021 \$1,133,608
Winnie Liang (Co-PI) Grant (Hendricks/Cowey) Baylor Scott & White Research Institute (BSWRI) Dissecting the role of hTERT across melanoma subtypes: Exploiting a cancer hallmark to develop a novel targeted treatment	09/01/2017 – 08/31/2019 \$223,000
Winnie Liang (Co-I) 1U01CA224153 (Cheryl London) NIH/Tufts University Subaward Precision Medicine for Pet Dogs with Lung Cancer	09/30/2017 - 08/31/2022 \$46,541
Winnie Liang (PI) Grant (Matthew Huentelman) Arizona Alzheimer's Research Consortium AARC FY 18: Alzheimer's Projects	07/01/2018 – 06/30/2019 \$100,000
Winnie Liang (Co-I) R01 CA223481 (Muhammed Murtaza) NIH/NCI Individualized monitoring of treatment response and resistance in patients with metastatic melanoma	08/15/2018 – 07/31/2023 \$179,316
Jonathan Lifshitz NS096515 NIH R21 Remote ischemic conditioning mitigates diffuse traumatic brain injury via specialized pro-resolving mediators	08/15/16-07/31/19 \$150,000
Jonathan Lifshitz	12/01/17-07/31/19

NS096515 NIH R21 Supplement Remote ischemic conditioning mitigates diffuse traumatic brain injury via specialized pro-resolving mediators	\$26,058
Jonathan Lifshitz AZ AD Consortium Neuroinflammation and neuroplasticity in traumatic brain injury (TBI) disease; cognition assessment in mouse and influence of blood transfusion in man	07/01/18-06/30/19 \$100,000
Jonathan Lifshitz RX002472 VA Merit I01 Brain injury rehabilitation modality, regulation, & structural plasticity	07/01/18-06/30/19 \$1,100,000
Jonathan Lifshitz DOD CDMRP Probing the mechanistic role of vascular dysfunction and vascular inflammation in TBI-mediated cognitive dysfunction	08/01/17-07/31/20 \$1,300,000
Jonathan Lifshitz HD084067 NIH DP2 Detecting and Treating Brain Injury – Alzheimer’s Disease Supplement	07/01/18-06/30/19 \$32,137
Maha Saber AG044402 NIH T32 Neurobiology of Aging and Alzheimer’s Disease	07/01/18-06/30/20
Beach, Thomas (Core Leader) P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer’s Disease Core Center	7/1/16 - 6/30/21 \$1,682,235
Thomas Beach (Co-I) R01 AG044372-02 (PI: Kanaan) NIH via Michigan State University Tau-induced axonal degeneration in Alzheimer’s disease and tauopathies	9/30/14-4/30/19 \$8,000
Thomas Beach (PI) MJFF Michael J. Fox Foundation for Parkinson’s Research Systemic Synuclein Sampling Study (S4)	4/1/18-3/31/19 \$125,636
Thomas Beach (Co-I) R03 AG055020 (PI: Su) NIH via University of Arizona Ultra-sensitive and label-free detection of Alzheimer’s disease biomarkers	7/15/18-4/30/19 \$10,000
Thomas Beach (Co-I/Mentor) Mayo via ABRC (Mehta/Beach) ADHS16-00005488 Arizona New Investigator Award A Clinico-Pathologic Study of Autonomic Dysfunction in Patients with Progressive Supranuclear Palsy	3/1/18-2/29/19 \$35,590

Thomas Beach (Co-I) Carl T. Hayden Medical Research Foundation (PI: Migrino) Phoenix VA Discovering novel mechanisms for aging-related dementia: probing medin and abeta vasculopathy	4/1/18-3/31/19 \$18,987
Thomas Beach (Co-I) Alzheimer's Association via Arizona State University (Mastroeni) Gender effects on identified cell population in Alzheimer's disease	1/17/19-1/16/20 \$9,110
Thomas Beach (Co-PI) AARC (Reiman, Project PIs: Beach, Zamrini) AZ DHS via AARC Developing a Shared Resource of Cerebrospinal Fluid, Plasma, Serum, and Peripheral Blood Mononuclear Cell (PBMC) Samples from Arizona's Longitudinal Brain and Body Donation and Apolipoprotein E4 (APOE4) Gene Dose Programs	7/1/18– 6/30/19 \$270,000
Thomas Beach (Co-PI) AARC (Reiman, Project PI: Beach) AZ DHS via AARC A Human Brain Single-Cell Suspension Resource	7/1/18– 6/30/19 \$144,000
Thomas Beach (Co-PI) AARC (Reiman, Project PIs: Shprecher, Beach) AZ DHS via AARC Clinicopathological Study Initiation for Incidental REM Sleep Behavior Disorder in Sun City, Arizona	7/1/16 – 6/30/18 \$36,000
Christine Belden (Co-I) P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center – Clinical Core	7/1/16 - 6/30/21 \$1,682,235
Lih-Fen Lue (PI) AARC (Reiman, Project PI: Lue) AZ DHS via AARC Establishing a bank for human subject-derived microglial and fibroblast primary cell cultures	7/1/18– 6/30/19 \$90,000
Lih-Fen Lue (Co-I) AARC (Reiman, Project PIs: Serrano, Beach) AZ DHS via AARC A Human Brain Single-Cell Suspension Resource	7/1/18– 6/30/19 \$144,000
Geidy Serrano (Co-PI) AARC (Reiman, Project PIs: Serrano, Beach) AZ DHS via AARC A Human Brain Single-Cell Suspension Resource	7/1/18– 6/30/19 \$144,000
David Shprecher (PI) AARC (Reiman, Project PIs: Shprecher, Beach)	7/1/18 – 6/30/19 \$36,000

AZ DHS via AARC
Clinicopathological Study Initiation for Incidental REM Sleep Behavior Disorder in Sun City, Arizona

Edward Zamrini (Co-I) 7/1/16 - 6/30/21
P30 AG019610 (Reiman) \$1,682,235
NIH/NIA
Arizona Alzheimer's Disease Core Center – Clinical Core

Edward Zamrini (Co-PI) 7/1/18– 6/30/19
AARC (Reiman, Project PIs: Beach, Zamrini) \$270,000
AZ DHS via AARC
Developing a Shared Resource of Cerebrospinal Fluid, Plasma, Serum, and Peripheral Blood Mononuclear Cell (PBMC) Samples from Arizona's Longitudinal Brain and Body Donation and Apolipoprotein E4 (APOE4) Gene Dose Programs

Edward Zamrini (Co-I) 6/1/18-5/31/19
R21 AG055852 \$29,321
NIH via UA (Toosizadeh)
MCI and Alzheimer's Disease Screening Using Upper-Extremity Dual-Task

Edward Zamrini (PI) 12/2/18-11/30/19
U24 AG057437 \$110,924
NIH via University of Southern California (Aisen)
Alzheimer's Clinical Trial Consortium

Ahern, Geoff (co-I; PI: Reiman) 7/1/16 - 6/30/21
NIH/NIA P30 AG019610 \$43,084
Arizona Alzheimer's Disease Core Center (UA Clinical Core)

Ahern, Geoff (PI) 2013 – present
Eisai \$107,194/patient
A Placebo-controlled, Double-blind, Parallel-group, Bayesian Adaptive Randomization Design and Dose Regimen-finding Study to Evaluate Safety, Tolerability and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease. Protocol # BAN2401-G000-201.

Ahern, Geoff (PI) 2013 – present
Lilly Pharmaceuticals \$32,863/patient
Effect of Passive Immunization on the Progression of Mild Alzheimer's Disease: Solanezumab (LY2062430) versus Placebo. Protocol # H8A-MC-LZAX.

Ahern, Geoff (PI) 2019 – present
Novartis Pharmaceutical Corporation \$172,970
A Randomized, Double-blind, Placebo-controlled, Two cohort Parallel Group Study to Evaluate the Efficacy Of Cad106 and Cnp520 in Participants at Risk for the Onset Of Clinical Symptoms of Alzheimer's Disease.

Alexander, Gene (multi-PI: Reiman, Caselli) 05/01/18 – 03/31/19
NIH/NIH RO1 AG031581 \$9,531 UA Annual Directs
Brain Imaging, APOE & the Preclinical Course of Alzheimer's disease

Alexander, Gene (PI's: Coleman, Barnes, Alexander; co-I's: Billheimer, Huentelman, Trouard) NIH/NIA 1 RO1 AG049464 Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain	08/01/14 – 05/31/20 \$458,236
Alexander, Gene (PI, UA Sub; co-I's: Trouard, Hischaw, Allen) NIH/NIA RO1 AG054077 Augmenting Cognitive Training in Older Adults	09/01/16 – 04/30/21 \$184,020
Alexander, Gene (UA PI, co-I's: Hischaw, Trouard) McKnight Brain Research Foundation McKnight Inter-Institutional Neuroimaging Core and Brain Aging Registry	01/01/15 – 12/31/18 \$228,730 UA Total Directs
Alexander, Gene (PI, co-I's: Glisky, Ryan) McKnight Brain Research Foundation McKnight Inter-institutional Cognitive Aging Assessment Core	09/01/15 – 12/31/18 \$200,000 UA Total Directs
Alexander, Gene (Co-I, PI: Reiman) NIH/NIA P30 AG019610 Arizona Alzheimer's Disease Core Center	7/1/16 - 6/30/21 \$12,345
Alexander, Gene (PI; co-I Raichlen) State of Arizona, DHS Grant Modifiable Health & Lifestyle Factors in Brain Aging and Alzheimer's Disease	07/01/18 – 06/30/19 \$60,987
Alexander, Gene (PI, co-I's: Glisky, Ryan) McKnight Brain Research Foundation A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults	05/18/18 – 04/30/20 \$60,000 Total Direct Costs
Andrews-Hanna, Jessica (UA PI; Bryan PI) NIH/NIA RO1 AG043452 (Pilot Grant) Enhancing Function in Later Life: Exercise and Function Network Connectivity	06/15/14 – 02/28/19 \$15,232 Annual Total Costs
Andrews-Hanna, Jessica (PI; co-I's: Grilli, O'Connor) NIH/NIA P30 AG019610 Uncovering Neurocognitive Links between Alzheimer's Disease and Depression in Mid-Life to Early Aging	07/01/18 – 06/30/19 \$30,000 Total Direct Costs
Barnes, Carol (PI) NIH/NIA 1 R01 AG050548 Cell Assemblies, Brain Adaptation and Cognitive Brain	09/1/15 – 05/31/20 \$516,626 Annual Total Costs
Barnes, Carol (PI) NIH/NIA 1 RO1 AG003376 Neurobehavioral Relations in Senescent Hippocampus	01/01/16 – 11/30/20 \$734,165 Annual Total Costs
Barnes, Carol (PI's: Barnes, Huentelman; co-I: Okuno) NIH/NIA 1 RO1 AG048907 CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox	09/30/14 – 05/31/19 \$251,270
Barnes, Carol (PI) (co-I's: Alexander, Billheimer, Huentleman, Trouard)	08/01/14 – 3/31/20

NIH/NIA RO1 AG049465 Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging	\$734,176 Annual Total Costs
Barnes, Carol (PI; co-I: Reiman, Coleman, Bimonte-Nelson, Huentelman) 05/15/16 – 04/30/21 NIA/NIA T32 AG044402 Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease	\$260,293 Annual Total Costs
Barnes, Carol (Co-I; PI: Reiman) NIH/NIA 5 P30 AG019610 Arizona Alzheimer's Disease Core Center Ad Hoc Review Program	08/15/17 – 06/30/18 \$15,945
Barnes, Carol (UA PI; PI Stern) NIH/NIA P30 AG061421 Collaboratory on Research for Cognitive Reserve and Resilience	10/1/18 – 9/30/21 \$18,945 Annual Total Costs
Barnes, Carol (PI; collaborators: Trouard, Worley) State of Arizona, DHS Grant Neuronal pentraxin receptor 2 (NPTX2): A promising target for preserving memory circuits in normative aging and in Alzheimer's disease	07/01/18 – 06/30/19 \$50,447
Barnes, Carol (mentor; NRSA to Daniel Gray) NIH/NIA 1 F31 AG055263 Neurobiological Basis of Age-Related Deficits in Attentional Shifting and Monitoring	01/01/17 – 12/31/18 \$36,185
Brinton, Roberta (PI) NIH/NIA1 PO1 AG026572 Perimenopause in Brain Aging and Alzheimer's Disease	09/01/16 – 08/31/21 \$2,070,810 Annual Total
Brinton, Roberta (PI) NIH/NIA R37 AG053589 Aging and Estrogenic Control of the Bioenergetic System in the Brain	03/15/17 – 02/28/22 \$309,287 Annual Total Costs
Brinton, Roberta (PI; co-I: Rodgers) NIH/NIA UO1 AG047222 Allopregnanolone as a Regenerative Therapy for Alzheimer's: FDA-Required Toxicology	06/15/14 – 02/28/19 \$215,348 Annual Total Costs
Brinton, Roberta (PI; co-I: Rodgers) Alzheimer's Drug Discovery Foundation Allopregnanolone Novel Patentable Formulations to Advance Commercialization	11/01/17 – 12/30/19 \$150,000 Total Direct Costs
Brinton, Roberta (PI) Alzheimer's Association Perimenopause in APoE4 Brain: Accelerated Myelin Catabolism for Fuel	11/01/17 – 4/30/20 \$248,280
Brinton, Roberta (PI; collaborators: Beach, Chang, Yin) State of Arizona, DHS Grant Convergence of Maternal History of AD, Mitochondrial Haplotype, ApoE Genotype and Ethnic Heritage: Relationship to Alzheimer's Disease	07/01/18 – 06/30/19 \$19,063
Brinton, Roberta (PI; co-I: Yin) NIH/NIA R01 AG057931	09/01/18 – 08/31/23 \$1,192,861 Annual Total

Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype

Brinton, Roberta (PI) NIH/NIA T32 AG061897 Translational Research in AD and related Dementias (TRADD)	09/01/18 – 08/31/23 \$146,989 Annual Total Costs
Chen, Nan-kuei (PI; collaborators: Chou, Ryan, Trouard) State of Arizona, DHS Grant High-resolution fMRI for mapping functional subfields of hippocampus and amygdala: Application to studies of Alzheimer's disease	07/01/18 – 06/30/19 \$39,063
Chen, Nan-kuei (PI, co-I's: Guzman, Rapcsak, Trouard) NIH/NINDS R01 NS102220 Development of High-Speed and Quantitative Neuro MRI Technologies for Challenging Patient Populations	07/01/18 – 03/31/23 \$285,904
Chen, Nan-kuei (UA Subcontract PI) NIA R01 DA045565 (Meade, Duke University, PI) MRI data fusion to investigate effects of drug abuse on HIV neurological complications	03/05/18 – 01/31/23 \$15,218
Chen, Nan-kuei (multi-PI: Chen, Liu, Madden) NIH/NIA R56 AG052576 Quantitative susceptibility mapping of iron accumulation in neurocognitive aging	09/30/17 – 03/31/19 \$378,204
Chou, Ying-hui (Pilot Grant PI) NIH/NIA 5 P30 AG019610 Use of TMS and fMRI Measures to Assess the Risk of Conversion of MCI to Dementia	07/01/17 – 06/30/19 \$30,000 Total Direct Costs
Chou, Ying-hui (PI; collaborator: Kuo) State of Arizona, DHS Grant Developing an Image-Guided Magnetic Brain Stimulation Protocol for Mild Cognitive Impairment	07/01/18 – 06/30/19 \$29,063
Edgin, Jamie (PI; collaborators: Andrews;Hanna, Glisky, Grilli, Rapcsak, Ryan) State of Arizona, DHS Grant Sleep's Role in Age-Related Changes in Memory and Cognition: A Pilot Study	07/01/18 – 06/30/19 \$24,532
Edgin, Jamie O. (PI) (Co-I's: Andrews-Hanna; Cowen) LuMind Foundation Brain Development, Sleep and Learning in Down Syndrome	07/01/17 – 06/30/18 \$225,000 Annual Total Costs
Edgin, Jamie O. (co-I; PI: Hughes) Jerome LeJeune Foundation Sleep as a Predictor of Memory Performance and Stability in ID Syndromes	07/01/18 – 06/30/20 \$45,934 Total Costs
Edgin, Jamie O. (PI) NIH/NICHD 1 RO1 HD088409 Memory Measures for Clinical Trials in Down Syndrome and Fragile X Syndrome	09/22/16 – 06/30/21 \$512,284
Edgin, Jamie O. (PI)	09/01/18 – 08/31/19

LuMind Foundation	\$225,000 Annual Total Costs
Sleep, Memory Assessment, and Cognitive Intervention in Down Syndrome	
Gaffney, Kevin (PI; collaborator: Langlais)	07/01/18 – 06/30/19
State of Arizona, DHS Grant	\$29,063
Chemical Proteomic Approach to Discover Novel Neuroinflammation Targets	
Glisky, Elizabeth (PI; collaborators: Ryan, Alexander, Grilli, Figueredo)	07/01/18 – 06/30/19
State of Arizona, DHS Grant	\$20,000
Longitudinal Aging Project: Completion, Analyses, and Publication of Two Projects	
Grilli, Matt (PI; collaborators: Andrews-Hanna, Edgin, Glisky Rapcsak, Ryan)	07/01/18 – 06/30/19
State of Arizona, DHS Grant	\$24,532
The status of personal semantic memory among cognitively healthy older adults	
Grilli, Matt (PI)	08/01/17 – 06/30/18
UA College of Science, Dean's Innovation and Education Fund	\$10,000
Detecting the earliest cognitive signs of Alzheimer's disease	
Grilli, Matt (PI)	07/01/17 – 06/30/18
UA Faculty Seed Grant, ORDI	\$10,000
Detecting the earliest signs of Alzheimer's disease: A new cognitive neuroscience approach	
Guzman, Gloria and Saranathan, Manof (multi-PI) (Collaborators: Ahern, Hirschaw, Reiman, Chen)	07/01/18 – 06/30/19
State of Arizona, DHS Grant	\$30,000
MRI and automated segmentation of thalamic nuclei for Alzheimer's disease	
Khanna, May (UA PI; Multi-PI: Mangravite, Brennan, Price, Schadt)	09/01/18 – 08/31/19
Sage Bionetworks	\$180,657 Total Costs
Expanding AMP-AD Target Enabling Packages to identify small molecule inhibitors that block protein-protein interactions	
Khanna, May (PI)	07/01/18 – 06/30/19
State of Arizona, DHS Grant	\$20,000
Identify small molecule inhibitors to block Protein-Protein interactions from AMP-AD targets	
Khanna, May (PI)	03/01/17 – 02/29/20
Arizona Biomedical Research Commission	\$225,000 Total Costs
Small Molecule Restoration of Translation Dysregulation in ALS	
McGovern, Kathryn (PI; mentors: Khanna, Brinton)	07/01/18 – 06/30/19
State of Arizona, DHS Grant	\$30,000
Pilot Project: Defining the mechanism of <i>T. gondii</i> induced plaque clearance	
McGovern, Kathryn (PI)	03/01/18 – 2/21/20
NIH/NIA F32 AG058440	\$61,610
Neuroinflammation as a therapeutic avenue for Alzheimer's disease treatment	

Rapcsak, Steve (co-I; PI: Reiman) NIH/NIA 5 P30 AG019610 Arizona Alzheimer's Disease Core Center (UA Clinical Core)	7/1/16 - 6/30/21 \$43,073
Rapcsak, Stephen (PI) Masaryk University Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioral Neurology	11/01/16 – 10/31/20 \$40,022 Total Direct Costs
Rodgers, Kathleen (PI; collaborator: Berghout) State of Arizona, DHS Grant Mechanisms of Neuroprotection by Mas Agonists	07/01/18 – 06/30/19 \$29,063
Rodgers, Kathleen (UA PI; PI: Nation) NIH/NIA R21 AG055034 (USC Subcontract) Vascular Reserve and Protective Mechanisms in Aging and Alzheimer's Dementia Risk	08/01/17 – 05/31/19 \$37,500 Total Direct Costs
Rodgers, Kathleen (PI) Department of Defense MH140084 Small Molecular Mas Agonists for the Amelioration of DMD-Associated Cardiomyopathy	09/01/17 – 08/31/19 \$863,011 Total Costs
Ryan, Lee; (Multi-PI: Sweitzer, Hay, Ryan Arai) NIH/NHLBI UO1 HL131014 Evaluation of the Safety and Efficacy of Angiotensin 1-7 to Enhance Cognitive Function in Participants Undergoing Coronary Artery Bypass Graft (CABG) Surgery	03/01/17 – 02/28/22 \$540,944
Ryan, Lee (PI; collaborators: Rapcsak, Saranathan) State of Arizona, DHS Grant A Novel Model of Medial Temporal Lobe Functions: Implications for Aging and Memory	07/01/18-06/30/19 \$85,556
Ryan, Lee (PI; collaborators: Alexander, Barnes, Trouard, Brinton, Huentelman, Beach) State of Arizona, DHS Grant Establishing pipelines for biomarker collection and data sharing for cognitively healthy older adults at the University of Arizona	07/01/18-06/30/19 \$110,000
Su, Judith (PI) NIH/NIMH R21 MH111109 Label-Free, Highly-Specific, Small Molecule Detection Using Microtoroid Optical Resonators	08/01/16 – 05/31/19 \$166,946 Annual Total Costs
Su, Judith (PI; co-I: Alexander) NIH/NIA R03 AG055020 Ultra-Sensitive and Label-Free Detection of Alzheimer's Disease Biomarkers	07/15/17 – 04/30/19 \$76,756 Annual Total Costs
Su, Judith (PI) Partnership for Clean Competition Sensitive and Rapid Detection of Performance Enhancing Drugs Using Microtoroid Optical Resonators	03/01/2017 – 02/28/2018 \$86,804
Su, Judith (PI; collaborators: Alexander, Beach) State of Arizona, DHS Grant Ultra-sensitive and label-free detection of Alzheimer's disease proteins	07/01/18-06/30/19 \$33,595

Su, Judith (PI) National Science Foundation High Precision Molecular Spectroscopy and Detection Using Microtoroid Optical Resonators	08/15/18 – 07/31/19 \$100,000
Su, Judith (PI) Defense Threat Reduction Agency Sensitive, Selective, and Affordable Chemical Threat Sensing Using Frequency Locked Microtoroid Optical Resonators	09/01/18 – 08/31/21 \$371,899
Su, Judith (PI) Gordon and Betty Moore Foundation Understanding Biological Systems Using Resonator-Mediated Single-Molecule Raman Detection and Spectroscopy	03/01/19 – 02/29/20 \$56,250 Annual Total Costs
Trouard, Ted (PI) NIH Bruker Biospec 7T Small Animal MRI Upgrade	03/01/18 – 02/29/20 \$600,000 Total Costs
Trouard, Ted (UA PI) ADHS-16-00005489 Arizona Biomedical Research Corporation Treatment of Parkinson's Disease with Enhanced Delivery of Antibody Therapy Selectively Targeting Toxic Proteins Variants	03/01/17 – 02/28/19 \$125,000
Trouard, Ted (co-I) NIH/NICHD R01 HD079498 Intense Physiotherapies to Improve Function in Young Children with Cerebral Palsy	05/01/14 – 04/31/19 \$227,043 Annual Total Costs
Trouard, Ted (PI; collaborators: Oddo, Huentelman) State of Arizona, DHS Grant Evaluation of amyloid in the blood and brain of Alzheimer's mice before and after treatment with focused ultrasound: A therapeutic and biomarkers study	07/01/18 – 06/30/19 \$34,063
Wilson, Robert C (Pilot Grant PI; co-I: Chou) NIH/NIA 5 P30 AG019610 (Pilot Grant) The Neural Substrates of Explore-Exploit Decisions in Old Age	07/01/17 – 06/30/19 \$30,000
Wilson, Robert C (PI; co-I: Grilli) McKnight Brain Research Foundation Vulnerability of older adults to financial deception schemes	9/30/18 - 8/31/19 \$31,555
Wilson, Robert C (PI; co-I's: Alexander, Andrews-Hanna, Chou) NIA R56 AG061888-01 Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults	9/30/18-8/31/19 \$215,613 Annual Total Costs
Yin, Fei (PI; collaborators: Chang, Brinton, Wang) State of Arizona, DHS Grant Mitochondrial Genome Stability and Late Onset AD	07/01/18 – 06/30/19 \$29,063
Zarnescu, Daniela (PI; co-I: Khanna)	09/01/15 – 5/31/20

NIH/NINDS R01 NS091299 \$321,921 Annual Total Costs
RNA Dysregulation in Neurodegeneration

Zarnescu, Daniela (PI; co-I's: Khanna, Gokhale) 07/01/18 – 06/30/13
United States Army Medical Research Acquisition Activity \$702,930 Total Costs
Small Molecules Targeting TDP-43 - RNA Interactions in ALS

Pending Grants:

Eric M. Reiman (Site Co-PI)
Diagnostics Accelerator: Peripheral Biomarkers (Stern) \$64,921
Alzheimer's Drug Discovery Foundation via BU
Plasma Biomarkers of Amyloid, Tau, Neurodegeneration,
and Vascular Disease: Validation and Utility in Alzheimer's Disease

Eric M. Reiman (Site PI)
National Alzheimer's Coordinating Center (NACC) \$16,949
2019-2020 Bridge Funding
NIH via University of Washington

Jessica Langbaum (PI) 07/01/19-06/30/24
1R01AG063954-01 (Langbaum/Bleakley) \$1,197,765
NIH/NIA
Establishing the science behind Alzheimer's recruitment registries

Jessica Langbaum (Co-I) 09/01/18-08/31/23
1R01AG061848-01 (Aisen) \$94,937
NIH/NIA
Combination anti-amyloid therapy for preclinical Alzheimer's Disease

Yi Su (Site Co-PI)
Diagnostics Accelerator: Peripheral Biomarkers (Stern) \$64,921
Alzheimer's Drug Discovery Foundation via BU
Plasma Biomarkers of Amyloid, Tau, Neurodegeneration,
and Vascular Disease: Validation and Utility in Alzheimer's Disease

Yi Su (Site PI) 07/01/19-06/30/24
NIH R01 (Schaefer) \$70,563
NIH via ASU
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 (Site PI) 12/01/19-11/30/24
NIH R01 (Stokes) \$57,928
NIH via BNI
Multi-Scale MRI Assessment of Neurovascular Factors
Associated with AD

Yi Su (Site PI) 11/01/19-04/30/23
NIH SBIR (Didsbury) \$62,823
NIH via T3D Therapeutics

Multi-Modality Image Data Fusion and Machine Learning
Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

Yi Su (Site Co-PI) 10/01/19-09/30/20
NIH STTR (Lure) \$45,373

NIH via MS Technologies

Multi-Modality Image Data Fusion and Machine Learning
Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

Yi Su (Site Co-PI) 10/01/19-09/30/20
NIH STTR (Lure) \$45,373

NIH via MS Technologies

Multi-Modality Image Data Fusion and Machine Learning
Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

David Weidman (Site PI) 10/01/19-09/30/20
NIH STTR (Lure) \$45,373

NIH via MS Technologies

Multi-Modality Image Data Fusion and Machine Learning
Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

Yalin Wang (PI) 7/1/2019-6/30/2021
University of California: San Diego \$68,007

Cerebellar morphometry in the blind via tensor-valued and random field statistics

Yalin Wang (PI) 9/1/2019-8/31/2021
HHS: National Institutes of Health (NIH) \$435,024

Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transportation

Yalin Wang (PI) 9/1/2019-8/31/2021
Children's Hospital Los Angeles \$137,758

Machine learning-based cortical biomarker identification of early neurodevelopment using a new parametric cortical thickness modeling

Velazquez, Ramon 4/1/2019-3/31/2024
K99NS107633-01A1 \$83,674.00

HHS: National Institutes of Health (NIH)

Dissecting novel molecular mechanisms associated with Alzheimer's disease

Caccamo, Antonella 4/1/2019-3/31/2024
R01AG062500-01 \$347,994.00

HHS: National Institutes of Health (NIH)

S6K1 as a novel link between aging and Alzheimer's disease

Oddo, Salvatore 4/1/2019-3/31/2024
R01AG063409-01 \$505,196.00

HHS: National Institutes of Health (NIH)

Identifying the role of RIPK1 in Alzheimer's disease

Oddo, Salvatore 4/1/2019-3/31/2024
R01AG063454-01 \$423,291.00

HHS: National Institutes of Health (NIH) mTOR at the crossroad between aging and Alzheimer's disease	
Jacobs, Bertram R01AG065576-01 HHS: National Institutes of Health (NIH) Involvement of DAI in Alzheimer's Disease	9/1/2019-8/31/2024 \$483,047.00
Oddo, Salvatore FP00019145 Translational Genomics Research Institute (TGen) Identification and development of TREM2 agonists to prevent Alzheimer's disease	9/1/2019-8/31/2024 \$67,704.00
Velazquez, Ramon FP00019288 Arizona Alzheimer's Consortium Dissecting the role of the Pim1 kinase in Alzheimer's disease	7/1/2019-6/30/2020 \$30,000.00
LaBaer, Joshua FP00019367 INanoBio, Inc. FP00012832 Supplement: Tools and Methods for Producing High Quality Functional protein Microarrays for Biomarker Discovery	9/1/2019-8/31/2020 \$29,618.00
Omar Khmour (Co-PI) National Institutes of Health (NIH) Alzheimer's Disease Specific Variant of Amyloid Target Mitochondria Early in Life	\$3,012,162
Cassandra Gipson-Reichardt (PI) Heather Bimonte-Nelson (Co-I) Foster Olive (Co-I) R01 DA049794 National Institute on Drug Abuse Nicotine Reward Circuitry: Impact of Ovarian Hormones, Contraceptive Estrogen, and Menopause	\$1,250,000
David Coon (Subcontract PI & Co-Leader Community Engagement Recruitment & Retention Core) Carol Barnes (PI) National Institute on Aging Total Budget: \$25M National Precision Aging Network: Closing the Gap between Cognitive Healthspan and Human Lifespan	ASU Budget: \$2.52M
David Coon (PI) Women and Philanthropy Sun Devil Caregiver Academy	ASU Budget: \$75,000
David Coon (Co-PI) Martin Reisslen (PI) National Science Foundation	ASU Budget: \$570,000

PAWR Platform Full Proposal: OCHITILLO: Open Connected-Health and Intelligent Transportation using Integrated Ultra-low-latency Wireless/Optical Orchestration

David Coon (PI & Project Director) Valley of the Sun United Way Health and Human Services Promotores III	\$75,000 Total Budget
Caccamo, Antonella R01AG062500-01 HHS: National Institutes of Health (NIH) S6K1 as a novel link between aging and Alzheimer's disease	4/1/2019-3/31/2024 \$347,994.00
Oddo, Salvatore R01AG063409-01 HHS: National Institutes of Health (NIH) Identifying the role of RIPK1 in Alzheimer's disease	4/1/2019-3/31/2024 \$505,196.00
Oddo, Salvatore R01AG063454-01 HHS: National Institutes of Health (NIH) mTOR at the crossroad between aging and Alzheimer's disease	4/1/2019-3/31/2024 \$423,291.00
David Brafman (PI) NSF 1757588 NSF REU Site: Systems Biology of Neuroengineering	05/01/2019-12/31/2020 \$488,020 Total Costs
David Brafman (PI) NIH-NIA A Pluripotent Stem Cell-Based Model to Investigate the Mechanisms of TBI-Induced	04/01/2019-12/31/2020 \$434,336 Total Costs
Salvatore Oddo (PI) David Brafman (Co-PI) NIH-NIA Identifying the role of RIPK1 in Alzheimer's disease	04/01/2019-03/31/2024 \$3,675,487 Total Costs
Griffin, Michael (PI) NIH R15 AREA Grant Transcriptional Regulation of Adipocyte Inflammation by Early B-Cell Factor-1 (Ebf1)	07/01/19-06/30/22 \$300,000
Murthy, Ashlesh (PI) NIH R15 AREA Grant Mechanism(s) of CD8 T Cell-mediated Chlamydia-induced Reproductive Pathology	07/01/19-06/30/22 \$300,000
Murthy, Ashlesh (Co-I) NIH R01 Sub from the Arkansas Children's Research Institute miRNA Activation of Inflammatory Signaling Pathways During Chlamydiae Infection	07/01/19-06/30/24 \$83,648
Murthy, Ashlesh (PI) Boehringer Ingelheim Boehringer Ingelheim Veterinary Scholar Program	05/01/19-10/31/19 \$20,000

Revill, Ann (PI) Whitehall Foundation Research Grant Cholinergic modulation of XII motoneurons and XII premotoneurons	07/01/19-06/30/22 \$206,315
Revill, Ann (PI) NIH R15 AREA Grant Cholinergic modulation of XII motoneurons and XII premotoneurons	07/01/19-06/30/22 \$300,000
Shim, Minsub (PI) NIH R15 REAP Grant Cyclooxygenase-2 Signaling in Cell Senescence and its Role in Chemotherapy-induced Long-term Adverse Sequelae	09/01/19-08/31/21 \$300,000
Cope, Emily/Caporaso, J Gregory (PI) NIH/NIAID R15 Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma.	07/01/2019 - 06/30/2021 \$471,963
Cope, Emily (PI) NIH/NIAID R15 Defining the role of the sinonasal mucosal mycobiome in chronic rhinosinusitis.	07/01/2019 - 06/30/2021 \$471,963
Cope, Emily Arizona Biomedical Research Commission (ABRC) Human genetic variation and the sinonasal microbiome in chronic rhinosinusitis.	07/01/2019 - 06/03/2022 \$225,000
Cope, Emily/Lee, Kehoon CFRI, Cystic Fibrosis Research Inc A Multi-'Omic Approach to Evaluate Concurrent Sinus and Pulmonary Disease in Cystic Fibrosis	07/01/2019 - 06/30/2021 \$120,000
Cope, Emily MDW IDSA, sub-contract to Midwestern University Exploring the association between the presence of bacterial DNA in brain tissue and the development of Alzheimer's disease.	07/01/2019 - 06/30/2020 \$16,190
Caporaso, J Gregory NIH R01, sub-contract to University of Arizona Oligofructose restores nutrient-sensing mechanisms regulating glucose production to improve glucose homeostasis via alterations in small intestinal microbiota.	09/1/2022 - 08/31/2024 \$145,052
Caporaso, J Gregory NIH/NCI U54, sub-contract to University of Arizona Decoding Cervical Cancer Health Disparity in Hispanic Women Through a Multi-Omics Approach.	07/01/2019 - 06/30/2024 \$192,274
Caporaso, J Gregory (Co-I) NIH U54 The Partnership for Native American Cancer Prevention.	09/01/2019 - 08/31/2024 \$7,582,050
Caporaso, J Gregory (Co-I) NSF	06/01/2019 - 05/31/2023 \$1,137,769

Collaborative Research: OSS-Doorway: An Informal Learning Environment for the Open Source Contribution Model.

Caporaso, J Gregory (PI) NIH U24 Advancing our Understanding of Cancer and the Human Microbiome with QIIME 2.	04/01/2019 - 03/31/2024 \$4,544,195
Matthew Huentelman (Co-I) NIH R01 (Oddo) Necroptosis as a novel mechanism of neurodegeneraton in Alzheimer's disease	06/01/2019 – 05/31/2020 \$56,774
Matthew Huentelman (Co-I) NIH R01 (Caccamo) Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome	7/01/2019 -08/31/2020 \$54,808
Matthew Huentelman (Co-I) W81XWH18PRMRPFPA DOD (Schwedt) A mulitidisciplinary translational approach to investigate the mechanisms, predictors and prevention of persistent post traumatic headache	10/01/2019 -09/30/2023 \$168,843
Matthew Huentelman (Co-I) NIH R01 (Oddo) Identifying the role of RIPK1 in Alzheimer's diseese	04/01/2020- 03/31/2021 \$38,558
Matthew Huentelman (PI) NIH U24 Integrated Genome Sequencing and Data Resource Center in Support of the Gabriella Miller Kids First Pediatric Research Program	07/01/2019 – 06/30/2022 \$7,353,650
Matthew Huentelman (Project and Core Lead) NIH U19 Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Lifespan	09/01/2019 – 08/31/2024 \$1,641,730
Matthew Huentelman (Co-I) NIH R01 Cognitively intact elderly with pathologically diagnosed Alzheimer's disease: Neuroprotection/Resilience	09/01/2019-08/31/2024 \$60,000
Kendall Van Keuren-Jensen (PI) Dept of the Army PR180487 Grant Genotypic and phenotypic examination of disease pathogeneis in C9orf72 FTD	07/01/2019 – 06/30/2022 \$587,368
Kendall Van Keuren-Jensen (Co-I) NIH UG3UH3 (Pendergrast) Validation of Rapid, Low-cost, Workflow for the Fractionation and Characterization of Distinct exRNA Carriers from Biofluids	07/01/2019 – 06/30/2020 \$32,592
Kendall Van Keuren-Jensen (Multi-PI) NIH UG3UH3	07/01/2019 – 06/30/2020 \$369,468

P.R.I.S.M.: Purification of exRNA by Immuno-capture and Sorting using Microfluidic

Kendall Van Keuren-Jensen (Consortium PI) 07/01/2019 – 06/30/2023
NIH UG3UH3 (Laurent) \$260,000
Development and application of a scalable workflow for immunomagnetic separation of exRNA carrier subclasses and molecular analysis of their cargo.

Kendall Van Keuren-Jensen (Consortium PI) 07/01/2020 – 06/30/2023
NIH UG3UH3 (Wong) \$145,000
Acoustofluidic (AF) Separation, Purification and Raman Spectral Fingerprinting of Single EVs: From Cell of Origin to Target Cell and Biofluids

Kendall Van Keuren-Jensen (Multi-PI) 07/01/2019 – 06/30/2023
NIH (Das) \$463,700
Molecular dissection and imaging of extracellular vesicles to define their origin and targets

Kendall Van Keuren-Jensen (Multi-PI) 04/01/2019 – 03/31/2021
Grant \$170,000
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 (Co-I) 04/01/2019 – 03/31/2021
Grant (Kim) \$19,999
Michael J Fox Foundation for Parkinson's Research
Pathway-guided biomarker discovery for neurodegenerative diseases

Kendall Van Keuren-Jensen (PI) 03/01/2019 – 02/28/2020
Grant \$289,940
Foundation for the National Institutes of Health
Data QC and analysis for BioFIND and PDBP

Kendall Van Keuren-Jensen (Co-I) 05/01/2019 – 04/30/2022
Grant (Craig) \$60,000
Michael J Fox Foundation for Parkinson's Research
Identification of RNA Isoform and Splicing Based Biomarkers For Parkinson's Disease

Kendall Van Keuren-Jensen (Co-I) 08/01/2019 – 07/31/2021
Grant (Bowser) \$17,673
Muscular Dystrophy Association
Novel Mouse Models of ALS and Myopathy-linked Matrin 3 Mutations

Kendall Van Keuren-Jensen (Co-I) 06/01/2019 – 05/31/2020
NIH R01 supplement (Zarnescu) \$30,000
RNA dysregulation in neurodegeneration

Winnie Liang (Co-I) 07/01/2019 – 06/30/2024
NIH U54 (Diego Mastroeni) \$13,624
Characterization of Toxic LBD Related Protein Variants Using Highly Selective Disease Specific Reagent

Winnie Liang (Co-I) NIH U01 (Jeffrey Weitzel) Enhancing Precision Prevention through Family Informative Genetic Testing (FIT)	09/01/2019 – 08/31/2023 \$95,000
Lifshitz, Jonathan NS112943 NIH R01 Sex Dependent Considerations for TBI Nanotherapeutics	07/01/19-06/30/24 \$3,761,651
Lifshitz, Jonathan NIH R21 Effectiveness of Cognitive Rehabilitation Depends on Hippocampal Plasticity Following Brain Injury	04/01/19-03/31/21 \$422,125
Sierks DOD W81XWH-18-PRARP-RPA Protein Variants Generated Following TBI and Their Link to AD	06/01/19-05/31/22 \$216,667
Lifshitz, Jonathan NS110795 NIH R01 Analytical Modeling of Acquired Neurological Injury with Rich Experimental Data Sets	04/01/19-03/31/24 \$3,640,957
Rowe NIH R01 Extinguishing the Fire: Eliminating Microglia to Attenuate Inflammation-Induced Sleep	04/01/19-03/31/24 \$1,918,750
Beach, Thomas (Co-I) NIH NIH U01 via TGen (Jensen) Large scale exRNAs analysis to support biomarker discovery in Parkinson's disease and related disorders	2/1/19-1/31/24 \$76,000
Beach, Thomas (Co-I) NIH NIH R01 via Michigan State University (Manfredsson) Targeting raphe-striatal neuroplasticity in L-DOPA-induced dyskinesia	7/1/19-6/30/20 \$17,000
Beach, Thomas (Co-I) NIH NIH R01 via Carl T. Hayden Medical Research Foundation (Migrino) Novel mechanistic determinant of cerebrovascular inflammation and vascular modulation of neuroinflammation in aging and VCID	3/1/19-2/28/24 \$43,758
Beach, Thomas (Co-I) NIH NIH via University of Alabama Birmingham (Yacoubian) 14-3-3 phosphorylation in Parkinson's disease	7/1/19-6/30/20 \$17,500
Beach, Thomas (Co-I) NIH NIH U01 via University of California-Los Angeles (Bitan)	2/1/19-1/31/22 \$24,000

Measurement of candidate biomarkers for differential diagnosis of Parkinson's disorders in Brain-derived exosomes

Beach, Thomas (Co-I) 4/1/19-3/31/20
NIH \$6,994

NIH R01 via Arizona State University (Sierks)
Structural characterization of toxic oligomeric beta-amyloid aggregates

Beach, Thomas (Co-I) 9/1/18-8/31/23
NIH \$15,000

NIH U01 via Arizona State University (Sierks)
Center for Neurodegenerative Structural Discovery

Beach, Thomas (Co-I) 9/1/19-8/31/20
NIH \$25,000

NIH R01 via Brigham & Women's Hospital/Harvard Medical School (LaVoie)
Pathologic LRRK2 signaling in Familial and Idiopathic Parkinson's Disease

Beach, Thomas (Co-I) 12/1/18-11/30/21
NIH \$25,000

NIH R01 via University of California-Irvine (Mukherjee)
PET Imaging Agents for $\alpha 4\beta 2$ Nicotinic Receptors

Beach, Thomas (Co-I) 12/1/18-11/30/21
NIH \$6,609

NIH R21 via Arizona State University (Tsow)
Novel biomarkers monitored with a non-destructive continuous volatile chemical sniffer for biospecimen quality control and workflow optimization

Beach, Thomas (Co-I) 4/1/19-3/31/20
NIH \$31,779

NIH U19 via University of Washington (MacCoss)
Next Generation Translational Proteomics for Alzheimer's and Related Dementias

Beach, Thomas (Co-I) 7/1/19-6/30/24
NIH \$10,000

NIH U54 via Arizona State University (Sierks)
Characterization of toxic-LBD-related protein variants using highly selective disease-specific reagents (Interdisciplinary Research Consortium)

Beach, Thomas (Co-I) 9/1/19-8/31/20
NIH \$15,240

NIH R01 via University of Alabama-Birmingham (Yacoubian)
Impact of 14-3-3 phosphorylation on cognitive decline in Alzheimer's disease

Beach, Thomas (Co-I) 7/1/19-6/30/21
American Heart Association \$7,383

AHA via Carl T. Hayden Medical Research Foundation (Migrino)
Medin-induced vasculopathy: a new paradigm in aging-associated vascular dementia

Beach, Thomas, (Co-I) 9/1/19-8/31/24

NIH	\$60,000
NIH via Arizona State University (Mastroeni)	
Oligomeric variants of alpha synuclein trigger microglial activation in Parkinson's disease	
Beach, Thomas (Co-I)	5/1/19-4/30/22
Michael J. Fox Foundation	\$11,167
MJFF via Mayo (Adler)	
Clinical algorithm for the diagnosis of Parkinson's disease	
Beach, Thomas (Co-I)	9/1/19-8/31/24
NIH	\$25,000
NIH R01 via Mayo-Jacksonville (Ebbert)	
Identifying functional mutations and aberrant RNA isoforms in top Alzheimer's disease genes using long-read sequencing in brain tissue	
Shprecher, David (Co-I)	5/1/19-4/30/20
NIH	\$16,000
NIH R34 via Washington University (Ju)	
Neuroprotective Treatment Trial Planning in REM Sleep Behavior Disorder	
Zamrini, Edward (Co-I)	4/1/19-3/31/23
NIH	\$35,172
NIH R01 via George Washington University (Zeng)	
Cardiorespiratory Fitness: Alzheimer's Disease and Related Dementias Incidence	
Zamrini, Edward (Co-I)	9/1/18-8/31/20
NIH	\$25,000
NIH R03 via Banner Alzheimer's Institute (Ahmadi)	
Alexander, Bowers, Woods (MPIs) (Co-I: Trouard, Hishaw)	07/01/19 – 06/30/24
NIA RO1 (UA Subcontract)	\$1,822,841 Total Costs
Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation.	
Barnes Carol (PI; co-I's: Albert, Bilgin, Brinton, N-K Chen, Z Chen, 09/01/19 – 03/31/24	
Coon, Doyle, Duarte, Ellingson, Hay, Huentelman Lafleur, Levin	\$55,564,780 Total Costs
Mehl, Merchant, Padi, Resnick, Rodgers, Rundek, Runyon, Ryan, Schork, Sternberg, Trouard, Worley)	
NIH/NIA U19 AG065169	
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	
Barnes, Carol (co-I; PI: Liang)	08/01/19 – 07/31/22
NIH	\$2,355,049 Total Costs
Mapping of Behavioral Circuits: A Scalable Acquisition and Data Management System	
Barnes, Carol (Subcontract PI)	09/30/19 – 09/29/26
NIH	\$114,726 Total Costs
Stroke Cognitive Network	
Brinton, Roberta (PI)	04/10/19 – 12/31/19
United States Biotest Incorporated	\$37,691,721 Total Costs

Novel Allopregnanolone Formulations for Alzheimer's Disease

Brinton, Roberta (PI; co-I: Hernandez, Rodgers) NIH Allopregnanolone as Regenerative Therapeutic for Alzheimer's: Phase 2 Clinical Trial	07/01/19 – 06/30/24 \$37,691,721 Total Costs
Chen, Nan-kuei (PI; co-I's: Kuo, Sherman) UC Berkeley Investigating Brain Iron Alterations in Parkinson's Disease: Mechanisms and Clinical Utilities	07/01/19 – 06/30/24 \$431,992 Total Costs
Chou (PI; co-I's Alexander, Bedrick, Mohler, Rapcsak, Ryan) NIH R01 Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation	04/01/19-03/31/24 \$3,540,234 Total Cost
Chou, Ying-huie (PI; co-I's Chen, Kuo, Roveda, Rapcsak, Bedrick, Ryan) NIH R01 Distinguishing the development of Alzheimer's disease from normal aging: Cortical excitability, plasticity, brain structure, and brain function	10/01/19 – 09/30/24 \$3,712,428 Total Cost
Edgin, Jamie (PI; co-I: Hughes) NIH Memory Measures for Clinical Trials in Down syndrome and Fragile X syndrome	07/01/19 – 06/30/21 \$744,949 Total Costs
Edgin, Jamie (PI) NIH Early risk for ADHD symptoms in young children with Down syndrome	09/01/19 – 08/31/21 \$21,790 Total Costs
Edgin, Jamie (Subcontract PI) NIH (Drexel University) fNIRS as an outcome measure of the prefrontal hemodynamic response in Down syndrome	09/01/19 – 08/31/21 \$61,252 Total Costs
Gaffney, Kevin (PI) US Dept of Defense Understanding the Mechanism of Action of Small Molecule Mas Agonist in the Treatment of Duchenne Muscular Dystrophy	05/01/19 – 04/01/21 \$421,764 Total Costs
Gaffney, Kevin (PI; co-I: Rodgers) Michael J. Fox Foundation for Parkinson's Research Assessment of Small Molecule Mas Agonist RASRx1902 in Models of Parkinson's Disease	06/01/19 – 05/31/21 \$305,213 Total Costs
Gaffney, Kevin (PI; co-I: Rodgers) NIH Small Molecule Mas Agonists for the Treatment of Muscular Dystrophies	09/01/19 – 08/31/24 \$1,918,750 Total Costs
Gaffney, Kevin (PI) RASRx Small Molecule Mas Agonists for the Treatment of Alzheimer's Disease	07/01/19 – 06/30/20 \$201,909 Total Costs
Gaffney, Kevin (PI; co-I: Brinton, Rodgers) NIH	02/01/20 – 01/31/25 \$1,918,750 Total Costs

Defining the Therapeutic Potential of Protective RAS in Alzheimer's Disease

Grilli, Matthew (PI; co-I's: Andrews-Hanna, Ryan) NIH	04/01/19 – 03/31/21 \$153,500 Total Costs
The episodic autobiographical memory hypothesis of preclinical Alzheimer's disease: Developing a new approach for early cognitive detection and measurement of Alzheimer's disease	
Khanna, May (PI) Johnson and Johnson	07/01/19 – 06/30/20 \$150,000 Total Costs
Development of aptamers neutralizing antibodies for demyelinating diseases	
Khanna, May (PI) NIH	07/01/19 – 06/30/20 \$1,918,750 Total Costs
Leveraging chemical biology to study neurodegenerative diseases	
Khanna, May (PI; co-I's: Yin, Churko, Wang, Buchan) NIH	09/01/19 – 03/31/24 \$3,771,281 Total Costs
Allosteric Modulation of TDP-43: A Novel Way to Modify Tau Pathology	
Khanna, May (PI; co-I: Rodgers) NIH	09/01/19 – 03/31/24 \$425,842 Total Costs
Development of Aptamers Neutralizing Antibodies for Demyelinating Diseases	
Khanna, May (PI) Arizona Alzheimer's Consortium Pilot Grant Program	07/01/19 – 06/30/20 \$46,050 Total Costs
Developing Inhibitors of lncRNAs through in silico targeting for AD therapeutics	
Hay, Meredith (PI) (co-I: Brinton, Konhilas, Polton, Rodgers) NIA	07/01/19 – 06/30/23 \$4,782,275 Total Costs
IND Enabling Studies for a Novel Mas Receptor Agonist for Treatment of Cognitive Impairment in Patients at Risk for Alzheimer's Disease Related Dementia	
Rodgers, Kathleen (PI) (co-I: Brinton) NIH	07/01/19 – 06/30/24 \$1,243,763 Total Costs
Undergraduate Readying for Burgeoning Research for American Indian Neuroscientists	
Rodgers, Kathleen (PI) (co-I: Brinton, Trouard, Yin) NIH	07/01/19 – 06/30/24 \$3,799,936 Total Costs
Defining Interactions Between Cardiovascular and Alzheimer's Disease Risk Factors in the Development of Dementia	
Rodgers, Kathleen (PI) DoD	07/01/19 – 08/31/21 \$342,018 Total Costs
The Use of RAS-Modifying Drugs for the Prevention of Kidney Damage in SLE: A Step Towards Personalized Medicine	
Rodgers, Kathleen (PI) NIH/University of Southern California	07/01/19 – 6/30/24 \$546,651 Total Costs
Endothelial progenitor cells and cerebrovascular injury in the aging brain	

Rodgers, Kathleen (PI; co-I: Gaffney) RASRx Mas Agonists for the Treatment of Alzheimer's Disease and Related Dementias	07/01/19 – 12/31/19 \$50,000 Total Costs
Rodgers, Kathleen (PI) (co-I: Brinton, Gaffney) NIH IND Enabling Studies for RASRx 1902, a novel Mas receptor agonist, for treatment of cognitive impairment in patients at risk for Alzheimer's disease	09/01/19 – 08/31/24 \$6,056,354 Total Costs
Rodgers, Kathleen (PI) (co-I: Brinton, Trouard, Yin) Alzheimer's Drug Discovery Foundation IND Enabling Studies for RASRx 1902, a novel Mas receptor agonist, for treatment of cognitive impairment in patients at risk for Alzheimer's disease	09/01/19 – 08/31/24 \$4,999,270 Total Costs
Rodgers, Kathleen (PI) (co-I: Trouard, Yin, Berghout, Hay, Konhilas, Trouard) NIH Defining Interactions Between Cardiovascular, Metabolic Dysfunction and Genetic Risk Factors in the Development of Dementia	09/01/19 – 08/31/24 \$3,658,851 Total Costs
Ryan, Lee (PI's: Hay, Rodgers, Switzer; co-I's: Bedrick, Konhilas) NIH Safety and Efficacy of Angiotensin-(1-7) on Cognitive Impairment in Heart Failure Patients At-Risk for Alzheimer's Disease	07/01/19 – 06/30/24 \$6,893,415 Total Costs
Su, Judith (PI) Pew Charitable Trusts Sensitive and Label-free Detection of DNA Shed by Tumor Cells using Microtoroid Optical Resonators	07/01/19 – 06/30/24 \$300,000 Total Costs
Su, Judith (PI) NIH Label-free single molecule detection for basic science and translational medicine	08/01/19 – 07/31/23 \$1,824,730 Total Costs
Su, Judith (PI) Gordon and Betty Moore Foundation Label-free, single molecule detection & spectroscopy	08/01/19 – 07/31/22 \$656,713 Total Costs
Su, Judith (PI) NIH Determining the binding energies of novel pain modulators for improved pain control	09/01/19 – 08/31/13 \$432,757 Total Costs
Su, Judith (Subcontract PI) University of Illinois at Chicago (NIH Prime) Label-free, Ultra-Sensitive Sensing Strategies for Ovarian Cancer Detection	12/01/19 – 11/30/21 \$121,671 Total Costs
Wilson (PI; co-I's: Alexander, Andrews-Hanna, Chou, Ekstrom) NIA R01 Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults	09/01/19-08/31/24 \$1,765,250 Total Costs



**Arizona Alzheimer's Consortium
21st Annual Scientific Conference
Thursday, May 16, 2019**

**Banner Health (Host Institution)
Tempe Center for the Arts
Tempe, Arizona**

Poster Abstracts

Poster 1

EVALUATION OF A VISUAL READ METHOD FOR FLORTAUCIPIR PET SCANS. Arora A, Pontecorvo M, Mintun M, Fleisher A, Devous M, Lu M, Galante N, Stevenson P, Flitter M, Beach T, Montine T, Serrano G, Sue L, Intorcchia A, Curtis C, Salloway S, Thein S, Wellman C, Perrin A, Lowe V, Grossman M, Irwin D, Ikonovic M, Seeley W, Rabinovici G, Masdeu J. Avid Radiopharmaceuticals; Banner Sun Health Research Institute; Mayo Clinic Rochester; Hospital of the University of Pennsylvania; University of Pittsburgh; University of California, San Francisco; Houston Methodist Neurological Institute; Stanford University; Compass Research; Banner Alzheimer's Institute; Butler Hospital; Pacific Research Network, Inc; Hospice of the Western Reserve; Arizona Alzheimer's Consortium.

Background: To evaluate a clinically applicable visual read method for flortaucipir PET scans.

Methods: Five imaging physicians were trained in-person using a predefined read methodology to visually interpret flortaucipir PET scans. After scaling images to cerebellum, they were instructed to evaluate regions of the neocortex (the posterolateral temporal (PLT), occipital, parietal and frontal regions) for increased tracer uptake, and interpret scans as either not consistent (tAD-) or consistent with an AD pattern (tAD+ or tAD++) using the following criteria: tAD-: no increased activity or increased activity isolated to the mesial temporal, anterior lateral temporal, and/or frontal region(s) tAD+: increased activity in the PLT or occipital region(s) tAD++: increased activity in the parietal/precuneus region(s) or frontal region with PLT, occipital, or parietal region(s) Read categories were derived from studies A05 and LZAX, where increased neocortical uptake in the PLT was associated with amyloid positivity, and activity beyond the PLT/occipital regions was associated with greater cognitive decline. After training on demonstration and practice cases, all readers independently read 105 scans from subjects enrolled in a Phase 3 clinical trial (study A16) plus 17 scans from a supplemental academic cohort (total n=122). The primary objectives tested the relationship between scan results and neuropathology of AD at autopsy.

Results: 82 cases came to autopsy and had evaluable scans. Median sensitivity and specificity for identifying Braak V/VI pathology were 89.1% and 83.3%, respectively. The median sensitivity and specificity for identifying high AD neuropathic change were 95.1% and 80.5%, respectively. Interrater reliability as measured by Fleiss' kappa for all interpreted scans (n=122) was 0.80 and overall agreement was 90.3%.

Conclusions: There was substantial agreement among readers. Using the proposed read method, readers were able to distinguish between scans consistent and not consistent with an AD pattern.

Poster 2

SINGLE CELL AND SINGLE NUCLEI RNASEQ OF FRESH FROZEN ALZHEIMER'S BRAIN.

Antone JV, Enriquez D, Elyaderani A, Geiger P, Adkins JR, Serrano G, Beach TG, Readhead B, Mastroeni D, Dudley J, Reiman EM, Liang WS. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona State University; Icahn School of Medicine at Mt. Sinai; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Understanding the transcriptomic alterations that characterize different brain cell types is key to elucidating the molecular pathways driving Alzheimer's disease (AD) pathogenesis. With the development of numerous strategies for cell sub-classification using single cell RNA sequencing (scRNAseq), investigating and optimizing laboratory and analytical methods for implementing this technology is needed. We thus designed a pilot study on the 10x Genomics platform to evaluate various sample preparation parameters, different library preparation kits, and as well as analysis parameters.

Methods: Fresh frozen superior frontal gyrus (SFG) from one healthy (ND) and one AD subject from the Banner Sun Health Research Institute's (BSHRI) Brain and Body Bank were used for analysis. For each subject, libraries were prepared in quadruplicate to compare 3' versus 5' mRNA preparations and whole cell versus nuclei preparations for a total of 32 libraries. Approximately 2,000-4,000 whole cells or nuclei were used to construct libraries on the 10x platform using the Chromium Single Cell A Chip Kit, Chromium Single Cell 3' Library and Gel Bead Kit v2 or Chromium Single Cell 5' Library and Gel Bead Kit and Chromium i7 Multiplex Kit. Sequencing was performed on the Illumina NextSeq or HiSeq4000 and analysis was performed using the Chromium Cell Ranger pipelines (v3.0.1) and Seurat v3.0. Cell population classification was performed using human RNAseq data sets available through the Allen Institute for Brain Science (<http://celltypes.brain-map.org/rnaseq>).

Results: Overall, we generated over 1.5 billion reads with a median of 31,143 mean reads per cell or nuclei across samples. Limited gene expression data was generated for 5 whole cell samples and were thus dropped from further analyses. As expected, in whole cell data, higher levels of mitochondrial transcripts were observed and in nuclei data, a higher prevalence of transcripts containing intronic sequences was observed. Merging of replicates revealed cell populations in each sample group with the most well-defined populations in nuclei data. Astrocytes, endothelial cells, neurons (GABAergic, granule, pyramidal), and oligodendrocytes were identified in both ND and AD brains. Microglial cells did not cluster out but interestingly, a neuronal stem cell population was also observed in the AD SFG.

Conclusions: Our pilot study analysis evaluated the performance of different library preparation approaches utilizing either whole cell or nuclei dissociation procedures. While analysis of larger numbers of samples is needed, we observed that a larger number of genes is detected using a 5' mRNA library preparation, that a whole cell approach does not perform as well as a nuclei approach when analyzing fresh frozen brain, and that utilization of replicates improves segregation of cell populations from the same sample. We are expanding our analyses to single nuclei RNAseq on 25 ND and 25 AD (SFG) and are also performing laser capture microdissection (LCM) of various cell types across differentially impacted brain regions in AD to generate a high resolution transcriptomic reference of brain cell types in healthy aging and AD.

Poster 3

APOLIPOPROTEIN E HOMOZYGOSITY ASSOCIATIONS WITH NEURODEGENERATIVE DISEASE CLINICAL AND NEUROPATHOLOGICAL CHARACTERISTICS. Beach TG, Adler CH, Serrano GE, Sue LI, Shill HA, Belden CM, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta SH, Burks T, Zamrini E, Shprecher DR, Spann B, Tariot PN, Davis KJ, Long KE, Nicholson LR, Intorcchia A, Glass M, Walker J, Oliver J, Arce R, Sauhagen A, Sabbagh MN, Lue L-F, Walker DG, Reiman EM. Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; University of Arizona; Banner Alzheimer's Institute; Cleveland Clinic Lou Ruvo Center for Brain Health; Shiga University of Medical Science; Arizona Alzheimer's Consortium.

Background: The major genetic risk factor for the most common type of Alzheimer disease dementia (ADD), sporadic late-onset ADD, is the apolipoprotein E (apoE) ϵ 4 allele. There are also ϵ 2 and ϵ 3 alleles, which are associated with lower and neutral ADD risk, respectively. The apoE- ϵ 4-related ADD effects are thought to be mediated by increased and earlier amyloid plaque deposition while tangle formation is thought to be unaffected by apoE genotype. The very low prevalence of ϵ 2 homozygosity, particularly in clinicopathological ADD studies where it is found in only 1 in 1,000 subjects, has made it difficult to completely assess the ϵ 2 influence on ADD risk, amyloid plaques and neurofibrillary tangles.

Methods: The Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and the Arizona Alzheimer's Disease Core Center are longitudinal clinicopathological studies with comprehensive phenotyping together with apoE genotyping. Statistical comparisons are made between ϵ 2, ϵ 3 and ϵ 4 homozygotes. We hypothesized that homozygosity for ϵ 2 would be associated with differential neurofibrillary tangle and/or neuritic plaque presence, severity or morphology (diffuse vs neuritic types of amyloid plaques).

Results: There were 1,439 autopsies with apoE genotyping and full neuropathological examinations. From these, there were 10 ϵ 2 homozygotes, 797 ϵ 3 homozygotes and 94 ϵ 4 homozygotes. The three groups were significantly different in several relevant clinical parameters including age at death, final MMSE score and final motor UPDRS score, and clinical diagnoses of cognitively normal, dementia or parkinsonism. Neuropathological significant differences included total plaque score, CERAD neuritic plaque density, total tangle score and Braak tangle stage, as well as neuropathological diagnoses of normal, ADD, progressive supranuclear palsy (PSP), corticobasal degeneration; dementia with Lewy bodies (DLB) and Parkinson's disease (PD). The ϵ 2 homozygotes group, in comparison with the ϵ 3s and ϵ 4s, had proportionately higher densities of the diffuse plaque type as compared to neuritic plaques, and proportionately lower neurofibrillary tangle densities for equivalent plaque loads.

Conclusions: This study confirms prior published findings linking the apolipoprotein ϵ 4 and ϵ 2 alleles with respectively increased and decreased associations with ADD and with decreased amyloid plaque loads. A new finding is that ϵ 2 homozygotes have a preponderance of diffuse plaques and fewer neurofibrillary tangles than expected for given plaque loads. Also, as reported by another group, ϵ 2 homozygotes may be more likely to develop the non-AD tauopathies PSP and CBD, although this association is limited by the small group size. The molecular mechanisms behind these findings may give clues for the development of ADD therapeutics.

Poster 4

HYPOSMIA IS MUCH MORE SEVERE IN NEUROPATHOLOGICALLY CONFIRMED DEMENTIA WITH LEWY BODIES AS COMPARED WITH ALZHEIMER'S DISEASE DEMENTIA. Beach TG, Adler CH, Serrano GE, Sue LI, Zhang N, Driver-Dunckley E, Mehta SH, Shprecher DR, Zamrini E, Sabbagh MN, Shill HA, Belden CM, Davis KJ, Long KE, Nicholson LR, Intorcica AJ, Glass MJ, Walker JE, Callan M, Oliver JC, Arce R, Caselli RJ, Woodruff BK, Rapscak SZ, Ahern GL, Shi J, Spann BM, Tariot PN, Reiman EM, Gerkin RC. Banner Sun Health Research Institute; Mayo Clinic Arizona; Cleveland Clinic Lou Ruvo Center for Brain Health; Barrow Neurological Institute; University of Arizona; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Due to the absence of core clinical features, 50% or more of subjects with neuropathologically-confirmed dementia with Lewy bodies (DLB) are never diagnosed as such during life. Most of these are diagnosed with Alzheimer's disease dementia (ADD) or dementia NOS. Unrecognized DLB therefore is a critical impediment to clinical studies and treatment trials of both ADD and DLB. There are numerous published studies that suggest that olfactory function tests may be able to differentiate some neurodegenerative conditions from each other and from normal subjects, but there are very few studies with neuropathological confirmation of diagnosis. We compared University of Pennsylvania Smell Identification Test (UPSIT) results in 30 subjects concurrently meeting intermediate or high consensus clinicopathological criteria for both DLB and ADD (no subjects with "pure" DLB were included due to low subject numbers), and 103 meeting criteria for ADD without DLB, as well as 87 control subjects that were cognitively normal and without parkinsonism at death.

Methods: Subjects were selected by database searches of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND)/ Banner Sun Health Research Institute Brain and Body Donation Program (www.brainandbodydonationprogram.org). Most subjects had serial standardized research cognitive evaluations, done by teams of nurses, medical assistants, behavioral neurologists, neuropsychologists and psychometrists using standardized research-quality assessment batteries, including the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). Subjects selected for this study also had one or more UPSITs done. All subjects received identical blinded neuropathological examinations by the same neuropathologist (TGB).

Results: Subjects with DLB were predominantly male (23M, 7F) while the other groups were more equally balanced (ADD: 52M, 51F; C: 42M, 49F). DLB subjects were significantly younger (85.1; $p=0.03$) than those with ADD (88.3) but not significantly different from controls (86.7). Mean MMSE score (22.2, SD 7.8 for ADD; 22.7, SD 4.6 for DLB) was not significantly different between dementia groups. Control subjects had significantly more UPSITs (mean 1.9, range 1-4; $p < 0.05$) than ADD (mean 1.6, range 1-4) or DLB subjects (mean 1.35, range 1-3) but this did not differ between ADD and DLB groups. The DLB subjects had significantly lower (one-way ANOVA $p < 0.0001$, pairwise Bonferroni $p < 0.05$) mean UPSIT scores (13.2, SD 3.9) than ADD (22.2, SD 7.9) or controls (28.9, SD 4.7). For subjects with an UPSIT score less than 20, Firth logistic regression analysis, adjusted for age, gender and mean MMSE score, conferred an odds ratio of 28.4 for predicting a DLB vs ADD diagnosis (95% CI 5.27 to 153.2).

Conclusions: To our knowledge, this is the first report of olfactory function in a large set of subjects with neuropathologically confirmed DLB and ADD. Subjects with DLB had much more severe olfactory impairment than those with ADD. Olfactory function testing may be a convenient and inexpensive strategy for enriching dementia studies or clinical trials with DLB subjects, or conversely, reducing the inclusion of DLB subjects in ADD studies or trials.

Poster 5

ASSESSMENT OF MULTI-PARAMETRIC DIFFUSION-WEIGHTED MRI METRICS IN ALZHEIMER'S DISEASE. Bergamino M, Nespodzany A, Baxter LC, Burke A, Caselli RJ, Sabbagh MN, Walsh RR, Stokes AM. Barrow Neurological Institute; Mayo Clinic Arizona; Cleveland Clinic Lou Ruvo Center for Brain Health; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease impacting aging populations. While several magnetic resonance imaging (MRI) techniques have been used to study AD, these methods are often limited in their sensitivity to underlying neuropathological changes. On the other hand, advanced multimodal neuroimaging approaches may provide novel metrics related to functional changes associated with Alzheimer's disease. The objective of this study is to assess complementary metrics from a voxel-based morphometry (VBM) analysis method and an intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) MRI technique in aging populations.

Methods: Twelve subjects with AD dementia (6 females; ageS.D: 778 years), eleven with mild cognitive impairment (MCI, 8 females; 765 years), and eleven healthy controls (HC, 7 females; 767 years) were included in this study. All participants completed the Montreal Cognitive Assessment (MoCA), the Clock-Draw, and the Functional Assessment Staging Tool (FAST) tests immediately prior to MRI scan. MRI data were acquired at 3T (Ingenia, Philips). FreeSurfer parcellation yielded grey matter (GM) masks from T1-weighted images for VBM analysis. The IVIM-DWI (IVIM-slow and IVIM-frac) and apparent diffusion coefficient (ADC) maps were generated using bi- and mono-exponential model fitting, respectively, using an in-house MATLAB script. All maps were normalized to the IIT standard space by using an ANTs-SyN coregistration and were smoothed by using an isotropic Gaussian kernel of 2 mm. A voxel-based (VB) approach was used to study the difference across groups and the correlations between MRI metrics and cognitive assessments.

Results: No significant differences in age were detected across groups (Kruskal-Wallis, $H=0.51$; $p=.774$). One-way ANOVA with a post-hoc Tukey test found differences in MoCA ($f=29.18$; $p<.001$), Clock-Draw ($f=12.45$; $p<.001$), and FAST ($f=15.08$; $p<.001$). One-way MANCOVA (with age and gender as covariates at $p<0.05$ FWE corrected) found significant differences across groups in several white and grey matter locations, including insula, putamen, temporal lobe, corpus callosum, fornix, anterior corona radiata, and sagittal striatum. Subsequent post-hoc analysis with Bonferroni correction showed differences between AD and HC for all methods, between AD and MCI for IVIM and ADC, and between MCI and HC for ADC. Several VB correlations between ADC/IVIM/VBM and cognitive tests were also found for cognitively impaired groups.

Conclusions: This study demonstrates that novel imaging biomarkers can be obtained using multimodal neuroimaging techniques, such as IVIM-DWI, ADC and VBM analysis. Moreover, IVIM-DWI biomarkers may provide unique insight into domain-specific cognitive deficits.

Poster 6

SPECIFICITY OF ACTIVITY-REGULATED TRANSCRIPT LOCALIZATION IN SOMATIC AND DENDRITIC NEURONAL COMPARTMENTS. Bleul C, Chawla MK, De Both MD, Barnes CA, Huentelman MJ. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: Next generation RNA sequencing (RNA-Seq) provides the ability to construct an unbiased whole transcriptome map, digitally quantify transcript levels, and can interrogate splice form abundance. Specific RNA species are known to be expressed and can redistribute within hours or less to the dendrites where local translation can occur. Much is left to be discovered about the function of these dendritic mRNAs, however, evidence suggests that they play a key role in synaptic plasticity and transmission.

Methods: In this study, we utilized RNA-Seq to identify transcripts from total RNA obtained from laser-capture microdissected (LCM) sub-fields of the hippocampal formation (dentate gyrus [DG], CA1, and CA3) of 9 month old Fisher344 rats. Three adjacent 15 um thick cryostat sections were rapidly stained with fluorescent Nissl green, the cell soma and corresponding neuropil regions (10 different regions in total) were laser captured and the RNA isolated and prepared for sequencing using the SMARTer Stranded Total RNA-Seq Pico Input Mammalian Library Prep Kit (Clontech-Takara). Results from caged control (CC) animals and electroconvulsive shock (ECS) treated animals sacrificed at 10 minutes, 30 minutes, 1 hour, 2 hours, 4 hours and 24 hours post exposure were analyzed and compared.

Results: Following ECS treatment, we found that known immediate early genes like Arc, Homer1, Egr1 and Fos were significantly differentially expressed in the different hippocampal regions. Of note however, specific patterns of activation were demonstrated. For example, Homer 1 only demonstrates activity regulation in the DG soma compartment. Arc, on the other hand, demonstrates activity regulation across the hippocampus and in both dendritic and soma compartments. We also explored the relationship between the neurotrophins and their receptors following ECS. Ngf is activity regulated in the DG soma, however the primary receptor for Ngf, Ntrk1, exhibits no activity regulation. Bdnf, on the other hand, is activity-regulated in the soma compartments across all three hippocampal sub-fields however its receptor, Ntrk2, is only activity-regulated in the DG soma.

Conclusions: We propose that the creation of a complete catalog of activity-regulated transcripts will enable a hypothesis-driven investigation of neurological disease with a focus entirely on verified activity regulated genes. These initial findings demonstrate the utility of our experimental approach to confirm known and identify novel discoveries related to activity-regulated transcription, potentially leading to a deeper understanding of the molecular mechanisms associated with cognition and possible treatments for neurological disease.

Poster 7

FACILITATING USER ACCESSIBILITY TO REGULATORY-ENDORSED DRUG DEVELOPMENT TOOLS FOR ALZHEIMER DISEASE (AD). Burton JK, Conrado DJ, Kern VD, Arnerić SP, Romero K, on behalf of the Critical Path for Alzheimer's Disease (CPAD) Consortium. Critical Path Institute; Arizona Alzheimer's Consortium.

Background: The long-term goal of this effort is to help optimize the design of clinical trials investigating drugs to treat the different stages of the AD continuum. Drug development in Alzheimer disease (AD) is focusing on earlier disease stages. Challenges in early AD clinical trials include: (a) uncertainty for adequate patient selection, (b) interindividual heterogeneity, and (c) slow rate of change in clinical outcomes. An understanding of the rate of change and its predictors, for registration endpoints, is critical for optimal trial design. This effort has three main goals: 1) To develop a user-friendly clinical trial enrichment (CTE) tool to optimize the design of clinical trials to evaluate therapeutic candidates intended to treat MCI; 2) To develop real-time solutions for the efficient application of the clinical trial simulation features of the CTE and clinical trial simulation (CTS) tools that are accessible to members of drug development teams and regulators; and 3) To develop a comprehensive, continued training mechanism for AD researchers on the use and application of the CTS and CTE tools, including computational efficiency solutions.

Methods: The update to the CTS tool was carried out using patient-level data exclusively from 15 clinical studies in mild-to-moderate AD within the CPAD database and individuals diagnosed as mild-to-moderate in the ADNI-1 database yielding a total of 4,726 subjects. The Richards model, a generalized logistic model, was used to describe the nonlinear time course of ADAS-Cog scores. A graphical user interface (GUI) was developed using Shiny, a package from RStudio that allows to build interactive web pages with the open-source statistical programming platform R. The MCI model was built using ADNI data (N=702), with the Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon trial data being reserved for external validation. The time course of CDR-SB was described by a non-linear mixed-effects model. Pre-specified covariates were: baseline intracranial volume-adjusted hippocampal volume, sex, baseline mini-mental-state-examination, baseline age, and APOE genotype. Of the evaluated models, the one following a Richards curve was most appropriate to describe the nonlinear time course of CDR-SB scores.

Results: A user-friendly CTE tool was developed to optimize the design of clinical trials to evaluate therapeutic candidates intended to treat the MCI stage of the AD continuum using Rshiny. The GUI provides users with a simple interface to optimize clinical trial design by customizing patient and trial design characteristics, and then allows simulation of clinical trials under those conditions. Users can calculate statistical power through those simulations based on the patient and trial characteristics chosen. This work was presented (oral and poster) at the 9th Annual Conference on Pharmacometrics. As part of the computational solutions for efficient application of the tools, efforts were first taken to make the tools widely available by implementing the GUI versions of the CTE and CTS tools on the shinyapps.io platform. Several different mechanisms have been utilized for continued training on the use and application of the tools. Documentation that describes various aspects of the tool and its use is being provided on the CTE web app.

Conclusions: The updated tool provides additional data-driven insights and regulatory input with the goal of endorsement will be pursued. The faster progression in individuals with concomitant medication use can be a reflection of underlying pathology. Those who are deemed as needing concomitant medication use have, inherently, a more severe underlying pathology, especially considering that all available drugs have symptomatic effects only. The development of the GUI is a key step in allowing non-technical researchers to utilize this robust and powerful tool.

Poster 8

MECHANISMS OF NEURODEGENERATION IN ALZHEIMER'S DISEASE. Caccamo A, Piras I, Huentelman MJ, Readhead B, Belfiore R, Winslow W, Vartak R, Oddo S. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by severe neuronal loss; however, the mechanisms by which neurons die remain elusive. Necroptosis, a programmed form of necrosis, is executed by the mixed lineage kinase domain-like (MLKL) protein, which is triggered by receptor-interactive protein kinases (RIPK) 1 and 3.

Methods: We used complementary genetic, pharmacological, and computational approaches to investigate the mechanisms of cell death in Alzheimer's disease. We also used postmortem human tissue, genetically-modified mice, gene-transfer techniques, and primary neuronal cultures.

Results: We found that necroptosis was activated in postmortem human AD brains, positively correlated with Braak stage, and inversely correlated with brain weight and cognitive scores. In addition, we found that the set of genes regulated by RIPK1 overlapped significantly with multiple independent AD transcriptomic signatures, indicating that RIPK1 activity could explain a substantial portion of transcriptomic changes in AD. Furthermore, we observed that necroptosis mediates tau-induced neuronal loss.

Conclusions: We anticipate that our findings will spur a new area of research in the AD field focused on developing new therapeutic strategies aimed at blocking its activation.

Poster 9

AGE-DEPENDENT CORRELATION BETWEEN SPATIAL AND WORKING MEMORY DOES NOT EXTEND TO OBJECT RECOGNITION. Carey NJ, Zempare MA, Nguyen CJ, Bohne KM, Chawla MK, Sinari S, Huentelman MJ, Billheimer D, Barnes CA. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: As average life expectancies continue to increase around the world, it is critical to understand the normative characteristics of brain and cognition during aging. While it is well-documented that certain changes in learning and memory are to be expected as we age, it is also well-appreciated that there is significant variability in the extent to which different domains of cognition are impacted in any given individual.

Methods: To better understand the complexity of individual differences in cognition during aging across the lifespan, we designed a battery of behavioral tests that assess the functional integrity of distinct brain regions. This battery consists of the spatial and cued versions of the Morris watermaze, spontaneous object recognition (SOR), and a delayed matching-to-place working memory task. Male Fisher 344 rats were examined at three ages: young adult (6mo), middle-aged (15mo), and aged (23mo) at the beginning of testing. The first step in our analysis process is to assign cognitive category levels on the basis of performance on the hippocampus-dependent spatial version of the Morris watermaze: low, average, or high within a given age group. These spatial cognition categories were then compared to working memory performance within young animals: the high-performing animals on the spatial task were also high performing on the prefrontal cortex-dependent working memory task. The opposite was true for the aged group of rats, however, as the old animals that performed poorly on the spatial version of the water maze, performed well for their age group on the working memory version of the task.

Results: The middle-aged rats showed relationships between spatial and working memory that were intermediate between the young and aged groups. With respect to the perirhinal cortex-dependent object recognition memory task, there were significant differences across age, consistent with previous observations in aged rats, monkeys (Burke et al., 2012), and humans (Ryan et al., 2012). These changes in recognition memory were not related to the spatial cognitive category for any age group, even though both the perirhinal cortex and hippocampus are required for adequately using cue recognition for processing spatial input (Burke et al., 2018 in press). Additionally, there was no correlation between SOR performance and working memory performance across age, where comparable delays were used in both tasks.

Conclusions: Taken together, these data emphasize the importance of understanding the relationship between the function of these brain regions across age, as it may provide insight into how these processes can be optimized for the highest quality of life as human life expectancy continues to rise.

Poster 10

APPLYING A NOVEL INTEGRATED PERSISTENT FEATURE TO UNDERSTAND TOPOGRAPHICAL NETWORK CONNECTIVITY IN OLDER ADULTS WITH AUTISM SPECTRUM DISORDER. Catchings MT, Wang Y, Kuang L, Braden BB. Arizona State University; Arizona Alzheimer's Consortium.

Background: Autism spectrum disorder (ASD) is a developmental neuropsychiatric condition with early childhood onset, thus most research has focused on characterizing brain function in young individuals. Little is understood about brain function differences in middle age and older adults with ASD, despite evidence of persistent and worsening cognitive symptoms. Functional MRI in younger persons with ASD demonstrate that large-scale networks containing nodes in the prefrontal cortex are preferentially affected. Further, various graph theoretical analyses have shown disrupted topological organization for younger individuals with ASD when compared to neurotypical (NT) individuals, but suffer from limited generalization because of the need to choose a threshold value. Building on other aging neuroscience work, we propose a novel graph theory metric that is free of threshold selection and quantifies the rate of information diffusion in prefrontal-containing networks and as a more robust and sensitive method for tracking brain aging in ASD. Here, we compare this novel metric against five well-accepted graph theoretical analysis methods in older men with ASD and matched NT participants.

Methods: Participants were 27 men with ASD (52 +/- 8.4 years) and 21 NT men (49.7 +/- 6.5 years). Resting-state functional MRI (fMRI) scans were collected for six minutes (repetition time=3s) with eyes closed. Data were preprocessed in SPM12 and Data Processing Assistant for Resting-State fMRI (DPARSF) was used to extract 116 regions-of-interest defined by the automated anatomical labeling (AAL) atlas. AAL regions were separated into six large-scale brain networks. Our novel metric of interest was the slope of a monotonically decreasing convergence function (Integrated Persistent Feature, IPF). The slope of the IPF (SIP) describes the construction rate from loose components to one fully connected component over a nested filtration graph. Results were analyzed in SPSS using ANCOVA, with IQ as a covariate.

Results: We found a reduced SIP in older men with ASD, compared to NT men, in the default mode network [DMN; $F(1,47)=6.48$; $p=0.02$; $\eta^2=0.13$] and executive network [$F(1,47)=4.40$; $p=0.04$; $\eta^2=0.09$], a trend in the fronto-parietal network [$F(1,47)=3.36$; $p=0.07$; $\eta^2=0.07$]. There were no differences in the non-prefrontal networks (sensory motor, auditory, and visual). The only other graph theory metric to reach significance was network diameter in the DMN [$F(1,47)=4.31$; $p=0.04$; $\eta^2=0.09$]; however, the effect size for the SIP was stronger. Modularity, Betti number, characteristic path length, and eigenvalue centrality were all non-significant.

Conclusions: These results identify a novel graph theory metric quantifying the rate of information diffusion in large-scale prefrontal networks as a more robust and sensitive method for detecting topographical brain organization differences between older men with and without ASD. Topological brain organization differences may underlie persistent and worsening symptoms, which warrants further investigation. The SIP holds promise for greater sensitivity to predict longitudinal cognitive and brain aging outcomes in ASD.

Poster 11

PREDICTIVE NETWORK ANALYSIS IDENTIFIES MICROGLIAL-SPECIFIC KEY DRIVERS FOR PHAGOSOME AND A β -CLEARANCE IN ALZHEIMER'S DISEASE. Chang R. University of Arizona; Arizona Alzheimer's Consortium.

Background: Late-Onset Alzheimer's Disease (LOAD) results from a complex pathological process influenced by genetic variation, aging and environment factors. Genetic susceptibility factors indicate that myeloid cells such as microglia play a significant role in the onset of LOAD.

Methods: Here, we developed a computational systems biology approach to construct probabilistic causal and predictive network models of genetic regulatory programs of microglial cells under LOAD diagnosis by integrating two independent brain transcriptome and genome-wide genotype datasets from the ROSMAP and Mayo Clinic studies in AMP-AD consortium.

Results: From this network model, we identified and replicated novel microglial-specific master regulators predicted to modulate network states associated with LOAD. We not only experimentally validated three master regulators associated with phagocytosis, a process associated with LOAD, that in turn causally links phagocytosis to Abeta burden, and revealed the causal relations among the three, but also we validated the molecular impact these master regulators have on modulating downstream genomic targets by perturbing them in primary human microglia-like cells (MDMi).

Conclusions: Thus, we propose three new master regulator genes that emerged from our network analyses as robust candidates for further evaluation in LOAD therapeutic development efforts.

Poster 12

PREDICTING LIKELIHOOD OF PROGRESSION FROM MCI TO PROBABLE ALZHEIMER'S DEMENTIA WITH CLINICAL RATINGS, BRAIN IMAGING MEASUREMENTS AND AGE USING MACHINE LEARNING TECHNIQUES. Chen Y, Pan R, Luo J, Lee W, Chen K, Devadas V, Bauer III R, Reiman EM, Su Y. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Predicting a patient's risk of afflicting Alzheimer's Disease (AD) is one of the most pressing goals of AD research. It allows researchers and clinicians to identify high-risk patients at the earliest possible stage so as to plan for effective interventions. Although various classification tools have been applied on clinical data to classify AD and MCI groups, the publications on predicting the conversion risk from NL to MCI and from MCI to AD are still sparse. In this study, we construct and compare several parametric and nonparametric models for predicting the conversion risk from MCI to AD using ADNI data. Our analysis also identifies the most important parameters that are predictive of the conversion risk.

Methods: ADNI data were downloaded including 129 converters (age 74.3 ± 7.0) and 253 non-converters (age 73.3 ± 7.7). A total of 14 variables (MMSE, CDR_SOB, AVLT_STM, AVLT_LTM, AVLT_Total, ADAS-cog13 [13-item AD Assessment Scale], age, education, gender, APOE status, HCI [hypo-metabolic convergence index for FDG-PET], sROI [a statistical region-of-interest based FDG measure], ventricle volume, and hippocampus volume), were included in the analysis. A Cox's proportional hazard (PH) model and a tree-based regression model were used to perform survival analysis on the ADNI dataset. The patient's cognitive test scores and brain features from the baseline visit were used as predictors, and the AD conversion age, which was determined at a subsequent visit, was the response variable. If a patient has not developed AD at his/her last visit, the age at the last visit is treated as a censored observation (i.e., a survival observation). Both the Cox's PH regression and survival random forests methods were applied on this dataset to predict the conversion probability for an individual at different ages. Ten-folded cross-validation on each model was conducted to evaluate the accuracy, sensitivity, and specificity of each model.

Results: Our preliminary results from the survival random forests analysis showed that the patient's age, ADAS13 and HCI were the three most important factors for predicting his/her AD risk in the future. Interestingly, the patient's gender and APOE status were identified as the least important factors by the models.

Conclusions: Our results indicate that we can use the random forests model to estimate the risk of afflicting AD for an MCI patient as a function of age. The finding that APOE status did not contribute to the predictive model is surprising, and might be attributable to the inclusion of other variables that were more directly affected by APOE status.

Poster 13

USING THE YEAST TWO-HYBRID SYSTEM TO STUDY PROTEINS INTERACTING WITH PRESENILIN-1. Chow AY, Artigas JA, Bae NS, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

Background: The ends of linear, eukaryotic chromosomes (telomeres) are protected from non-homologous end-joining and homologous recombination by a complex called shelterin. Unique among the proteins in shelterin is TERF2IP, which has non-telomeric functions in both the nucleus and cytoplasm. In studying additional functions of TERF2IP, we sought to identify proteins that interact with it and identified GFAP ϵ . GFAP ϵ has been shown to interact with presenilin proteins that are involved in development of neurodegenerative diseases. Early onset familial Alzheimer's disease (eFAD) is associated with mutations in the APP, PSEN1 and PSEN2 genes. APP encodes amyloid precursor protein (APP), a substrate for proteolytic secretase complexes. Sequential cleavage of APP by β -secretase followed by γ -secretase produces amyloid (A β) peptides of varying lengths. Shorter peptides are soluble, but longer peptides aggregate to form amyloid plaques, a hallmark of the Alzheimer's disease brain. PSEN1 and PSEN2 encode presenilin proteins (PS1 and PS2, respectively) that are the catalytic subunits of γ -secretases. eFAD-associated mutations lead to an increase in the total A β or an increase in the ratio of the insoluble to the soluble peptides. Presenilins are integral membrane proteins, and the amino-terminal, cytoplasmic domain of PS1 was shown to interact with a form of glial fibrillary acidic protein (GFAP), the epsilon (ϵ) isoform. Unlike the most common isoform, GFAP ϵ does not form intermediate filaments. GFAP ϵ is polymorphic, and its three alleles differ by a single amino acid.

Methods: The yeast two-hybrid (Y2H) system is a genetic method to detect protein-protein interactions. A yeast genetic screen using TERF2IP as a bait identified GFAP ϵ as an interacting protein from a human fetal brain cDNA library. Additional Y2H studies are being done to determine the interactions among TERF2IP, GFAP ϵ and PS1. Variants of the proteins were made to determine any effects on the interactions.

Results: We identified GFAP ϵ as a protein interacting with TERF2IP. Additional expression of PS1 in the yeast cells lead to a stronger TERF2IP-GFAP ϵ interaction, suggesting the interaction among the three proteins is cooperative. Different allelic variants of GFAP ϵ showed different strengths of interaction with TERF2IP. Non-human primates are monomorphic for GFAP ϵ , encoding an allele that is shared with humans, and this allele interacts only weakly with human TERF2IP. They encode a TERF2IP protein that differs in a single amino acid from humans, and their TERF2IP does not interact with any allelic variant of GFAP ϵ .

Conclusions: We identified a cooperative interaction among the telomeric protection protein TERF2IP, an isoform of GFAP and the eFAD-associated PS1. The interaction between TERF2IP and GFAP ϵ depends upon the specific GFAP ϵ variant tested, and the ape version of TERF2IP does not interact with GFAP ϵ .

Poster 14

LATERAL BUT NOT MEDIAL ENTORHINAL CORTEX POPULATION REPRESENTATIONS BECOME MORE SPARSE WITH AGE. Comrie AE, Lister JP, Chawla MK, Barnes CA. University of Arizona; University of California, San Francisco; University of California, Los Angeles; Arizona Alzheimer's Consortium.

Background: The hippocampus undergoes biological changes with age that are associated with changes in memory function. Subregions of the hippocampus receive major inputs from and send back projections to superficial and deep layers of Entorhinal Cortex (EC), respectively. Yet, how behaviorally-relevant neural activity in EC may change with age remains poorly understood. In contrast to the well-studied Medial Entorhinal Cortex (MEC), Lateral Entorhinal Cortex (LEC) neurons do not show substantial spatial selectivity in their firing patterns. Rather, LEC is thought to be involved in representing non-spatial features of experiences, including odors.

Methods: In this study, we examined whether LEC and MEC neuron populations are selectively activated in response to distinct odors during track running, and hypothesize that aging may alter EC activity patterns that contribute to memory dysfunction. To test this, adult and aged rats were trained to run on a track in a constant environment. After training, one behavioral group (AA) experienced the same set of 6 odors around the track during two run sessions separated by 20 mins. A second group (AB) also ran two sessions, but the odor stimuli were distinct between the epochs. We used cellular compartment analysis of temporal activity by fluorescence in situ hybridization (catFISH) to visualize the time-dependent subcellular distribution of Arc mRNA in EC principal cells. We identified neurons activated during the first, second, or both sessions in superficial and deep layers of EC.

Results: We found that AA and AB behaviors elevated LEC and MEC activity compared to a control condition. Population activity, however, failed to distinguish the distinct A and B odor experiences. This suggests that EC neural population activity stably represents higher order features of the behavioral experience regardless of altered odor input. Surprisingly, more cells reached Arc activation thresholds during the second epoch than the first in LEC, but not in MEC. This may indicate that LEC circuits are sensitive to priming by similar past experience. Furthermore, a lower proportion of LEC neurons participated during the behavior in aged rats than in adult rats, while activation in MEC was preserved in aged animals.

Conclusions: This result is in line with data from humans that show that anterolateral, but not dorsomedial, EC becomes hypoactive with age and that this reduction is related to cognitive deficits (Reagh et al., 2018). Exactly how the sparser network representations in aged rat LEC contribute to altered behavioral function across the lifespan awaits further investigation.

Poster 15

LESSONS FROM A COMMUNITY-LEVEL, MUSIC-BASED INTERVENTION FOR PEOPLE WITH ADRD. Coon DW, McCarthy M, Cortes M, Carll P, Jaszweski A, Gomez Morales A, Rio R, Belgrave M, Todd M, Bontrager V, Burleson M. Arizona State University; The Phoenix Symphony; Arizona Alzheimer's Consortium.

Background: Few studies have examined interdisciplinary and/or community-level efforts to deliver music-based interventions for people with dementia in memory care settings. Moreover, most research focuses on standardized measures that fail to capture changes immediately before, after, and/or during music. This collaboration advances research in this arena by combining nurse and activity coordinator ratings of mood and behavior with biomarkers of stress (salivary alpha amylase and salivary cortisol) across three distinct long-term care communities serving high, middle, and low-income populations.

Methods: Guided by an interprofessional protocol (music, music therapy, nursing, and behavioral science), symphony musicians and music therapists delivered this intervention via 7 music-based events across 6 weeks. Nurses and activity coordinators rated resident affect and behavior before and after each event. Symphony musicians, facility staff, and family caregivers completed analogous self-ratings. Participants provided saliva samples to help measure biomarkers of stress (salivary alpha-amylase and cortisol). In addition, senior project staff evaluated residents using standardized measures (e.g. Cornell Depression Inventory, Dementia QoL) within 2 weeks pre-post the overall project. Night nurses provided feedback on the overall environment on evenings with and without music events. Debriefings with musicians, music therapists, and nurses and activity coordinators gathered qualitative data of their experience.

Results: Mood and behavior ratings as well as saliva samples provided evidence to support the intervention. Significant changes emerged in participant mood and behavioral activation. A sub-study measuring salivary cortisol suggested that music events might have enabled residents to better regulate their stress responses around a stressor (i/e/. bathing). Night nurse ratings varied across facilities; however, environmental factors were often rated more positively on evenings when morning music events occurred: levels of verbal/physical disruption; resident cooperation during evening care; overall unit mood; and, number of critical events (e.g., falls, acute illness, deaths, staff shortages). Standardized measures were less conclusive, as results varied across facilities. Lessons learned from the findings and debriefings indicate key challenges regarding research set up at facilities; scheduling conflicts for family caregivers and musicians; staff rotations and staff turnover; and musician variability in experience with dementia.

Conclusions: Overall, the findings (a) provide evidence for the project's conceptual model integrating three key parameters (receptive to active; observation to relationship; and planned to improvisation), (b) help bridge science and practice in this arena, and (c) emphasize the importance of community-level music-based interventions. It extends the scientific and practice literatures by assessing mood and behavior changes immediately before and after music-based events, gathering feedback on environmental changes, and examining feasibility and perceptions of benefit.

Poster 16

FINDING THE NEEDLE IN A HAYSTACK – IDENTIFICATION OF CIRCULAR RNAs USING RNA SEQUENCING. Cuyugan L, Sekar S, Geiger P, Serrano G, Beach TG, Liang WS. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Circular RNAs (circRNAs) are a class of non-coding RNAs involved in functions including micro-RNA (miRNA) regulation, mediation of protein-protein interactions, and regulation of parental gene transcription. In classical next generation RNA sequencing (RNA-seq), circRNAs are typically overlooked as a result of poly-A selection during construction of mRNA libraries, or found at very low abundance and are therefore difficult to isolate and detect.

Methods: Here, we optimized a circRNA library construction protocol by comparing library preparation kits, pre-treatment options and various total RNA input amounts. We tested two commercially available whole transcriptome library preparation kits (Illumina's TruSeq Stranded Total RNA Library Prep Kit, cat# 20020596; and Roche's Kapa Total RNA Kit, cat# KK8400), with and without RNase R pre-treatment (Lucigen, cat#RNR07250), and using variable amounts of total RNA input (1 to 4 µg). Lastly, we compared multiple tissue types including liver, lung, lymph node and pancreas, as well as multiple brain regions including the cerebellum, inferior parietal lobe, middle temporal gyrus, occipital cortex and superior frontal gyrus to evaluate circRNA abundance across tissue types.

Results: Analysis of the generated RNA-seq data using six different circRNA detection tools (find_circ, CIRI, Mapsplice, KNIFE, DCC and CIRCexplorer) revealed that the Illumina TruSeq Stranded Total RNA library kit with RNase R pre-treatment and 4ug RNA input is the optimal method for identifying the highest relative number of circRNAs. Consistent with previous findings, we observed the highest enrichment of circRNAs in brain tissues compared to other tissue types.

Conclusions: We present here an optimized workflow for preparing sequencing libraries for the goal of identifying circRNAs.

Poster 17

STRATEGIC MEMORY ALZHEIMERS REHABILITATION TRAINING (SMART): COGNITIVE PROTECTION AND INTERVENTION FOR AMNESTIC-TYPE MILD COGNITIVE IMPAIRMENT (MCI). DenBoer JW, Siegel E. SMART Brain Aging, Inc.; Midwestern University; Arizona Alzheimer's Consortium.

Background: Dementia is a world-wide phenomenon, impacting more than 6 million people in the United States. Despite its projected prevalence, this is a significantly under-represented phenomena, with underestimate ranges from 15-35%. The combined effects of the aging of the population (caused by the shift of the baby boomer generation into dementia) and significant increase in life expectancy has combined to put dementia into the range of our largest medical, if not societal, problems.

Methods: The SMART Memory Program (DenBoer, 2008) is a cognitive intervention designed to promote the reduction of early-stage dementia. Although it has been found useful in all forms of dementia, it is particularly useful in amnesic-type MCI/VCI.

Results: The current longitudinal study examined 356 non-paid clients (all with amnesic type MCI, mean baseline MoCA = 20) across a two year span of this program, finding an average improvement of 4.25 MoCA points at the conclusion of this 6-week program.

Conclusions: Improvements in QOL and mood were also observed as a result of this program.

Poster 18

STRATEGIC MEMORY ALZHEIMERS REHABILITATION TRAINING (SMART) MEMORY PROGRAM FOR AMNESTIC MILD COGNITIVE IMPAIRMENT (AMCI): REPORTING THE RESULTS OF A RANDOMIZED CLINICAL TRIAL. DenBoer J. SMART Brain Aging, Inc; Arizona Alzheimer's Consortium.

Background: The combined effects of the aging of the population (caused by the shift of the baby boomer generation into dementia) and significant increase in life expectancy has combined to put dementia into the range of our largest medical, if not societal, problems. In the state of Arizona, there is a projected 44-72% increase in dementia. Research has supported the use of cognitive intervention exercises to reduce early-stage dementia. Valenzuela and Sachdev (2009), in a literature review of 22 studies (involving approximately almost 30,000 individuals), found an overall risk reduction of 46% in individuals that were found to engage in a high level of regular cognitive activity. Perhaps more importantly, they found a dose-dependent relationship between cognitive exercise and reduction of dementia, which had not been found previously.

Methods: The SMART Memory Program (DenBoer, 2008) is a cognitive intervention designed to promote the reduction of early-stage dementia. Results of this program have shown significant promise (e.g., DenBoer, 2013), and the present researchers are currently engaging in multiple research studies. The program is effective via the use of new and novel cognitive exercises.

Results: The researchers have conducted a randomized clinical trial (RCT), which is considered the gold-standard of research in this area.

Conclusions: This presentation focuses on the results of a joint study with UCLA in which the researchers examined the effects of the SMART Brain U Online program on individuals with amnesic MCI (aMCI).

Poster 19

TEMPORARY IMPROVEMENT FOR MCI/VCI VIA SYSTEMATIC NOVEL COGNITIVE EXERCISE: THE SMART PROGRAM. DenBoer JW, Kline J. SMART Brain Aging, Inc.; University of Arizona; Arizona Alzheimer's Consortium.

Background: The combined effects of the aging of the population (caused by the shift of the baby boomer generation into dementia) and significant increase in life expectancy has combined to put dementia into the range of our largest medical, if not societal, problems. In the state of Arizona, there is a projected 44-72% increase in dementia. Research has supported the use of cognitive intervention exercises to reduce early-stage dementia. Valenzuela and Sachdev (2009), in a literature review of 22 studies (involving approximately almost 30,000 individuals), found an overall risk reduction of 46% in individuals that were found to engage in a high level of regular cognitive activity. Perhaps more importantly, they found a dose-dependent relationship between cognitive exercise and reduction of dementia, which had not been found previously.

Methods: The SMART Memory Program (DenBoer, 2008) is a cognitive intervention designed to promote the reduction of early-stage dementia. Results of this program have shown significant promise (e.g., DenBoer, 2013), and the present researchers are currently engaging in multiple research studies. The program is effective via the use of new and novel cognitive exercises.

Results: This study focused on the cognitive and functional trajectory demonstrated by research subjects. Specifically, volunteer participants (all amnesic MCI individuals, n = 525) demonstrated significant improvement as a result of the program, but only while doing it and immediately after completion.

Conclusions: Commensurate with previous research, the current research study demonstrated cognitive improvement, but this improvement only persisted on a temporary basis and did not persist beyond current completion of the program.

Poster 20

AMPLISEQ TRANSCRIPTOME ANALYSIS OF LASER CAPTURED NEURONS FROM ALZHEIMER BRAIN: COMPARISON OF SINGLE CELL VERSUS NEURON POOLS. Deng W, Xing C, David R, Mastroeni D, Ning M, Lo EH, Coleman P. Massachusetts General Hospital, Harvard Medical School; University of Texas Southwestern Medical Center; Thermo-Fisher Scientific; Arizona State University; Arizona Alzheimer's Consortium.

Background: The possibility of obtaining expression profile from single neurons has been demonstrated since the early 90s. With the advances in RNA sequencing technology, it now becomes possible to precisely profile the genome of thousands of cells in a single assay. Recently, Thermo-Fisher Scientific developed an accurate and sensitive RNA sequencing platform, Ion AmpliSeq, which is capable of simultaneously amplifying and sequencing over 20,000 pre-defined genes with as little as 100 pg RNA input.

Methods: Frozen unfixed tissue containing samples of human CA1 hippocampus were secured from one AD (Braak IV) and one ND case (Braak III). Subjects were obtained at autopsy at the Banner Sun Health Research Institute Tissue Bank (BSHRI) in accordance with local IRB approval. The AD and ND cases were well matched for age (AD: 71 years; ND: 71 years), gender (2 males), postmortem interval (PMI) (AD: 2.1 hours; ND: 2.2 hours) and ApoE genotype E3/E3. RIN values for AD subject was 7.7 and ND subject 7.9.

Laser capture of pyramidal neurons: Frozen brain sections were cut at 15um, stained with 1% neutral red (Fisher Scientific) and mounted onto PEN slides required for laser capture microdissection. Immediately after staining, sections were dipped in 100% ethanol and loaded onto a Leica AS-LMD laser capture microscope. One, ten and one-hundred neurons were cut from control and AD brain and dropped into an invert cap for RNA extraction.

Ion AmpliSeq™ Transcriptome Human Gene Expression: Briefly, total RNA was reverse transcribed into cDNA. Targeted genes were amplified with the Ion AmpliSeq human transcriptome panel, which contains a pool of oligonucleotide primer pairs, each pair designed to amplify a specified genomic region.

Results: Here, we present the utility of Ion AmpliSeq technology on a single laser captured cell, and its ability to detect differential expression patterns in AD compared to control. Our results confirmed the potential of the Ion AmpliSeq approach in profiling the transcriptome of single neuron. We also provided evidence that single cell sequencing may be more informative compared to heterogenous AD-related neural alterations, which may be masked when profiling average gene responses in pooled cell populations (e.g. 10 and 100 neurons).

Conclusions: The major purpose of the work described here was to determine whether the ThermoFisher Ion AmpliSeq system could be used to obtain valid data from single neurons or small sets of neurons obtained by laser capture microdissection from postmortem human brain. The importance of spatial information cannot be understated, and to date, no other method is capable of obtaining such data. We found that the Ion AmpliSeq approach is a robust and sensitive method of measuring transcriptomic data at a single cell resolution.

Poster 21

SURFACE-BASED HIPPOCAMPAL MORPHOMETRY ANALYSIS FOR STUDYING EFFECTS OF APOE-E4 ALLELE LOAD IN COGNITIVELY UNIMPAIRED SUBJECTS. Dong Q, Zhang W, Wu J, Li B, Schron EH, McMahon T, Shi J, Gutman BA, Chen K, Baxter LC, Thompson PM, Reiman EM, Caselli RJ, Wang Y. Arizona State University; Wellesley College; Illinois Institute of Technology; Banner Alzheimer's Institute; Barrow Neurological Institute; University of Southern California; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Apolipoprotein E (APOE) e4 is the major genetic risk factor for Alzheimer's disease (AD) and it has been shown to be less efficient in clearing extracellular fibrillary amyloid β ($A\beta$) plaques, which would accelerate brain deformations from the hippocampus and medial temporal regions to the rest cortical regions. So it is valuable and necessary to study and reveal and intervene the hippocampal degenerations related to APOE-e4 before the onset of AD. The dose-dependent impact of APOE-e4 on hippocampal volumes has been documented, but its influence on general hippocampal morphology in cognitively unimpaired individuals is still elusive. Capitalizing on the study of a large number of cognitively unimpaired late middle aged and older adults with two, one and no APOE-e4 alleles, the current study aims to characterize the ability of our automated surface-based hippocampal morphometry algorithm to distinguish between these three levels of genetic risk for AD and demonstrate its superiority to a commonly used hippocampal volume measurement.

Methods: The proposed automated framework includes hippocampal surface segmentation and reconstruction, higher-order hippocampal surface correspondence computation, and hippocampal surface deformation analysis with multivariate statistics. This pipeline was conducted applied on a magnetic resonance imaging (MRI) database dataset from the Arizona APOE cohort, a longitudinal study of cognitive aging. The dataset consists of 117 cognitively unimpaired subjects aged between 50 to 85 years (mean=57.4, SD=6.3), including 36 heterozygotes (HT: e3/e4), 37 homozygotes (HM: e4/e4) and 44 non-carriers (NC: e3/e3), the demographic information between group subjects were matched.

Results: In our experiments, using our surface multivariate statistics, we analyzed hippocampal morphometry differences of the group contrasts of HM vs. NC, HT vs NC, and HM vs. HT. Statistical hippocampal morphometry differences were analyzed between different genotype groups with Hotelling's T2 test, vertex by vertex. After calculating the ground truth group difference of two groups at each vertex, we ran a permutation test with 10,000 repeats and got the overall (corrected) grouped significance. Further their corresponding effect sizes were estimated and compared using the cumulative distribution functions (CDF). Our hippocampal morphometry statistics showed greater statistical power by distinguishing cognitively unimpaired subjects with two, one, and no APOE-e4 alleles and discovering that APOE-e4 had a dose effect on the acceleration of hippocampal deformities.

Conclusions: The results, combined with our previous findings in the ADNI database, support prior reports that the APOE-e4 genotype is associated with accelerated brain deformations along with disease progression, and that these differences can be mapped to morphological changes in subsections of the hippocampal surfaces. The work also demonstrated that our surface-based morphometry analysis may serve as a useful brain imaging marker to study AD induced brain morphometry changes in the preclinical AD stage.

Poster 22

EFFECTS OF PLASMA INSULIN LEVELS ON CEREBRAL METABOLIC RATE OF GLUCOSE AND GRAY MATTER VOLUME IN COGNITIVELY UNIMPAIRED APOE3/APOE4 CARRIERS.

Edlund AK, Lee W, Chen K, Su Y, Reiman EM, Caselli RJ, Nielsen HM. Stockholm University; Banner Alzheimer's Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Reduced cerebral glucose metabolism has been documented in Alzheimer's disease (AD) patients. We previously investigated relationships between plasma apoE levels and the regional cerebral metabolic rate for glucose (CMRgl) in cognitively normal individuals from the Arizona APOE cohort (APOE3/APOE4 genotype). We found a relationship between higher plasma apoE4/apoE3 isoform ratio and lower hippocampal CMRgl. Here, we assessed relationships between plasma insulin levels and regional measurements of CMRgl and gray matter (GMV) in the same subjects.

Methods: Plasma insulin levels were quantified using ELISA whereas plasma apoE3 and apoE4 levels were measured using quantitative mass spectroscopy in the 128 enrolled subjects. FDG-PET and MRI images were acquired in 25 of the subjects (65.7±5 years of age), and relationships between plasma insulin levels to PET measurements of regional CMRgl and T1-weighted MRI measurements of regional GMV was explored.

Results: Plasma insulin levels were associated with higher CMRgl in right parietal, right precuneus and bilateral prefrontal regions and lower CMRgl in left hippocampal, precuneus and prefrontal and bilateral precuneus regions. Plasma insulin levels were also associated with decreased GMV in bilateral lateral temporal regions and increased GMV in left hippocampal and other bilateral lateral temporal regions. Potential effects of the plasma apoE4/E3 ratio on the described associations are currently being investigated.

Conclusions: Plasma insulin levels appear to be associated with altered regional CMRgl and GMV in cognitively normal individuals with the APOE3/APOE4 genotype. The relationship between plasma insulin and apoE levels, and the development of AD remain to be further investigated.

Poster 23

ASPIRIN AMELIORATES THE LONG-TERM ADVERSE EFFECTS OF DOXORUBICIN THROUGH SUPPRESSION OF CELLULAR SENESCENCE. Feng M, Kim J, Field K, Reid C, Chatzistamou I, Shim M. University of South Carolina; University of North Carolina at Chapel Hill; Midwestern University; Arizona Alzheimer's Consortium.

Background: A number of childhood cancer survivors develop adverse, late-onset side effects of earlier cancer treatments, known as the late effects of cancer therapy. As the number of survivors continues to increase, this growing population is at increased risk for a number of health-related problems.

Methods: In the present study, we have examined the effect of aspirin, a classical non-steroidal anti-inflammatory agent, on the late effects of chemotherapy by treating juvenile mice with doxorubicin (DOX). This novel mouse model produced various long-term adverse effects, some of which resemble premature aging phenotypes.

Results: The exposure of juvenile mice to DOX also resulted in accumulation of senescent cells and up-regulation of cyclooxygenase-2 (COX2) expression in the tissues of adult mice. Treatment with aspirin following juvenile exposure to DOX significantly improved body weight gain and ameliorated the long-term adverse effects including low white blood cell count, fat loss, and muscle atrophy. Aspirin treatment also significantly reduced the levels of senescent markers in tissues of adult mice treated with DOX at their juvenile stage. Moreover, aspirin reduced p53 and p21 accumulation in DOX-treated human and mouse fibroblasts. However, the suppressive effect of aspirin on DOX-induced p53 accumulation was significantly decreased in COX2 knockout mouse embryonic fibroblasts. Additionally, treatment of senescent fibroblasts with aspirin or celecoxib, a COX2 specific inhibitor, reduced cell viability and decreased levels of Bcl-xL protein.

Conclusions: These studies suggest that aspirin may be able to reduce the late effects of chemotherapy through suppression of cellular senescence.

Poster 24

AMYLOID BETA-INDUCED ALTERATIONS IN BASAL FOREBRAIN CHOLINERGIC INTRINSIC EXCITABILITY ARE MEDIATED BY $\alpha 7$ AND $\alpha 7\beta 2$ -CONTAINING NICOTINIC ACETYLCHOLINE RECEPTORS (NACHRS). George AA, Bimonte-Nelson HA, Lukas RJ, Whiteaker P. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD), a progressive neurodegenerative disorder, is one of the most common causes of mental deterioration in the elderly. Hallmarks of AD pathology include alterations in brain regions associated with higher cognitive functions. Several studies have correlated the severity of cognitive decline in early AD with a loss of basal forebrain cholinergic neurons (BFCNs). Mechanisms underlying cholinergic neurodegeneration and subsequent memory impairments remain unknown. However, interactions between amyloid-beta ($A\beta$), a suspected etiopathogenic agent in AD, with a nicotinic acetylcholine receptor (nAChR) subtype containing $\alpha 7$ subunits trigger an increase in hippocampal neuronal excitability. Heteromeric $\alpha 7\beta 2$ -nAChRs have similar pharmacological properties to those of homomeric $\alpha 7$ -nAChRs and are highly sensitive to functional modulation by $A\beta$. Toward understanding the roles played by nAChRs in BFCN function we used single-channel electrophysiology to explore the functional relationship between $A\beta$ and $\alpha 7$ and $\alpha 7\beta 2$ -containing nAChRs.

Methods: Organotypic Slice electrophysiology; Whole-Cell Patch Clamp Electrophysiology; Single-Channel Electrophysiology; Morris Water Maze Behavioral Test.

Results: Toward understanding the roles played by nAChRs in BFCN function we used single-channel electrophysiology to explore the functional relationship between $A\beta$ and $\alpha 7$ and $\alpha 7\beta 2$ -containing nAChRs. We demonstrate that oligomeric $A\beta$ activates both $\alpha 7$ and $\alpha 7\beta 2$ -nAChRs and preferentially enhances $\alpha 7\beta 2$ -nAChR single-channel open dwell-times (representing a 3.5-fold increase), effects that can be abrogated using the known nAChR antagonists MLA or mecamylamine. Using organotypic slice cultures and whole-cell patch clamp electrophysiology we demonstrate that chronic incubation with oligomeric $A\beta$ increases BFCN firing rates in the medial septum and horizontal diagonal band (MSDB: $64 \pm 8\%$ and HDB: $25 \pm 3.5\%$, respectively). BFCN firing rates were mirrored by 1) reduced afterhyperpolarization (AHP) magnitude (reduction of $44 \pm 6.5\%$ and $15 \pm 2.5\%$, respectively), 2) attenuation in action potential amplitude ($38 \pm 6.5\%$ reduction), 3) reduced spike-frequency adaptation (i.e. reduced interspike interval ratio) and 4) increased AP repolarization rates when compared to controls (scrambled $A\beta$). These $A\beta$ -induced alterations were absent in the nucleus basalis (NB). Interestingly, regionally-specific changes in BFCN intrinsic excitability were normalized in $\beta 2$ nAChR subunit knockout, suggesting that $A\beta$ alters cholinergic intrinsic excitability by interacting with $\alpha 7$ and $\beta 2$ -containing nAChRs. Lastly, we demonstrate that spatial memory deficits in APP/PS1 mice can be ameliorated by genetically deleting the $\beta 2$ nAChR subunit, indicating a role for $\alpha 7\beta 2$ -containing nAChRs in facilitating amyloid-induced cognitive decline.

Conclusions: These interactions may be specific to certain cholinergic circuits within the basal forebrain and suggest novel and potentially productive therapeutic strategies to combat neurodegeneration in a brain region affected early in AD.

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Poster 25

AMYLOID PET, TAU PET, AND MRI MEASUREMENTS IN COGNITIVELY UNIMPAIRED PERSONS WITH TWO, ONE, & NO COPIES OF THE APOE4 ALLELE. Ghisays V, Goradia DD, Protas H, Bauer R, Devadas V, Tariot PN, Lowe VJ, Knopman D, Petersen RC, Jack CR, Caselli RJ, Su Y, Chen K, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Mayo Clinic Arizona; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: We recently characterized relationships between tau PET measurements and apolipoprotein E4 (APOE4) gene dose in cognitively unimpaired late middle-aged and older adults and the extent to which these relationships are associated with age, amyloid- β (A β) positivity, and long-term verbal memory decline. We now extend those findings to a larger number of research participants, incorporate MRI measurements of cortical atrophy and provide new information about the AD biomarker classification of those with two, one, and no APOE4 alleles using the (A β /tau[neurodegeneration]) "AT(N)" framework.

Methods: Pittsburgh Compound-B (PiB) PET, flortaucipir PET, and T1-weighted volumetric MRI were used to assess fibrillar A β burden, paired helical tau burden, and cortical atrophy in 165 participants, ages 47-86, in the Arizona APOE Cohort Study and Mayo Clinic Study of Aging, including 26 APOE4 homozygotes, 48 heterozygotes, and 91 non-carriers matched for age, sex, and education. SPM12 and previously described regions-of-interest (ROIs) were used to characterize composite cortical-to-cerebellar PiB standard uptake value ratios (SUVRs) and entorhinal cortex, inferior temporal cortex, and composite cortical-to-cerebellar flortaucipir SUVRs; FreeSurfer and previously described cortical ROIs were used to provide a composite measure of cortical thickness. Previously described composite PiB SUV \geq 1.42, flortaucipir SUV \geq 1.23, and cortical thickness \leq 2.67mm thresholds were used to classify participants using the AT(N) framework.

Results: 38%, 35%, and 12% of the APOE4 homozygotes, heterozygotes, and non-carriers had a "positive" PiB PET scan. Compared to non-carriers, the homozygotes and heterozygotes had higher PiB SUVRs ($p < 0.01$). They also had higher entorhinal flortaucipir SUVRs and greater associations between composite flortaucipir SUVRs and age, findings that were solely attributable to those carriers with a positive PiB PET scan ($p < 0.05$). We will discuss these and other findings, including the percentages of each AT(N) classifications and the extent to which downstream biomarkers are influenced by A β positivity, age, and their interaction with two, one or no APOE4 alleles.

Conclusions: This study provides new information about AT(N) measurements and classifications in an unusually large number of cognitively unimpaired persons at three levels of genetic risk for late-onset AD. Tau pathology is preferentially affected in unimpaired APOE4 carriers with a positive A β PET scan.

Poster 26

DEPRESSION IN AGING AND ITS ASSOCIATION TO AGE-RELATED NEURODEGENERATIVE PATHOLOGY. Glass M, Intorcchia A, Walker J, Arce R, Oliver J, Nelson C, Papa J, Arce A, Vargas D, Sue L, Beach TG, Serrano G. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Depression is a common neuropsychiatric symptom commonly observed in the elderly, and especially in those with age related neurodegenerative disorders such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and Alzheimer's disease dementia (ADD). It is possible that pathological-protein aggregation in specific brain areas may alter emotion-related neurotransmitters, leading to depression. Nevertheless, very few studies have systematically correlated standardized cognitive and neuropsychological depression-related assessments with age-related neurodegenerative pathology.

Methods: In this study we hypothesized that the prevalence and severity of depression would be correlated with one or more of the common age-related neurodegenerative conditions. Cases were selected by a database search of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Case selection aimed to include only individuals with at least one neuropsychological assessment including the Hamilton depression scale (HAMD) and Geriatric Depression Scale, as well as a full neuropathological assessment (n=628). For both depression scales, a score of 10 or higher was used to identify significant depression (n=241), and multiple regression analysis was used to correlate with neuropathological diagnoses and density scores for microscopic lesions including neurofibrillary tangles, senile plaques and Lewy-type synucleinopathy (LTS)

Results: Depression was present with variable prevalence by diagnostic category: cognitive and movement control subjects – 30%; mild cognitive impairment – 40%; incidental Lewy body disease – 37%; ADD – 37%; DLB - 35%; VAD – 44%; progressive supranuclear palsy (PSP) – 42%; PD – 59%. Only for PD was the prevalence significantly different than controls ($p < 0.00001$). Multiple logistic regression showed that only LTS was a significant predictor of depression ($p < 0.001$; Odds Ratio = 1.03; confidence interval = 1.01-1.043).

Conclusions: Depression was more common in neurodegenerative disease than normal subjects and was most common in PD. As deficits in serotonin, norepinephrine and dopamine levels have been implicated in depression, and as these monoaminergic neurotransmitters mostly arise from brainstem nuclei that are heavily affected in PD, DLB and ADD, this may be the underlying mechanism. However, depression is complex, and there are many possibly confounds to this study, for example the effect of any chronic disease to cause depression. More work is needed to further the understanding of late-life depression.

Poster 27

COMPARISON OF CROSS-SECTIONAL AND LONGITUDINAL FREESURFER PIPELINE FOR ESTIMATION OF FLORBETAPIR PET SUVR MEASUREMENTS. Goradia DD, VanGilder PS, Thiyyagura P, Devadas V, Chen Y, Luo J, Reiman EM, Su Y. Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: Longitudinal imaging data has become increasingly common in clinical studies of aging and dementia. A procedure that specifically takes longitudinally acquired data into consideration has been developed and implemented in the FreeSurfer package (Reuter 2012), which has demonstrated improved precision and statistical power in detecting longitudinal changes. It is reasonable to assume this finding can be generalized to other quantitative imaging analysis tasks such as positron emission tomography (PET) measurements of amyloid burden. We therefore test this hypothesis using longitudinal florbetapir PET data.

Methods: Baseline and follow-up florbetapir PET and T1-MRI data of 36 A β -positive participants from ADNI database were included in this study. T1-weighted structural MRI were preprocessed using cross-sectional and longitudinal Freesurfer pipelines. Florbetapir PET images were subsequently analyzed using PET Unified Pipeline (Su 2015) based on Freesurfer generated ROIs with and without longitudinal processing, and a mean cortical standard uptake value ratio (SUVR) was calculated using cerebellum cortex as the reference region to quantify overall amyloid burden. The impact of longitudinal pipeline relative to cross-sectional pipeline was evaluated by estimating the sample size needed to detect a 25% treatment effect in hypothetical 24-mo AD prevention trials with 80% power and two-tailed P=0.05.

Results: Estimated sample sizes need to detect 25% treatment effects on mean cortical to cerebellum SUVR are approximately 756 for cross-sectional pipeline and 1122 for longitudinal pipeline. There was a subtle difference in the correlation coefficient between baseline and follow-up total cerebellum volume with longitudinal pipeline ($r^2=0.96$) showing weaker correlation than cross-sectional pipeline ($r^2=0.98$). However, this difference was not statistically significant.

Conclusions: These finds suggest that using the longitudinal Freesurfer pipeline does not provide any advantage over cross-sectional pipeline for Florbetapir PET SUVR estimation. These results could be partly attributed to the variability in cerebellum delineation between the 2 pipelines. Additional studies with larger sample sizes and other reference regions are needed to confirm these findings.

Poster 28

GENEMATCH: A NOVEL RECRUITMENT REGISTRY OF APOE CHARACTERIZED ADULTS TO ACCELERATE RECRUITMENT AND ENROLLMENT INTO ALZHEIMER'S PREVENTION STUDIES. Gordon D, Graf H, Walsh T, High N, Reiman EM, Tariot PN, Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Considerable effort has focused on creating programs to accelerate enrollment into Alzheimer's disease (AD) prevention studies. GeneMatch was launched in 2015 to accelerate enrollment into AD prevention studies by enriching referrals based on APOE4.

Methods: GeneMatch is a US-based, trial-independent recruitment program of the Alzheimer's Prevention Registry (APR) performing APOE testing in cognitively unimpaired individuals ages 55-75. A variety of tactics are used to recruit participants into GeneMatch; participants can enroll online and have a cheek swab kit mailed to their home or at a partner healthcare site and receive their kit onsite. APOE results and other demographic information are used to match and invite participants to enrolling studies. GeneMatch does not disclose APOE results to participants directly and steps are taken to not disclose inadvertently through study invitations.

Results: As of December 2018, 86,361 participants joined GeneMatch. Online advertisements are the most successful outreach tactic for enrollment into GeneMatch (54,857), followed by people who first joined the APR before GeneMatch ("APR referrals") (18,361), and partner healthcare site referrals (3,894); 9,249 people joined directly via the GeneMatch website. APOE genotype differs by enrollment source, with APR and GeneMatch direct referrals having the highest percentage of APOE4 homozygotes (4.1% and 4.2%, respectively) and heterozygotes (e3/e4)(29.4% and 28.3%, respectively); referrals from partner sites and online advertising having slightly lower percentages of APOE4 homozygotes (3.7% and 2.5%, respectively) and heterozygotes (26.9% and 24.8%, respectively). As of December 2018, >10,000 GeneMatch participants had been invited to the Alzheimer's Prevention Initiative (API) Generation Program. GeneMatch direct referrals accept their study invitation at the highest rate (44.7%), followed by referrals from APR (39.8%), partner sites (37.2%), and online advertising (31.2%).

Conclusions: GeneMatch is the first trial-independent program designed to recruit and connect healthy adults to AD prevention studies based in part on APOE results, providing a novel mechanism to accelerate prescreening and enrollment for AD prevention studies. GeneMatch will expand its study portfolio in 2019 and we anticipate broadening the age eligibility to accommodate new studies. Future efforts will examine the cost effectiveness of recruitment tactics, taking into account study invitation acceptance rate.

Poster 29

THALAMOCORTICAL WHITE-MATTER INTEGRITY AND THE RELATIONSHIP BETWEEN AUDITORY FUNCTION AND COGNITIVE DECLINE IN AGED MACAQUE MONKEYS. Gray DT, Burke SN, Engle JR, Umapathy L, Trouard TP, Barnes CA. University of Arizona; University of Florida; University of California, Davis; Arizona Alzheimer's Consortium.

Background: Hearing loss, or presbycusis, is a hallmark of normative brain aging, with an estimated eighty percent of individuals over age 50 experiencing reduced hearing capacity to some degree. It has been known for some time that auditory processing abilities correlate with cognitive function, even when cognition is assessed using non-auditory tasks (e.g., Humes et al., 2013). Despite these relationships, no direct brain measurements have been made in an attempt to link age-related cognitive decline with presbycusis.

Methods: To this end, we assessed a colony of adult and aged macaque monkeys 1) on a battery of behavioral tasks meant to probe multiple cognitive functions, 2) with temporally precise physiological estimates of auditory function (auditory brainstem and mid latency responses), and 3) with structural and diffusion-weighted magnetic resonance images to extract quantitative estimates of volume and connectivity between distinct auditory and cognitive brain regions using probabilistic tractography.

Results: Our results suggest that aged macaques are impaired on several tasks thought to require both frontal and medial temporal lobe function, as well as show a reduction in temporal processing of auditory information, both findings that have been reported previously (e.g., Hara et al., 2012; Ng et al., 2015). Only performance from specific tasks significantly correlated with estimates of temporal auditory processing, whereas other tasks did not relate to these same measures. Estimates of the white-matter integrity along the thalamic auditory radiations correlated both with estimates of temporal auditory processing and with reversal learning memory, but not any other cognitive domain tested here.

Conclusions: These correlations preliminarily suggest that the white-matter integrity of thalamocortical fibers may contribute to the observed relationships between specific aspects of cognitive decline and presbycusis. To expand upon this concept, these correlations will be presented alongside similar analyses using estimates from the thalamic radiations connecting anterior and midline thalamic nuclei with the prefrontal cortices and medial temporal lobes.

Poster 30

EVIDENCE FOR NEUROPROTECTIVE EFFECTS OF AN OVER-THE-COUNTER CURCUMIN SUPPLEMENT AGAINST ROTENONE INDUCED NEUROTOXICITY. Hall DA, Estrella MV, Thomason SC, Schilperoort LR, Anderson ML. Grand Canyon University.

Background: Curcumin is a natural phenol and commonly used yellow spice found in turmeric (*Curcuma longa*). In cell culture and animal models curcumin has demonstrated neuroprotective effects against cellular changes associated with Alzheimer's disease (AD) such as: stimulation of neurogenesis, prevention of β -amyloid aggregation, reduction of production of reactive oxygen species (ROS). Unfortunately clinical trials have had little success due to minimal bioavailability stemming from poor absorption, rapid metabolism, and rapid elimination. Recently, multiple over the counter (OTC) dietary supplements were developed claiming to have overcome this issue. One such supplement, Longvida, encapsulates curcumin within solid lipid particles in order to improve bioavailability through enhanced gastrointestinal absorption. Since mitochondrial dysfunction and oxidative stress have been implicated in the pathogenesis of AD, the study presented here investigated the neuroprotective effects of Longvida compared to curcumin against rotenone induced neurotoxicity. This was done in an effort to determine if the modifications to curcumin altered its protective effects.

Methods: SH-SY5Y neuroblastoma cells were either pretreated with vehicle, or pretreated with curcumin or Longvida for two hours. Cells were then incubated with rotenone or vehicle for 24 hours. Cell viability was then assessed using an MTT assay.

Results: Similar to previous studies, curcumin pretreatment significantly reduced rotenone induced cell death. Additionally, our results indicate that the OTC curcumin supplement also significantly reduced cell death to a similar extent as curcumin.

Conclusions: This study is meant to assess whether an OTC curcumin supplement formulated to improve bioavailability has similar antioxidant capabilities as pure curcumin. Thus far our results demonstrate similar neuroprotective effects between purified curcumin and an OTC curcumin supplement. This finding indicates that further investigation into the potential therapeutic value OTC curcumin is warranted.

Poster 31

COGNITIVE IMPROVEMENTS IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE THROUGH A PERSONALIZED MITO FOOD PLAN DIET AND CELL REPAIR THERAPY. Hank NC, Pereira J, McCravey B, Christians L, Hoggan C, Dechoux F. Perseverance Research Center, LLC; Cerulean Advanced Wellness and Fitness.

Background: Currently, over 50 million people worldwide are diagnosed with Alzheimer's Disease and more than 16 million Americans suffer from Mild Cognitive Impairment. Despite unremitting scientific and clinical efforts, there has yet to be therapy that has abated disease progression. In the last two decades, clinical trials have focused on beta amyloid ($A\beta$), which has been known to play a key role in the pathogenesis of AD; however, drug therapies in AD research have had a 99.6% failure rate.

Methods: In study NCT0360419, 3 MCI and 2 AD patients who met eligibility criteria underwent cognitive and physiological testing to test degrees of cognitive impairment, chronic inflammation and cellular health. All study patients were provided with a personalized Mito Food Plan and Cellular Repair Therapy.

Results: Results demonstrated significant improvements in cognitive testing, inflammation, and Quality of Life were correlated to decreased inflammation in all study subjects.

Conclusions: Results suggest cognition can improve with the decrease of chronic inflammation in those with cognitive impairments.

Poster 32

FACEBOOK AS A RESOURCE FOR HISPANIC/LATINO RECRUITMENT: A PILOT PROGRAM OF THE ALZHEIMER'S PREVENTION REGISTRY. High NM, DeMarco KL, Parkhurst DK, Herbert EE, Ward AK, Reiman EM, Langbaum J. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Hispanics are about one to 1.5 times as likely as non-Hispanic whites to have Alzheimer's disease (AD) and other dementias. In addition, Hispanics are severely underrepresented in AD research. To address the disproportionate representation of the Hispanic population in current AD research studies, the Alzheimer's Prevention Registry (APR) piloted an online Facebook advertising campaign targeting Hispanics/Latinos aged 47-68 in the Phoenix, AZ area to accelerate enrollment into a longitudinal study of age-related memory decline and the effect of APOE4.

Methods: The standard recruitment model for the longitudinal study is community outreach events. The APR tested eight advertisements that ran concurrently over two months. Three of the advertisements included Hispanic/Latino models within the study age range, four advertisement variations featured scientist and laboratory imagery, and one advertisement used a quiz image. Advertisements used advanced targeting options that characterize current APR members and identifies users that meet similar online attributes. Advertisement clicks led users to a study summary page hosted on the APR website that asked interested individuals to call study site staff to learn more.

Results: Over the course of the two-month campaign, 43,598 online advertisement impressions were made resulting in 563 clicks on the advertisements, at a \$2.11 cost per online click. Of the 563 clicks, 85 called, bringing the cost per call to \$14.32. Of these callers, 22 were pre-screen eligible, and 19 were scheduled for screening visits at a cost of \$62.59 per referral. This campaign did not show a difference in click response to the different advertisements (quiz vs scientific vs Hispanic/Latino model). In comparison, the standard recruitment model averages 1-2 screening visits/month.

Conclusions: Facebook advanced targeting for recruitment of Hispanic/Latino research participants is an effective and cost-efficient method of recruitment for observational AD research studies and serves as a low-effort approach to connecting potential Hispanic/Latino research participants to study opportunities in their communities. Future study protocol updates to include expanding eligibility criteria will allow for further use of this online recruitment method.

Poster 33

BENEFICIAL EFFECTS OF RESVERATROL AND EXERCISE TRAINING ON CARDIAC AND AORTIC FUNCTION AND STRUCTURE IN THE 3XTG MOUSE MODEL OF ALZHEIMER'S DISEASE. Hoxha B, Esfandiarei M, Talley NA, Anderson MA, Alkhouli MF, Squire MA, Eckman DM, Jeganathan RB, Lopaschuk GL, Broderick TL. Midwestern University; Auburn University; Mazankowski Alberta Heart Institute, University of Alberta; Arizona Alzheimer's Consortium.

Background: Studies have indicated an association between Alzheimer's disease (AD) and increased risk of developing cardiovascular complications. Lifestyle modifiable factors, such as exercise and diet, are known to prevent cardio-cerebral disease. Recent studies demonstrate that hearts from early onset triple-transgenic AD mice exhibit pathologies, but it is not clear whether cardiovascular function is altered in this model.

Methods: In this study, we measured in vivo cardiovascular function in 7-month old male 3xTg mice and age-matched wild-type mice using high-frequency high-resolution ultrasound imaging (Vevo 2100, Fujifilm, Visualsonics).

Results: Our findings indicated that aortic root measurements and interventricular septal dimensions were similar in 3xTg and wild-type mice. Systolic function, expressed as ejection fraction and fractional shortening, were decreased in 3xTg mice. Late (A) ventricular filling velocities, the E/A ratio, and mitral valve deceleration time, all indices of diastolic function, were increased in 3xTg mice compared to wild-type mice. Treadmill exercise training and resveratrol supplementation in the diet for 5 months improved ejection fraction, fractional shortening, and restored diastolic deceleration times. Pulse wave velocity was ~33% higher in 3xTg, and accompanied by a significant increase in elastin fiber fragmentation within the aortic wall, which was associated with decrease in elastin content and fiber length. Aortic wall and adventitia thickness were increased in 3xTg mice compared to the wild-type group. Exercise training and resveratrol supplementation, or both, improved overall aortic morphology with no change in pulse wave velocity.

Conclusions: Taken together, the results indicate that the aberrations in cardiac function and aortic elastin morphology observed in the 3xTg mouse model of AD can be prevented with exercise training and treatment with resveratrol. The study demonstrates the potential roles of regular exercise and resveratrol for cardiovascular health in patients with AD, and warrant further studies to evaluate the long-term effects of such interventions on overall cardiovascular health in the 3xTg mouse model of AD.

Poster 34

BACTERIAL LIPOPOLYSACCHARIDE (LPS) AND LIPOTECHOIC ACID (LTA) DETECTED IN THE SERUM AND BRAIN TISSUE OF AD PATIENTS AND CONTROLS. Jentarra G, Chu P, Elliott N, Jones TB, Kaufman J, Vallejo-Elias J, Jones D, Gonzalez F, Tullot T, Potter P. Midwestern University; Arizona Alzheimer's Consortium.

Background: Many pathological features in the brains of Alzheimer's disease (AD) patients are suggestive of an infectious process. We previously performed 16S rRNA gene sequencing analysis of DNA from post-mortem brain tissue of AD patients and controls. We found that all subjects, had bacterial DNA in their brain tissue although the numbers of taxonomic classes varied by subject group. As a secondary method of confirming bacterial presence and establishing that previous data did not result from DNA contamination, we analyzed tissue from the same subjects for gram-negative (LPS) and gram-positive (LTA) bacterial products. Published studies have shown LPS in the brains of AD patients in association with amyloid plaques and suggested that this LPS derives from gut bacteria. As this study analyzed both serum and brain LPS, it was designed to provide some indication of whether LPS in the brain was likely to derive from the bloodstream (leaked from the gut) or if it may instead originate from bacteria resident in the brain.

Methods: Tissues used were serum plus remaining portions of superior frontal gyrus previously acquired from the BSHRI Brain and Tissue Bank and used for 16S rRNA gene sequencing. There were four subject groups: normal controls, high pathology controls, patients with mild cognitive impairment (MCI), and AD patients. For all brain tissue samples, and for matched serum samples from MCI and AD patients, $n = 12$. However, serum was not available for all normal and high pathology controls ($n = 8$ for normal controls and $n = 11$ for high pathology controls). LPS and LTA ELISAs from LSBio were used to quantitate LPS in serum and brain tissue lysates, and LTA in brain tissue lysates. Lysates were made by sonication of brain tissue in cold, sterile PBS.

Results: Serum LPS levels in normal controls were significantly different from AD patients ($p = 0.0073$). No significant differences in LPS levels were found between other subject groups. Females had significantly higher serum LPS than males ($p = 0.0143$). Brain LPS was relatively high in all subjects but not significantly different between groups. Correlations of brain LPS with subject characteristics (age, sex, post-mortem interval (PMI), MMSE, APOE status, plaques, Braak score, and CAA) were negative when all subjects were considered, and largely negative within groups. However, while other subject groups showed no correlation with post-mortem interval (PMI), MCI patients showed a high positive correlation between brain LPS and PMI ($r = 0.8788$, $p = 0.0002$) suggesting active growth of bacteria after death. Serum LPS did not correlate with the brain LPS levels of subjects. Brain tissue LTA levels were easily detectable although at least 1000 fold lower than LPS levels. LTA levels were not significantly different between groups.

Conclusions: Serum LPS does not predict brain LPS levels, suggesting that brain LPS may not be derived from the gut, but may instead be evidence of resident bacteria in the brain. Serum LPS in AD patients is significantly higher than in normal controls, but this could result from greater immune compromise in AD patients. Substantial levels of LPS and LTA were present in all brain tissue, with no significant differences between groups. This data does align with our previous sequencing data and suggests that the presence of bacteria in the brain is not uncommon. As many AD risk genes are involved in immune function and inflammation, if AD is associated with microbes, AD may develop from aberrant responses to microbes related to genetic differences.

Poster 35

TARGETING NECROPTOSIS FOR AD THERAPEUTICS. Khanna M, Sanchez-Lares J, Oddo S. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Severe neuronal loss is a hallmark of Alzheimer's disease (AD); however, the mechanisms by which neurons die remain elusive. One form of cell death that has gained merit recently is necroptosis, a programmed form of necrosis, triggered by the receptor-interactive protein kinase (RIPK) 1 and 3 and executed by the mixed lineage kinase domain-like (MLKL) protein. Upon activation by multiple inflammatory stressors, RIPK1 can trigger cell survival or cell death pathways, with the former being a default response to inflammatory stimuli.

Growing evidence suggests that RIPK1 is involved in AD pathogenesis. Our collaborator at ASU, Dr. Salvatore Oddo reported that necroptosis is activated in AD and may contribute to neurodegeneration. His group also reported that in AD brains RIPK1 is upregulated in microglia and neurons. He generated a causal gene regulatory network to model RIPK1 interactions in AD and found that RIPK1 activity could explain a significant portion of transcriptomic changes in AD. Pharmacologically decreasing RIPK1 activity reduces neuronal loss in 5xFAD mice. These novel and exciting data led us to the formulation of the following hypothesis: RIPK1 contributes to neurodegeneration in AD.

Based on these observations and that pharmacological alteration did reduce neuronal loss, we propose a more targeted approach to disrupt the RIPK1/RIPK3 interaction that is specific to necrosome formation.

Upon activation by multiple inflammatory stressors, RIPK1 can trigger cell survival or cell death pathways, with the former being a default response to inflammatory stimuli. Consistent with the role of RIPK1 in cell survival, conventional RIPK1 knockout mice die 1-3 days after birth. During necroptosis activation, RIPK1 binds to RIPK3 to form the necrosome, which is necessary and sufficient for necroptosis activation (Fig. 1). Our collaborator, Dr. Salvatore Oddo, recently reported that necroptosis is i) activated in postmortem human AD brains and ii) decreasing RIPK1 activity and mitigating neuronal loss in 5xFAD mice. Based on these observations, we propose to develop small molecules probes to prevent necrosome formation. We hypothesize that blocking the interaction between RIPK1 and RIPK3 will prevent necrosome formation, thereby precluding necroptosis activation.

Methods: We utilize in silico docking to target the RIPK1/RIPK3 complex. We utilize a phenotypic screen to define binders of RIPK3. Finally, we recently developed CETSA to define the binding of small molecules in cells.

Results: We have identified two top hits that bind to RIPK3 and inhibit necroptosis.

Conclusions: These compounds will be further tested to define the mechanism of action.

Poster 36

CONVOLUTIONAL NEURAL NETWORKS FOR FAST AND ACCURATE 3D RECONSTRUCTION OF HISTOLOGICAL SECTIONS. Kyle CT, Stokes J, Meltzer J, Permenter MR, Vogt JA, Ekstrom A, Barnes CA. University of Arizona; University of California, Davis; Arizona Alzheimer's Consortium.

Background: While in vivo imaging offers an excellent view of the brain's "macro" structure, it lacks the resolution and intensity markers required to identify details of interest to many neuroscientists. Histological sectioning offers the ability to identify chemical and cytoarchitectural markers, but does not maintain the structure of the intact brain. This necessitates methods of 3D histological reconstruction. A significant remaining challenge of this field is to balance the computation time with the accuracy of a reconstruction scheme. Previous work on histological reconstruction has used either intensity-based warping techniques, which are slow due to iterative image-wide multiplication, or landmark or feature-based registration which reduces computational complexity at the expense of accuracy (Pichat et al., 2018, Medical Image Analysis). We propose a new automated approach for histological leveraging recent advancements in machine learning to perform image registration using convolutional "spatial transformer networks", which accurately perform non-rigid registration without iteration.

Methods: Our method involves a global search strategy. First the MRI is resampled for a given θ -yaw, θ -pitch, z-position, xy-plane resolution, and z-plane resolution. These terms account for position and for shrinkage or expansion that occurs during sectioning. Next, histological sections are registered to the MRI, estimating x-position, y-position, θ -roll, and non-rigid terms for each section. These terms account for deformations that occur during the tissue mounting process. Next, a cost function is computed that considers: 1) The intensity-based similarity between the histology and MRI, 2) regularization terms that quantify the deformation energy of the registration, and 3) an estimate of the probability of reconstruction derived from pre-computed intensity-based similarity distributions $S(dx, dy, d\theta)$ between neighboring histological sections. This process is used to search θ -yaw, θ -pitch, z-position, xy-plane resolution, and z-plane resolution for the optimal solution. With these parameters selected, we overtrain the spatial transformer networks to find the best x, y, θ -roll, and non-rigid terms for each section.

Results: We find this approach is extremely accurate and drastically reduces execution time allowing researchers to integrate histological data into 3D structural MRI images quickly, accurately, and automatically.

Conclusions: Applications include quick integration of new histological data into existing brain atlases, creation of de novo brain atlases, and construction of MRI-based probabilistic atlases that provide information on histological markers.

Poster 37

A CONCISE AND PERSISTENT FEATURE TO STUDY BRAIN RESTING-STATE NETWORK DYNAMICS: FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE.

Kuang L, Dong Q, Han X, Chen K, Caselli RJ, Reiman EM, Wang Y, Alzheimer's Disease Neuroimaging Initiative. Arizona State University; North University of China; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Resting-state functional magnetic resonance imaging (rs-fMRI) with graph theoretical analysis have shown that patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) exhibit disrupted topological organization in large-scale brain networks. In previous work, it is a common practice to threshold such networks. However, it is not only difficult to make a principled choice of threshold values, but also worse is the discard of potential important information. To address this issue, we propose a threshold-free network measure to complement the mathematical theory of the zeroth Betti number plot (BNP) by integrating a prior persistent homology-based topological feature and a newly defined connected component aggregation cost feature to model brain networks over all possible scales.

Methods: The proposed pipeline includes: rs-fMRI data preprocessing, functional connectivity matrices calculation, integrated persistent feature (IPF) plot based on BNP, the slope of IPF plot (SIP) calculation, and comparison of rs-fMRI network (RSN) structures with SIP measure. This pipeline was applied on a rs-fMRI dataset from the publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI). The dataset consisted of 106 subjects, including 31 AD, 38 MCI and 37 normal control (NC) subjects. We further compared the performance of our proposed approach with five other widely used graph measures across five parcellation schemes ranging from 90 to 1,024 region-of-interests.

Results: In our experiments, using our proposed SIP, we measured RSNs of AD, MCI and NC groups and analyzed RSN differences among these three groups. We applied nonparametric permutation test with 10,000 permutations and the Kruskal-Wallis test to detect RSN group differences of AD vs. MCI vs. NC. We found that the absolute SIP values showing a pattern: $AD < MCI < NC$, with the significance level $p = .002$ based on the Kruskal-Wallis test, which provided empirical evidence for decreased functional integration in AD dementia and MCI. The statistical group difference analysis of our proposed approach together with five other measures showed that the proposed network measure had more statistical power and stronger robustness.

Conclusions: This work presents a novel network measure, SIP, by integrating an additional feature of connected component aggregation cost with BNP to achieve holistic descriptions of graph evolutions and quantify brain network dynamics. SIP measure offers a novel insight into the whole-brain network analysis and differentiates AD dementia and MCI patients from healthy individuals with improved statistical power compared to some other widely used measures. The experimental results provide empirical evidence for disrupted network organization in AD dementia and MCI patients at a global level, and suggest that SIP measure may be a potential imaging biomarker of AD.

Poster 38

AGED-RELATED IMPAIRMENTS IN SPATIAL REFERENCE FRAME UPDATING. Lester AW, Blum CJ, Kapellusch AJ, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Both the hippocampus and the medial portion of the entorhinal cortex (MEC) contain functionally distinct sub-networks of spatially modulated neurons which are believed to work cooperatively to support spatial navigation. The two broad categories of spatial feedback utilized to anchor and update the spatial firing of these cells are allocentric (i.e., external) and egocentric (i.e., self-motion). As with older adults, aged rats show robust impairments on a number of different spatial navigation tasks (Lester et al., 2017). There is some evidence that these navigation impairments are accompanied by a bias away from using an allocentric navigation strategy towards relying on an egocentric strategy.

Methods: To test the degree and timing with which aged animals utilize these two forms of spatial information, a novel behavioral arena was developed in which rats are trained to traverse a circular track and to stop at a learned goal location that is fixed with respect to a panorama of visual cues projected onto the surrounding walls. By instantaneously rotating the cues we are able to put allocentric and egocentric reference frames in direct and immediate conflict and characterize how quickly and accurately aged animals utilize allocentric feedback to navigate to a new rotated goal location.

Results: Behavioral data collected from five young (9 – 15 mo) and four aged (23 - 30 mo) animals reveal that both age groups are able to update their behavior following cue rotation, although aged rats tend to perseverate to the original goal location more often. Young rats, by comparison, were more likely to stop at some intermediate location between the original and rotated goal location. These findings suggest that when spatial reference frames are put in conflict, young rats settle on a strategy that combines both sources of spatial information, while aged animals adhere more rigidly to only one spatial reference frame. We are currently collecting electrophysiology from both CA1 and MEC while animals perform the task.

Conclusions: Based on our behavioral findings, we predict that when spatial reference frames are put into conflict, the CA1 place cells in young animals will show variability in terms of which reference frame they anchor to (as in Lee et. Al., 2004). We predict that aged CA1 place cells, by comparison, will have a greater tendency to remain anchored to the already established reference frame. If the age-related behavioral changes we observe are due to intrahippocampal network impairments, spatially-modulated cells of upstream MEC should show comparable realignment in both age groups.

Poster 39

PROTECTING DNA IS A FAMILY AFFAIR: TELOMERE LENGTH AND COGNITION IN AFFECTED INDIVIDUALS, UNAFFECTED SIBLINGS, AND PARENTS. Lewis CR, Taquinod F, Cohen J, Walker N, Agrawal K, Jepsen WM, Huentelman MJ, Smith CJ, Ringenbach S, Braden BB. Translational Genomics Research Institute; Southwest Autism Research and Resource Center; Arizona State University; Arizona Alzheimer's Consortium.

Background: Although not a diagnostic criterion, individuals with ASD commonly experience cognitive difficulties. One possible mechanism is shortened telomeres. Telomeres are repetitive non-coding DNA nucleotides that protect genes by capping chromosome ends and progressively shorten with age. Recently, two reports associated shortened telomere length (TL) with ASD or familial relation. Further, shortened telomeres have been associated with age-related cognitive decline. While previous studies found no relationship between TL and ASD core symptoms, the relationship between TL and cognitive function or sensory symptoms in individuals with ASD and family members is unknown. We aimed to replicate the finding of shortened TL in children with ASD compared to neurotypical (NT) controls, and add new findings concerning TL in unaffected siblings. We investigated relationships between TL, cognition, and ASD-related behaviors in affected individuals, unaffected siblings, and parents.

Methods: Our participants (n=380) included 69 male NT controls (7.1±2.3 years), 108 individuals with ASD (11 female; 8.3±8.4 years), 136 unaffected siblings (66 female; 10.3±7.3 years), and 67 parents (43 female; 38.7±8.4 years). TL of DNA derived from blood leukocytes was determined using an established quantitative polymerase chain reaction method. Cognitive function was measured via Stanford-Binet Intelligence Scale-5, core symptoms via Autism Diagnostic Observation Schedule-2, sensory symptoms via Sensory Profile, and ASD-related behaviors in parents via Broader Autism Phenotype Questionnaire (BAPq).

Results: Among male NT, ASD, and unaffected siblings, there was a significant ANCOVA [F(2, 232)=6.12, p=0.003], with NT males having longer TL than males with ASD (p=0.001) and unaffected siblings (p=0.05), controlling for age (Fig. 1a). In a mixed-model, males with ASD were not different from male unaffected siblings [F(1, 160)=2.48, p=0.12; Fig. 1b], controlling for age. However, when including both sexes (with sex covariate), unaffected sibling's TL were longer than individuals with ASD [F(1, 232)=5.39, p=0.02], driven by females [F(1, 70)=4.77, p=0.03]. In individuals with ASD, TL was not related to core symptoms, but negatively related to sensory symptoms [vestibular: r(86)=-0.27; p=0.001 (Fig. 2a); visual: r(84)=-0.25; p=0.02; touch: r(80)=-0.23; p=0.03]. TL was positively related to cognition in parents only [knowledge: r(44)=0.40; p=0.006 (Fig. 2b); working memory: r(44)=0.29; p=0.05]. Parent's TL was also positively related to the BAPq aloof domain [r(41)=0.43 p=0.004].

Conclusions: We replicated shortened TL in individuals with ASD compared to NT controls. This is the first study to demonstrate unaffected siblings' TL is also reduced, but to a lesser degree than their affected siblings, which may be driven by females with ASD. We replicated findings of no relationship between TL and core ASD symptoms, but add new findings of relationships with sensory symptoms. Further, we demonstrate TL is more tightly coupled with cognition in parents, which is concerning for cognitive aging outcomes in affected individuals with reduced TL at young ages. We observed a surprising correlation between longer TL and greater aloof traits in parents, which may reflect a protective mechanism to social stress. Further research is warranted to determine if TL is both a biological mechanism of symptoms in individuals with ASD and a potential treatment target.

Poster 40

ADDRESSING THE GAP OF IMAGING ACCESSIBILITY IN EARLY DETECTION OF AD BY A NOVEL TRANSFER LEARNING MODEL: A LONGITUDINAL STUDY. Liu X, Li J, Chen K, Wu T, Lure F, Su Y, Weidman D, Wang P. Arizona State University; Banner Alzheimer's Institute; MS Technologies; Shanghai Tongji Hospital; Arizona Alzheimer's Consortium.

Background: Detection of AD at the earlier symptomatic stage of mild cognitive impairment (MCI) is important for effective therapeutic intervention. Because MCI is a research construct that has heterogeneous etiologies, it is an important task to differentiate if an individual with MCI has early ongoing AD pathology (a.k.a. MCI due to AD). This can be accomplished by building a machine learning classifier to integrate images of different but complementary modalities together with clinical variables. The challenge is that multi-modality images are not universally available for all patients due to accessibility constraints (cost, insurance coverage, etc). In a previous study, we developed a transfer learning (TL) model capable of training a classifier using incomplete multimodality images collected at baseline. In the present study, we include longitudinal multi-modality images in the TL model to further improve the classification accuracy.

Methods: 214 MCI patients from ADNI were included. We downloaded MRI, FDG-PET, and amyloid-PET images (as three modalities) at baseline and a follow up. 97 patients were found to be A β + at the follow up, an indicator of MCI due to AD. The patients were divided into four sub-cohorts: MRI only; MRI & FDG-PET; MRI & amyloid-PET; all three modalities available. We extracted commonly used imaging features including 3, 4, and 6 features from MRI, FDG-PET, and amyloid-PET, respectively. Clinical variables such as age, APOE 4 status, MMSE and CDR were also included. We applied TL to integrate the incomplete longitudinal multi-modality image features and clinical variables to build a classifier to differentiate MCI due to AD at the follow up.

Results: TL achieved 0.92 cross-validated AUC, 0.90 sensitivity, and 0.84 specificity. This is a significant improvement over using baseline images only ($p < 0.001$). As a competing method, separate modeling of each sub-cohort by logistic regression achieved 0.86 AUC, 0.83 sensitivity, and 0.83 specificity, which were significantly outperformed by TL in AUC ($p < 0.001$) and sensitivity ($p < 0.001$)

Conclusions: We proposed a novel TL model to accurately detect MCI due to AD for patients with varying availability of imaging modalities. This capability benefited a broader patient population especially those susceptible to resource or accessibility constraints.

Poster 41

HUMAN IN VITRO CO-CULTURE SYSTEM OF C9ORF72-FTD/ALS PATIENT-DERIVED IPSC NEURONS AND MICROGLIAL CELLS TO STUDY MECHANISMS OF SYNAPTOPATHY.

Lorenzini I, Levy J, Burciu C, Bhatia D, Rabichow B, Almeida S, Gao FB, Van Keuren-Jensen K, Sattler R. Barrow Neurological Institute; University of Massachusetts Medical School; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The mutation in the C9orf72 (C9) gene represents the most common genetic abnormality in frontotemporal dementia (FTD) (10-30%) and amyotrophic lateral sclerosis (ALS) (40-50%). This discovery strengthened the genetic and symptomatic overlap between the second most common form of early-onset dementia and a fatal motor neuron disease. FTD is characterized by synaptic loss and dysfunction. Recent studies in postmortem ALS tissue and preliminary data from our laboratory using human induced pluripotent stem cells (hiPSC) suggest that similar events occur in C9 patients with dementia. Published research suggests that synaptic pruning mediated by microglial cells can be re-activated during neurodegeneration, leading to synapse loss and dysfunction. Interestingly, C9orf72 knockout mice display altered immune responses in microglia, with age-related neuroinflammation exhibiting similarities seen in C9 patient tissue. These findings suggest that inappropriate neural-immune interactions may contribute to synaptic impairment and ultimately cognitive decline in C9-FTD/ALS. We hypothesize that synaptic defects in C9 dementia are mediated by microglial cells and the neural-immune complement pathway.

Methods: C9orf72 patient-derived human induced pluripotent stem cells (hiPSCs) were differentiated into forebrain cortical neurons (hiPSC-CNs) and microglial cells (hiPSC-MGs) using modifications of previously published protocols. hiPSC-CN mono-cultures were analyzed for neuronal morphology including dendritic branching and dendrite length. In addition, hiPSC-CN mono-cultures were examined for neuronal function by measuring dendritic synapse densities via immunofluorescent confocal microscopy and neuronal firing via a multi-electrode array (MEA) system. hiPSC-MG mono-cultures were analyzed for microglial marker gene expression and protein localization. In addition, phagocytic activity of hiPSC-MGs was determined by exogenously applied A-beta engulfment assays.

Results: To test our hypothesis we first examined hiPSCs cortical neuron mono-cultures and found significant changes in dendritic branching, dendritic length and synapse density. We further detected aberrant expression of synaptic proteins in conjunction with changes in neuronal excitability measured via longitudinal micro-electrode array (MEA) analyses. We also generated hiPSCs differentiated microglial cells from healthy and C9-FTD/ALS patients and examined changes in microglial gene expression and microglial-specific brain functions, such as phagocytosis. Preliminary experiments support the co-culturing of hiPSC-CNs with hiPSC-MGs, which are currently being studied for neuronal and microglial activities in different co-culture combinations (healthy/healthy, diseased/diseased, healthy/diseased and diseased/healthy).

Conclusions: We established disease-relevant phenotypes in both hiPSC CNs and MGs as mono-cultures. The in vitro co-culture system of hiPSC-derived neuron-microglial cells will not be used to determine the role of microglial cells in neuronal synaptic dysfunction in C9-FTD/ALS. This human in vitro co-culture model not only allows for the studies of C9 FTD/ALS disease pathogenesis, but any other neurodegenerative disorder characterized by synapse loss and synaptic dysfunction, including other subtypes of FTD, Alzheimer's disease and Down's Syndrome.

Poster 42

AMYLOID BETA AND TOTAL TAU LEVELS IN POSTMORTEM CEREBROSPINAL FLUID SAMPLES FROM NEUROPATHOLOGICALLY-CONFIRMED PATIENTS: A STUDY OF IMMUNOMAGNETIC REDUCTION TECHNOLOGY. Lue LF, Chen W, Guerra A, Kuo W, Yang SY, Beach TG. Banner Sun Health Research Institute; Arizona State University, MagQu Corp, LLC; MagQu Corp, Ltd; Arizona Alzheimer's Consortium.

Background: Plasma A β 42 and total tau (t-tau) levels measured by ImmunoMagnetic Reduction (IMR) technology have previously classified clinically diagnosed Alzheimer's disease (AD) from normal controls (NC) at high sensitivity and specificity when used as a composite marker. When considering these two biomarkers separately, there was a non-significant trend for increases in A β 42 and significant increases in t-tau in AD plasma (Lue et al., 2017). The objective of this pilot study was to test IMR technology in postmortem cerebrospinal fluid (CSF) samples, comparing neuropathologically-confirmed NC and AD cases.

Methods: Postmortem CSF samples, obtained from the Brain and Body Donation Program (BBDP) of Banner Sun Health Research Institute (BSHRI), were centrifuged, aliquoted, and frozen. For IMR assays, CSF samples were diluted to 1:20. The magnetic fluids containing the specific antibodies for A β 40, A β 42, and t-tau were mixed with CSF samples in appropriate ratios according to the manufacturer's manuals. Each sample was assayed in duplicate for each marker. The final concentrations in the CSF samples were converted from the IMR% to pg/ml concentrations according to the established standard curve. Neuropathological and demographic information from BBDP data base were provided for correlation analysis with IMR results. Independent Sample t-tests were used for comparisons of continuous data while Spearman correlations were used to relate biomarker measures to postmortem brain pathology (MedCal software version 18.5).

Results: This study was performed on postmortem ventricular CSF samples from 15 NC and 13 AD neuropathologically-confirmed cases. The means of postmortem intervals were 3 hours in both NC and AD groups. There was no difference in expired ages. The NC group had significantly higher brain weights than the AD group. The means and standard deviations of last MMSE scores in NC were 28.41 ± 1.46 , in contrast to 14.77 ± 9.24 in AD. We detected no disease-associated differences in the levels of A β 42 ($P = 0.2028$) and t-Tau ($P = 0.0631$). However, the product of A β 42 and t-tau showed significant increases in AD ($P = 0.0296$). There were significant positive correlations between the values of the product of A β 42 and t-tau and total plaque counts ($P = 0.030$, $r = 0.41$) or total tangle counts ($P = 0.049$, $r = 0.38$).

Conclusions: Measurements of CSF A β 42 and t-tau by ELISA methods have led to the findings that AD has lower A β 42 and higher t-tau levels than NC, and the ratios of the two markers have been used to identify mild cognitive impairment (MCI) and AD but studies to date have been limited by their usage of the relatively inaccurate clinical diagnosis as gold standard. The present study is the first to use IMR technology to assay CSF A β 42 and t-tau levels in neuropathologically-confirmed cases. Our study detected significant increases in the product of these two markers in AD. Future study will be conducted with larger subject numbers to further test the relationship between IMR-assayed CSF and plasma A β 42 and t-tau, as well as the relationship between ELISA-assayed CSF A β 42 and t-tau and IMR-assayed A β 42 and t-tau.

Poster 43

HUMAN CELLS CORE FOR TRANSLATIONAL RESEARCH AT BANNER SUN HEALTH RESEARCH INSTITUTE. Lue LF, Serrano GE, Walker JE, Nunez T, Walker DG, Brafman D, Reiman EM, Beach TG. Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Animal models are widely used for research in neurodegenerative diseases and have made significant contributions to the understanding of disease mechanisms and developing potential therapeutics. However, there are distinct human features that cannot be entirely recapitulated in animal models. To improve translation from animal research to effective treatment, utilization of cellular models developed from human subject tissues offer promise. At Banner Sun Health Research Institute (BSHRI), the Brain and Body Donation Program (BBDP) yearly receives and processes 50-75 autopsy cases and to provides brain tissues from rapid autopsy (postmortem delay median: 3.5 hours) for neuropathological research. This is a unique resource, as each autopsy case has longitudinal clinical and medical data available from the time of enrollment to death, and neuropathological diagnosis from autopsied tissues. Here, we describe the strategy and progress in using our experiences to establish a comprehensive aged human cell core resource at BSHRI.

Methods: Procedures have been developed for processing human scalp and brain tissues on a routine basis. Scalp tissue obtained from autopsy cases were processed < 20 hours after autopsy. Dermal tissues cut into approximately 1-mm² cubes were used for explant cultures in at 37°C in a cell culture incubator supplied with 5% CO₂ and 95% air until cell outgrowth. Confluent cell cultures from original plating are expanded for three generations before cryo-storage. For microglia, our previously published procedure is used. We plan to use magnetic beads selection methods to obtain pure microglia and astrocytes.

Results: We have implemented procedures for routine culturing of postmortem scalp explants to obtain fibroblasts and for isolating and culturing microglia from cortical tissues. Averagely, we processed 2-3 autopsy cases each month. Currently, 6 cases were used for isolation of both microglia and fibroblasts. The other cases were used either for microglia or fibroblast cultures. The clinical diagnoses of these cases were 6 normal controls, 4 Alzheimer's disease, 4 Parkinson's disease, and 2 mild cognitive impairment. All these cases have demographic information, postmortem delay intervals, detailed clinical assessment for cognitive and movement disorders along with ApoE genotypes. Identification of ApoE genotype is an important feature for all cases in this cell bank. Among 12 cases from which fibroblasts were isolated, there are 2 ApoE allele 3/4 cases, with the remainder being ApoE allele 3/3. No ApoE allele 4/4 or ApoE allele 2 carrier cases have been done yet. The total cell yields varied from case to case. We were able to bank 3-10 vials of 0.5-1.0 million fibroblasts per case. The fibroblasts from a collection of cases with known genotypes will be used for neuron production using hiPSC-technology in a collaboration with stem cell research scientists at Arizona State University. As for microglia, we are testing selection methodology using the surface markers CD11b with antibody-conjugated magnetic beads from Miltenyi Biotec and StemCell Technologies. These procedures are being optimized in our laboratory. After optimization of the microglia selection procedure, we will test a similar procedure for selecting astrocytes.

Conclusions: The initial effort for establishing Human Cells Core for Translational Research using autopsy scalp tissues and cortical tissues has made substantial progress. Characterization of the banked cells is ongoing. We anticipate that the characterized banked cells will be available as a shared resource to research scientists by the third quarter of 2019.

Poster 44

HDAC2 NUCLEAR PROTEIN REDUCTION WITHIN CHOLINERGIC BASAL FOREBRAIN NEURONS IS ASSOCIATED WITH NFT FORMATION DURING THE PROGRESSION OF ALZHEIMER'S DISEASE. Mahady L, Nadeem M, He B, Perez SE, Mufson EJ. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Cholinergic basal forebrain (CBF) neurons within the nucleus basalis of Meynert (nbM), which provide the major source of acetylcholine to the entire cortical mantle, degenerate and display neurofibrillary tangles (NFTs) early in the onset of AD. The balance between histone acetyltransferases and histone deacetylases (HDACs) regulates choline acetyltransferase (ChAT) expression, the synthesizing enzyme for acetylcholine, and HDAC2 accumulates in neurons in preclinical AD [Braak stages (I/II)]. Thus HDAC dysregulation may be an early event related to the selective vulnerability of CBF neurons. Whether alterations in HDAC2 nuclear levels in CBF neurons occur during the early or late stages of NFT formation remains unknown.

Methods: Here we quantified changes in HDAC2 immunoreactivity within CBF neurons by triple immunohistochemistry using antibodies directed against p75NTR (an excellent marker for CBF neurons), AT8 (pretangle), TauC3 (late stage), and dual staining for AT8/Thioflavin-S, and TauC3/Thioflavin-S from tissue obtained from subjects who died with a premortem clinical diagnosis of NCI (n=5), MCI (n=5), mild/moderate AD (n=5) and severe AD (n=5) from the Rush Religious Orders Study (RROS) and the Rush RADC, respectively. Groups were matched by age and postmortem interval (PMI=5 hr) and underwent detailed postmortem neuropathologic evaluations.

Results: HDAC2-ir was significantly decreased in single labeled CBF neurons across disease progression ($p < 0.001$, NCI>mAD, sAD; MCI>mAD, sAD; mAD>sAD). However, in each clinical group p75NTR neurons displayed higher HDAC2 compared to AT8, TauC3, AT8/Thioflavin, or TauC3/Thioflavin positive neurons ($p < 0.05$). CBF AT8 or TauC3 positive neurons displayed a decrease in nuclear HDAC2-ir across clinical groups ($p < 0.001$, NCI, MCI, mAD>sAD). HDAC2-ir was also decreased in AT8/Thioflavin-S and TauC3/Thioflavin-S stained neurons ($p < 0.001$, NCI>sAD, MCI>mAD>sAD; NCI, MCI, mAD>sAD, respectively). In MCI, HDAC2-ir was greater in CBF neurons that were AT8, TauC3 or AT8/Thioflavin-S positive compared to TauC3/Thioflavin-S perikarya ($p < 0.05$). In mAD, HDAC2-ir was higher in p75NTR neurons dual stained for AT8 or TauC3 compared with p75NTR neurons triple stained for AT8/Thioflavin-S or TauC3/Thioflavin-S NFTs ($p < 0.05$).

Conclusions: These data indicate that CBF neurons display reduced HDAC2 nuclear immunoreactivity during AD progression. The reduction in CBF HDAC2-ir in neurons containing AT8, TauC3, and Thioflavin-S in prodromal AD suggests that drugs which enhance HDAC2 and reduce pathological tau may prevent CBF neuronal degeneration during the onset of AD.

Poster 45

APOE-DEPENDENT VERBAL LEARNING EFFECTS IN COGNITIVELY UNIMPAIRED OLDER ADULTS. Malek-Ahmadi M, Su Y, Devadas V, Henslin B, Locke DEC, Woodruff BK, Dueck AC, Caselli RJ, Reiman EM. Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Previous studies in the Arizona APOE ϵ 4 Gene Does Study have shown differential effects of APOE ϵ 4 status on delayed recall verbal memory trajectories in cognitively unimpaired (CU) older adults. Specifically, ϵ 4 homozygotes (HMs) showed accelerating declines relative to ϵ 4 heterozygotes (HTs) and non-carriers (NCs). However, very few studies have investigated the trajectory of verbal learning changes in CU older adults. The aim of this study was to determine if APOE ϵ 4 status has differential effects on three complimentary indices of verbal learning from the auditory verbal learning test (AVLT) in CU older adults.

Methods: Data from 545 CU older adults participating in a longitudinal imaging and cognition study were analyzed. APOE ϵ 4 status breakdown was: HM = 73, HT = 158, NC = 314. Mean age at baseline was 60.0 ± 7.4 years and the mean education level was 15.8 ± 2.3 years. The average follow-up length was 10.0 ± 5.8 years. Verbal learning measures included Total Learning (TL), Learning Over Trials (LOT), and Learning Slope (LS). Linear mixed effects models that adjusted for age, education, sex, and baseline scores were used to derive subject-based slopes that were compared between NCs, HTs, and HMs using a one-way ANOVA. Cohen's d was used to quantify the effect size for significant groupwise comparisons.

Results: At baseline, TL ($p = 0.50$), LOT ($p = 0.81$), and LS ($p = 0.81$) showed no significant APOE group differences. Subject-based slopes for TL showed significant differences (HM<HT, NC; both $p < 0.001$; NC vs HM $d = 0.63$, NC vs HM $d = 0.41$). LOT was significantly different between HMs and NCs (NC>HM, $p < 0.001$, $d = 0.43$) and LS showed no significant differences ($p = 0.08$).

Conclusions: These results demonstrate APOE-dependent verbal learning differences in CU older adults. Greater decline among HMs on these indices suggests their utility in detecting subtle cognitive changes that may precede clinically manifest MCI/AD. These findings also suggest that cognitive changes beyond delayed recall are present in those at high risk of developing MCI/AD.

Poster 46

IMPACT OF CEREBRAL ISCHEMIA SCORES, FIBRILLAR AMYLOID- β BURDEN AND AGE ON WHITE MATTER HYPERINTENSITY VOLUMES IN COGNITIVELY UNIMPAIRED OLDER ADULT APOE4 CARRIERS AND NON-CARRIERS. Malek-Ahmadi M, Luo J, Methuku V, Devadas V, Goradia D, Su Y, Reiman EM, Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium

Background: The Hachinski Ischemia Scale (HIS) scores, indicators of cerebral ischemia risk factor and symptom severity, are associated with MRI measurements of white matter hyperintensity (WMH) volume and cerebral ischemia in persons with cognitive impairment. In this study, we sought to characterize the extent to which HIS scores, fibrillar amyloid- β ($A\beta$) burden, and age are associated with WMH volume in cognitively unimpaired older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and to explore the extent to which these relationships are influenced by presence or absence of the APOE4 allele.

Methods: We analyzed cross-sectional data from 297 cognitively unimpaired research participants 73 ± 6 (56-94) years of age, including 86 APOE4 carriers and 211 non-carriers. WMH volumes were derived using T1-weighted MRIs, the Lesion Segmentation Toolbox in SPM 12, and a threshold of $k = 0.15$. Mean cortical-to-cerebellar florbetapir standard-uptake-value ratios (SUVRs) were used to provide an indicator of fibrillar $A\beta$ burden. Generalized linear models were used to characterize the extent to which HIS scores, SUVRs and age are associated with WMH volume, explore differential effects in APOE4 carriers and non-carriers, and account for potentially confounding effects of age, sex, education, SUVRs, and APOE4.

Results: HIS scores ($p=0.003$) were associated with greater WMH volumes. There was an unexpected differential impact of HIS scores on WMH volume in the APOE4 carriers and non-carriers ($p=0.002$), such that HIS scores were associated with lower WMH volumes in the carriers ($p=0.02$) and higher WMH volumes in the non-carriers ($p=0.002$). Relationships between HIS scores and on WMH volumes were not solely attributable to age, sex, education level, or florbetapir SUVRs. SUVRs ($p=0.008$) and age ($p<0.001$) were also associated with WMH volume, and these relationships were not significantly different in the APOE4 non-carrier groups (2/3 vs 3/3).

Conclusions: This study provides new information about the impact of cerebral ischemia scores, $A\beta$ burden, and age on WMH volume in cognitive unimpaired older adults. It suggests that the relationship between cerebral ischemia scores and WMH volumes is significantly greater in APOE4 non-carriers than carriers, an exploratory finding that will need to be replicated in future studies.

Poster 47

RELATIONSHIPS BETWEEN LONGITUDINAL RATES OF LEARNING AND MEMORY DECLINE AND DIFFERENT FORMS OF CEREBROVASCULAR PATHOLOGY IN COGNITIVELY UNIMPAIRED BRAIN DONORS. Malek-Ahmadi M, Belden CM, Powell JJ, Zamrini E, Adler CA, Sabbagh MN, Shill HA, Jacobson SA, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta SH, Shprecher DR, Spann BM, Tariot PN, Davis KJ, Long KE, Nicholson LR, Intorcchia A, Glass MJ, Walker JE, Callan M, Curry J, Cutler B, Oliver J, Arce R, Walker DG, Lue L, Serrano GE, Sue LI, Reiman EM, Beach TG. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Midwestern University; Mayo Clinic Arizona; Cleveland Clinic Lou Ruvo Center for Brain Health; Barrow Neurological Institute; University of Arizona; Molecular Neuroscience Research Center, Shiga University of Medical Science; Arizona Alzheimer's Consortium.

Background: Antemortem MRI studies have shown that white matter hyperintensity (WMH) volumes are associated with accelerated rates of verbal learning decline in older adults. Antemortem-postmortem studies are needed to clarify whether that association is attributable to the extent or type of cerebrovascular disease. We sought to determine the extent to which longitudinal rates of verbal learning and recall memory decline are related to the severity of five different manifestations of cerebrovascular disease in cognitively unimpaired brain donors.

Methods: We analyzed annual auditory verbal learning test (AVLT) total learning and delayed recall test scores and neuropathological measurements of cerebral amyloid angiopathy, white matter rarefaction, Circle of Willis atherosclerosis, total infarct volume, and microinfarct volume in 81 research participants who had longitudinal cognitive assessments, remained cognitively unimpaired at the time of their death, and donated their brains. The participants had been cognitively assessed over 5 ± 3 years and were 88 ± 6 years old when they died. Linear mixed models were used to determine whether longitudinal rates of total learning and delayed recall were associated with each form of cerebrovascular lesion interaction after adjusting for baseline test scores, sex, education, neuritic plaque score, Braak stage, and presence or absence of the APOE4 allele.

Results: Longitudinal rates of total learning decline were associated with cerebral amyloid angiopathy ($p=0.03$) severity, even after controlling for neuritic plaque and neurofibrillary tangle severity, but not with white matter rarefaction ($p=0.27$), Circle of Willis atherosclerosis ($p=0.97$), total infarct volume ($p=0.15$), or microinfarct volume ($p=0.19$). Longitudinal rates of delayed recall memory decline were associated with cerebral amyloid angiopathy severity ($p=0.01$), even after controlling for plaque and tangle severity, and microinfarct volume ($p=0.01$), but not with white matter rarefaction ($p=0.71$), Circle of Willis atherosclerosis ($p=0.85$), or total infarct volume ($p=0.26$).

Conclusions: This study provides new information about the extent to which longitudinal learning and memory declines are related to different forms of cerebrovascular pathology, in cognitively unimpaired older adults. Learning and memory declines are preferentially associated with cerebral amyloid angiopathy, even after adjustment for neuritic plaque and tangle pathology; memory declines are also associated with microinfarct volume.

Poster 48

EGR3 IS REQUIRED FOR ACTIVITY DEPENDENT BDNF FACTOR EXON IV AND VI INDUCTION IN THE MOUSE HIPPOCAMPUS. Marballi KK, Meyers KT, Zhao X, Campbell JM, Gallitano AL. University of Arizona; Arizona State University; Neural Stem Cell Institute; Arizona Alzheimer's Consortium.

Background: Early growth response 3 (Egr3) is an immediate early gene transcription factor (IEG TF) that is decreased in the brains of Alzheimer's disease (AD) patients. Prior studies have shown that increased levels of EGR3 protein are associated with rescue of cognitive deficits in AD transgenic mouse by the curcumin - derived compound J147. We previously reported Egr3 to be essential for hippocampal long-term depression (LTD) and spatial memory. However, the molecular mechanisms by which Egr3 influences these processes remain unknown.

Methods: To identify activity-dependent transcriptional targets of EGR3 in the hippocampus, we conducted an expression microarray in both wildtype (WT) and Egr3^{-/-} mice following electroconvulsive stimulation (ECS), a potent inducer of IEGs. Of the differentially expressed genes identified, brain derive neurotrophic factor (Bdnf) stood out as the sole growth factor. Quantitative real time PCR (qRT-PCR) showed that Bdnf was upregulated in WT mice after ECS, consistent with prior reports that hippocampal Bdnf is upregulated by seizure. However, this induction was absent in Egr3^{-/-} mice. We validated these data in two independent cohorts using qRT-PCR.

Results: BDNF is a multifunctional protein in the nervous system, an important player in hippocampal LTD, and a known upstream regulator of Egr3. In addition, higher BDNF gene expression levels in the brain are associated with slower cognitive decline in aging individuals. Based on our data we hypothesized that Egr3 regulates activity-dependent induction of Bdnf in the hippocampus. We focused our studies on Bdnf exons IV and VI, two activity dependent exons that are highly expressed in the hippocampus. Using the same three cohorts from our previous study, we assayed levels of transcripts containing Bdnf exons IV and VI, using qRT PCR. Bdnf exon IV and VI mRNAs were each highly induced by ECS in WT mice, but not in Egr3^{-/-} mice, across all cohorts. Follow-up in vitro luciferase reporter studies showed that Egr3 overexpression in mouse neuro2a cells activates Bdnf -promoter driven exon IV and VI containing transcripts. These data demonstrate that Egr3 is necessary for induction of exon IV and, to a lesser extent, of exon VI Bdnf transcripts, in the mouse hippocampus following ECS.

Conclusions: Our findings suggest the possibility that Egr3 may regulate activity-dependent Bdnf expression following physiologic stimuli, such as learning and memory, which are altered in AD. Our results identify EGR3 as a novel transcriptional regulator of activity-dependent hippocampal Bdnf expression.

Poster 49

PIN1 IS AN INDICATOR OF AGE ASSOCIATED RISK OF MILD COGNITIVE IMPAIRMENT AND SUBSEQUENT ALZHEIMER'S DISEASE. Mastroeni D, Velazquez R, Shireby G, Lu A, Delvaux E, Nolz J, Liang W, Lunnon K, Horvath S, Coleman P. Arizona State University; University of Exeter; University of California, Los Angeles; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Multiple lines of evidence converge on the fact that Alzheimer's disease (AD) starts damaging the brain decades prior to clinical diagnosis. Thus, there is an urgent need for the development of new therapeutic targets that identify disease early. Excessive post-translational modifications (e.g. phosphorylation) are known early events in AD. Phosphorylation events are critical intermediates of "normal" protein function, but excessive phosphorylation (e.g. hyperphosphorylation) is unfavorable. Hyperphosphorylation of tau and amyloid triggers the formation of neurofibrillary tangles (NFTs) and toxic A β aggregates, both of which have been described as classical hallmarks of AD. Recent efforts have identified the peptidyl-prolyl cis/trans isomerase (Pin1) as a key regulator of the phosphorylation signaling pathway.

Methods: 1. Hippocampal homogenates and Affymetrix arrays; 2. Laser capture of glial and neuronal cells and RNA sequencing; 3. Laser Capture of neurons containing neurofibrillary tangle and neurons without neurofibrillary tangles and Affymetrix arrays.

Results: Here, we demonstrate that Pin1 is significantly down-regulated as a function of age (22yrs-99yrs) in limbic and neocortical brain regions, up-regulated in the mild cognitively impaired state (MCI), and down-regulated in AD. Subsequent analysis in laser capture CA1 tangle bearing neurons, microglia and astrocytes from AD and normal control subjects' show that Pin1 expression changes are specific to neurons, not glia. Moreover, we show a significant positive linear relationship between pre/post synaptic molecules and Pin1 in both limbic and neocortical regions.

Conclusions: Collectively, our results show that Pin1 expression changes occur prior to clinical symptoms of AD, correlate to early events associated with AD-risk, these changes are specific to neurons, and may be a potential prognostic marker to assess AD risk in the aging population. These results set the stage for the development of therapeutic strategies to target Pin1 in preclinical AD as a method of preventing, and monitoring the progression of healthy aging and AD.

Poster 50

USING DISTINCT STRAINS OF THE NEUROTROPIC PARASITE TOXOPLASMA GONDII AS A TOOL TO PROBE PROTECTION AGAINST AMYLOID BETA DEPOSITION. McGovern KE, Cabral CM, Koshy AA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Genetic and pathologic data suggest that amyloid beta (A β), produced by processing of the amyloid precursor protein, is a major initiator of Alzheimer's disease (AD). To gain new insights into A β modulation, we sought to harness the power of the coevolution between the neurotropic parasite *Toxoplasma gondii* and the mammalian brain. Prior studies attributed *Toxoplasma*-associated protection against A β to increases in anti-inflammatory cytokines (TGF- β and IL-10) and infiltrating phagocytic monocytes. These studies only used one *Toxoplasma* strain making it difficult to determine if the noted changes were associated with A β protection or simply infection.

Methods: To address this limitation, we infected an AD mouse model with each of the genetically distinct, canonical strains of *Toxoplasma* (type I, type II, or type III) and assessed plaque burden, immune cell infiltration, and cytokine levels in the brain.

Results: We found that despite both type II and type III strains establishing a chronic CNS infection and inflammatory response, only type II infection was protective against A β deposition. Both strains elicited increased numbers of CNS T cells and myeloid lineage cells as well as elevated pro-inflammatory cytokines, but neither group showed a >2-fold elevation of TGF- β or IL-10 at the protein level. In addition to providing protection, we have gone on to show that type II infection can reduce amyloid plaque burden in mice that already exhibited plaque deposition.

Conclusions: These data suggest that we can now use our identification of protective (type II) and nonprotective (type III) *Toxoplasma* strains to determine what parasite and host factors are linked to decreased A β burden rather than simply with infection. Current work is focused on defining the point at which amyloid clearance peaks and phenotyping the immune cell infiltrates that contribute to clearance.

Poster 51

FRONTAL CORTEX CHI3L1 AND CHI3L2 ALTERATIONS DURING PROGRESSION OF ALZHEIMER DISEASE. Moreno-Rodriguez M, Nadeem M, Perez SE, Mufson EJ. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Chitinase 3-like proteins (CHI3L1 and CHI3L2) are markers of inflammation in several neurodegenerative diseases, including Alzheimer's disease (AD). While studies have demonstrated that cerebrospinal fluid CHI3L1 levels are increased in pre-clinical and prodromal AD, no studies have examined changes in this and CHI3L2 protein levels in brain during the early stages of AD.

Methods: The present study evaluated levels of both CHI3L1 and CHI3L2 and inflammatory-related markers (Iba1, C1q, GFAP, NPTX2 and CD44) in the frontal cortex (FC) obtained from people who died with an antemortem clinical diagnosis of non-cognitive impairment (NCI, n=15), mild cognitive impairment (MCI, n=15), mild/moderate AD (mAD, n=12) and severe AD (sAD, n=11) using immunoblot and immunohistochemical techniques.

Results: CHI3L1-immunoreactive (-ir) neurons number was increased in FC and white matter in sAD compared to NCI. On the other hand, an increase in GFAP and Iba1-ir cell number was observed in MCI compared to NCI, but only in white matter. Western blot analyses revealed significantly lower levels CHI3L2 in the FC, while CD44 levels was increased in sAD. No significant differences for CHI3L1, GFAP, C1q and NPTX2 protein levels were detected between clinical groups. Strong significant correlations were found between FC CHI3L1 and Iba1-ir cell number in white matter ($r = 0.63$) and CHI3L1 and C1q protein levels ($r = 0.44$) in the early stages of the disease. C1q and Iba1 ($r = 0.57$), CHI3L2 and CD44 ($r = -0.65$) and GFAP and CD44 ($r = -0.49$) protein levels were associated during disease progression. However, these inflammatory markers did not show significant correlations with β -amyloid ($A\beta$) and neurofibrillary tangles in the FC at any stage of the disease.

Conclusions: This data suggest that CHI3L1 and CHI3L2 changes in the FC occur late in AD. On the contrary, the association between CHI3L1 and Iba1 in FC white matter indicates that CHI3L1 might play a critical role in early inflammatory responses in prodromal AD.

Poster 52

NEUROFIBRILLARY TANGLE EVOLUTION IN THE FRONTAL CORTEX OF DEMENTED AND NON-DEMENTED SUBJECTS WITH DOWN SYNDROME. Perez SE, Miguel JC, Nadeem M, Sabbagh MN, Lott IT, Doran E, Mufson E. Barrow Neurological Institute; University of California, Irvine Medical Center; Arizona Alzheimer's Consortium.

Background: Although all individuals with Down syndrome (DS) exhibit an age-related increase in A β plaque and tau neurofibrillary tangle (NFT) pathology, not every case develops dementia. We found that phosphorylated NFT pathology in the frontal cortex was greater in demented compared to non-demented DS, while A β pathology was similar in both groups, suggesting that tau pathology plays a greater role in the dementia seen in DS.

Methods: The present study examined the appearance of phosphorylation, truncation and conformational posttranslational tau epitopes in frontal cortex pyramidal layers V-VI neurons in age-matched DS without dementia (n=6) and DS with dementia (DS-D) (n=10) using immunofluorescence combined with quantitative analysis. Triple immunofluorescence was performed using antibodies against early and late tau markers: phosphorylated AT8 (1:50), early phosphorylated pre-tangle pS422 (1:50), conformational Alz50 (1:50) or truncated TauC3 (1:50) epitopes.

Results: Quantitation revealed that the number of AT8+pS422+Alz50, TauC3+pS422+Alz50, pS422+Alz50 and TauC3+pS422 positive NFTs were significantly higher in DS-D compared to DS, suggesting a differential evolution of frontal cortex NFT formation in DS-D. A within group analysis revealed that cortical AT8+pS422+Alz50 positive NFT numbers were significantly greater than pS422+Alz50 NFTs in DS with and without dementia, while AT8+pS422+Alz50 NFTs were greater than AT8+Alz50 NFTs in DS-D, but not in DS. Numbers of NFTs reactive for TauC3+pS422+Alz50 were significantly greater than those displaying pS422+Alz50 and TauC3+Alz50 in DS-D. TauC3+pS422 positive NFTs were significantly greater than pS422+Alz50 NFTs in DS-D. Conversely no differences were found between double or triple labeled NFTs containing TauC3 in DS.

Conclusions: In conclusion, the large number of pS422, Alz50, TauC3 as well as pS422+TauC3 NFTs in DS-D compared to DS, suggest that truncation at glutamic 421 (TauC3) and phosphorylation at serine 422 (pS422) are differentially altered between DS groups. In addition, the observation that NFT numbers containing Alz50+pS422 and Alz50+TauC3 are lower compared to AT8+pS422+Alz50 and TauC3+pS422+Alz50 NFTs respectively, in DS and DS-D, indicates that phosphorylation and truncation changes precede conformational tau events in DS.

Poster 53

RNA PROFILING ON CEREBELLUM WHITE MATTER REVEALS A POTENTIAL ROLE OF APP AND ENDOTHELIAL GENES IN CEREBELLAR MULTIPLE SYSTEM ATROPHY. Piras IS, Bleul C, Schrauwen I, Talboom J, DeBoth MD, Naymik MA, Hallyday G, Holton J, Serrano G, Sue L, Beach TG, Huentelman MJ. Translational Genomics Research Institute; The University of Sydney School of Medicine; Queen Square Brain Bank for Neurological Disorders; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: We reported the results of the RNA expression profiling of the cerebellum white matter (CWM) from two independent cohorts of Multiple System Atrophy (MSA; n = 66) patients and healthy controls (HC; n = 66).

Methods: RNA samples from bulk brain tissue and from oligodendrocytes obtained by laser capture Microdissection (LCM) were sequenced using Illumina HiSeq2500. Differentially expressed genes (DEGs) were detected using DESeq2, also stratifying for MSA subtype (MSA-C and MSA-P). DEGs were classified according their expression in brain cells using an external database.

Results: We detected the highest number of DEGs in the MSA-C group (n = 747) but only 1 gene in MSA-P, highlighting larger dysregulation in the MSA-C CWM than in MSA-P. The LCM study showed 187 DEGs, with the top genes mostly involved in myelination process. The PPI network reveals sub-network enriched for "collagen genes" (MSA), "cytoskeleton organization" and "cell death" (MSA-C), and "chaperone folding" (oligodendrocytes). These processes can be related to neurodegeneration (collagen genes and cell death) and production of abnormal proteins (chaperone folding). Furthermore, the APP gene (amyloid- β precursor protein, downregulated in MSA-C) was identified as top ranked hub in both MSA-C and Oligodendrocytes networks. The cell-classification of MSA-C DEGs in bulk brain tissue reveals a relevant downregulation of oligodendrocytes genes (enriched for myelination associated processes), and upregulation of microglia, astrocytes, endothelial cells and neurons. Microglia genes were enriched for "I-kappaB kinase/NF-kappaB signaling", a pathway associated with inflammatory response. Finally, endothelial genes were enriched for angiogenesis and vasculature development, a process also reported in neurodegenerative disease as Alzheimer's. Despite we detected a key role of APP gene in the disease, ELISA assays did not reveal β -amyloid in MSA cerebellum.

Conclusions: This is the largest RNA profiling study ever conducted on post-mortem brains from MSA patients. We were able to define specific RNA profiling signatures for MSA-C, detect several candidate genes associated with the disease. We also reported the association of endothelial specific genes with angiogenesis. Finally, several results points to a β -amyloid independent role for APP in MSA. An analogue mechanism is being recently considered in Alzheimer's Disease, related to an impairment of APP metabolism and accumulation of APP C-terminal fragments, rather than A β production and A β amyloid formation.

Poster 54

COVARYING SPATIAL PATTERNS OF TAU DEPOSITION AND GRAY MATTER ATROPHY UNEARTHED BY THE INFORMED MULTIMODAL PARTIAL LEAST SQUARES (MMPLS) IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE: FINDINGS FROM THE COLBOS PROJECT. Protas H, Pardilla-Delgado E, Lopera F, Johnson K, Sperling RA, Artola A, Baena A, Bocanegra Y, Gatchel J, Guzman-Velez E, Fuller J, Goradia D, Thiyyagura P, VanGilder PS, Luo J, Ghisays V, Lee W, Malek-Ahmadi M, Chen Y, Devadas V, Chen K, Reiman EM, Su Y, Quiroz YT. Banner Alzheimer's Institute; Massachusetts General Hospital, Harvard Medical School; Universidad de Antioquia; Arizona Alzheimer's Consortium.

Background: We have shown that presenilin-1 (PSEN1) mutation carriers from the Colombian kindred with autosomal dominant Alzheimer's disease (ADAD) have elevated tau levels 6-10 years before their estimated clinical onset, which are associated with cognitive decline (Quiroz et al., 2018). However, the interaction between tau pathology and neurodegeneration as measured by brain atrophy is unclear in this population. In this study, we investigated this interaction in cognitively unimpaired carriers and noncarriers from this kindred using an informed multimodal partial least squares (MMPLS) approach, previously developed to jointly examine hypometabolism and brain atrophy in late-onset Alzheimer's disease (Chen et al., 2009, 2012).

Methods: Flortaucipir PET and sMRI images were analyzed from 32 members of the Colombia-Boston Longitudinal Biomarker Study (COLBOS); 14 unimpaired carriers and 18 age-matched noncarriers. Tau PET images were coregistered to the T1 MRI. T1 images were warped into template space and the warp was applied to coregistered tau PET images. The cerebellum crux was used as reference region for PET. Gray matter density maps were calculated. Voxel-wise Informed MMPLS was applied to gray matter density and tau PET images of the unimpaired carriers and noncarriers as well as SPM12 voxel-wise univariate analyses for each gray matter density and PET separately.

Results: Using a univariate approach, PSEN1 mutation carriers had higher levels of tau binding throughout the lateral parietal, temporal cortices, precuneus, and medial temporal regions. There were no significant differences in levels of atrophy between carriers and noncarriers. In contrast, MMPLS showed that covarying elevated tau levels were confined to medial regions (precuneus, medial temporal), while the covarying pattern of atrophy seemed to spread to parietal, left medial temporal, and precuneus. Further, the elevated tau levels in medial regions corresponded to areas with atrophy.

Conclusions: Compared to commonly used univariate analyses, a multivariate approach provides enriched information of the interaction of the spatial patterns of tau burden and atrophy in preclinical stages of ADAD. Longitudinal analyses in ADAD with larger samples are needed to further investigate the interaction of tau pathology and atrophy in the clinical progression of the disease, from asymptomatic to symptomatic stages.

Poster 55

INDIVIDUAL-BASED NETWORK ANALYSIS: A NOVEL APPROACH TO INVESTIGATE THE PATHOLOGICAL SPREAD OF PHF TAU USING GRAPH THEORY IN CLINICAL AND PRECLINICAL STAGES OF ALZHEIMER'S DISEASE. Protas HD, Goradia DD, Ghisays V, Luo JL, VanGilder P, Thiyyagura P, Malek- Ahmadi M, Lee W, Chen Y, Devadas V, Bauer III R, Landau SM, Weiner M, Jagust WJ, Chen K, Su Y, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona State University; University of California, San Francisco; University of California, Berkeley; Arizona Alzheimer's Consortium.

Background: The spread of paired helical filaments (PHF) tau in the brain is currently under investigation. Different groups suggest tau could be either propagating from a seed or an imbalance in local production and clearance that leads to increased deposition. Studies have used resting state fMRI with tau PET to understand the spread of tau in humans. In this study, we introduce a new subject-based measure of tau PET connectivity that describes the spread of tau using only Flortaucipir (FTP) PET images. Here we demonstrate how FTP PET network measurements of tau spread differentiates probable Alzheimer's dementia (pAD), mild cognitive impairment (MCI), and cognitively unimpaired (CU) study participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI), and suggest its promise to detect differences in networks measures in CU persons at genetic risk for AD.

Methods: We determined a FTP network for each subject using a method from graph theory. From the undirected weighted graph created from the inter-regional distances, the global and local (efficiency, network strength) measurements of spread of tau in the network were calculated. Next, we compared our measurements to SUVR in common regions such as prespecified ROIs (entorhinal, parahippocampal, inferior temporal, precuneus) as well as mean cortical region from Mayo and partial volume corrected (PVC) SUVR BraakI-II, BraakIII-IV, and BraakV-VI from Berkeley in their ability to distinguish 15 pAD, 63 MCI, and 81 CU research participants from one another. Finally, we compared these novel and established measurements in their ability to distinguish in CU 49 APOE4 carriers from 24 non-carriers.

Results: Like several of the established ROI flortaucipir PET measurements, each of the global and several of the local flortaucipir connectivity measurements were significantly different in the three subject groups (pAD>MCI>CU, p<E-5). As expected, we found higher FTP efficiency (spread) for AD patients. In contrast to all but one of the ROI methods (PVC_Braak_V-VI_SUVR, p=0.03), flortaucipir global efficiency, strength measurements were significantly different in the CU APOE4 carrier and non-carrier groups (p=0.004, 0.005).

Conclusions: This study introduces previously untapped information from FTP PET. It suggests that these measurements may offer greater power than conventional ROI measurements in the preclinical stages. Additional studies are needed to clarify the value of FTP connectivity measurements in the detection and tracking of AD.

Poster 56

APOE ISOFORMS DIFFERENTIATE NEURONAL- AND ASTROCYTIC MITOCHONDRIAL BIOENERGETIC CAPACITY AND FUEL DEPENDENCY. Qi GY, Mi YS, Chen SH, Brinton RD, Yin F. University of Arizona; Arizona Alzheimer's Consortium.

Background: Late-onset Alzheimer's disease (LOAD) has a multifactorial nature and is associated with an early decline in brain glucose metabolism and a less efficient mitochondrion population. As the greatest genetic risk factor for LOAD, APOE4 allele has been found to not only impair amyloid- β (A β) clearance and promote its aggregation, but also affect energy metabolism and mitochondrial function. While the exaggeration of age-related brain hypometabolism and mitochondrial inefficiency by APOE4 is well established in both AD patients and animal models of late stage AD, mixed results have thus far been reported regarding APOE4 effect on brain bioenergetics in young animals or in vitro models. We propose that such a discrepancy is partially due to the heterogeneous cellular composition of the brain and the distinct capacity of these cells to metabolize various energy substrates.

Methods: To distinguish the direct effect of APOE4 on regulating neuronal- and astrocytic mitochondrial function and their preference to energetic fuels, primary neurons and astrocytes were isolated from forebrains of humanized APOE4 and APOE3 mice (Jackson Laboratory). Mitochondrial bioenergetic profile and their dependency and capacity of metabolizing different substrates were characterized.

Results: As expected, both APOE3 and APOE4 embryonic neurons relied primarily on glucose than other fuels in terms of both dependency and capacity, whereas astrocytes could metabolize more fatty acids than neurons. Our results further revealed that APOE4 neurons and adult astrocytes exhibited lower spare respiration capacity ratio compared to APOE3 cells, although the basal respiration of APOE4 astrocytes was higher than that of APOE3 astrocytes. Across energy fuels, APOE4 astrocytes had higher capacity metabolizing glucose than fatty acids upon high energetic demand while such a fuel preference was much less significant in APOE3 astrocytes. Consistently, the maximal capacity in metabolizing fatty acids was significantly lower in APOE4 astrocytes when compared to that of APOE3 astrocytes.

Conclusions: Our findings indicated that the impact of APOE genotype on brain bioenergetics is not only cell type dependent, but also age- and AD stage-dependent. It was suggested that the development of strategies to restore brain energy metabolism against AD should consider APOE genotype, age- and disease-stage, and the fuel preference of different cell types in the brain.

Poster 57

RELATION OF PHYSICAL ACTIVITY TO REGIONAL MAPS OF CORTICAL GRAY MATTER VOLUME IN THE HEALTHY OLDEST OLD: FINDINGS FROM THE MCKNIGHT BRAIN AGING REGISTRY. Raichlen DA, Bharadwaj PK, Franchetti MK, Sims S, Rezaei RF, Merritt S, Jessup CJ, Porges ES, Geldmacher D, Hishaw GA, Alperin N, Trouard TP, Wadley VG, Levin BE, Woods AJ, Rundek T, Visscher K, Cohen RA, Alexander GE. University of Arizona; University of Alabama at Birmingham; University of Miami Miller School of Medicine; University of Florida; Arizona Alzheimer's Consortium.

Background: Physical activity (PA) may play an important role in maintaining cognitive and brain health during aging. Wrist-worn accelerometers provide a way to objectively measure engagement in moderate to vigorous physical activity (MVPA). We sought to determine whether having high levels of MVPA are associated with greater cortical regional volumes in a cohort of oldest-old adults from the McKnight Brain Aging Registry.

Methods: For this initial analysis, 40 community-dwelling, cognitively unimpaired older adults, ages 85 to 95 were included (mean±sd age = 88.6±3.2; M/F = 17/23; mean±sd MMSE = 28.4±1.5). T1-weighted 3T MRI scans were acquired across the McKnight Brain Institutes at the University of Arizona, University of Alabama at Birmingham, University of Miami, and University of Florida – Gainesville. The T1 scans were processed using FreeSurfer v6.0 and total intracranial volume (TIV) was computed using SPM12 to adjust the vertex-wise maps of cortical gray matter (GM) volume for head-size differences. Measures of MVPA were acquired with Actigraph accelerometers worn on the non-dominant wrist for up to seven consecutive days. Analyses tested the relation of MVPA to cortical gray matter volume maps using CFT and Monte Carlo extent thresholds to maintain an overall $p < 0.05$ false positive rate (Greve and Fischl, 2018).

Results: Results showed that, after adjusting for TIV, higher levels of MVPA were significantly associated with increased volumes in the vicinity of left and right precentral cortical regions. Linear regression analysis showed that the average cortical GM volumes extracted from the two prefrontal regions was positively associated with MoCA scores after controlling for gender, years of education, and age differences ($p \leq 0.03$).

Conclusions: These findings suggest that, among oldest old adults, engaging in more moderate to vigorous activity is associated with greater brain volume in regions of frontal cortex. Together these results provide further support for the role of PA in maintaining brain health in the context of successful cognitive aging.

Poster 58

TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE ASSOCIATED CHANGES IN SLEEP BEHAVIOR OCCURS THROUGH COMPARABLE INFLAMMATORY MECHANISMS.

Saber M, Hur Y, Rowe R, Lifshitz J. Barrow Neurological Institute; University of Arizona College of Medicine–Phoenix; Phoenix Veterans Affairs Health Care System; Arizona Alzheimer's Consortium.

Background: Individuals exposed to traumatic brain injury (TBI) have increased risk of developing multiple neurodegenerative conditions, including Alzheimer disease (AD). Following both injury and AD, there are increases in both peripheral and central inflammation, which have been associated with changes in sleep behavior. Furthermore, interventions to modulate inflammation may improve the quality of life for both TBI and AD patients. One intervention to reduce inflammation and TBI induced behavioral changes is remote ischemic conditioning (RIC). In our hands, RIC can reduce the peripheral component of TBI-induced inflammation, particularly, in female mice. In the current study, we hypothesized that diffuse TBI would significantly increase markers of inflammation and sleep behavior similarly to AD and modulation of inflammation through RIC would reduce changes in cognitive and sleep behavior.

Methods: Female 18- month 3xTg-AD (B6;129-Psen1 Tg[APP^{Swe},tauP301L]1Lfa) and wild type mice were singly housed in non-invasive, piezoelectric sleep cages for three days for baseline measurements. Mice were removed from cages for baseline blood draws through the submandibular vein. After baseline blood draws, wild-type mice received a midline fluid percussion injury (mFPI) to induce a concussive like brain injury. One hour after injury, half of the uninjured 3xTgAD and brain- injured wild-type mice received a 4x5 minute sessions of RIC with 5 minute reperfusion in between each session. Mice were then returned to their cages for continued sleep measurement. After 24 hours, all mice were taken out of sleep cages for blood draws to measure peripheral inflammatory markers and for a second RIC treatment. After RIC, all mice were put back into sleep cages for three days of uninterrupted sleep. Mice were, given one final RIC treatment and tested for anxiety and cognitive behaviors using open field and novel object recognition testing, respectively. Mice were then euthanized and blood, brains, and spleens were collected for analysis for inflammatory markers.

Results: Both wild-type brain injured mice and 3xTg-AD mice had an increase in the percentage of sleep during the dark cycle the day after injury and RIC treatment compared to naive controls. There were differences in IL-6 expression in plasma. However, there were significant difference in neutrophil populations in the blood and spleen at the terminal time point between wild-type brain injured mice and 3xTg-AD mice.

Conclusions: Discovering the exact inflammatory mechanism that links TBI, AD, and changes in sleep behavior can be used to elucidate mechanisms of AD pathophysiology. Further analysis and more chronic studies will be necessary to determine this inflammatory link.

Poster 59

TARGETING RIPK3-MLKL PROTEIN-PROTEIN INTERACTIONS IN NECROPTOSIS. Sanchez J. Gokhale V, Oddo S, Khanna M. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Cell death is a necessary biological process required for proper development, homeostasis, and other biological roles. Recent studies have shown a particular cell death pathway termed necroptosis to be involved in many neurodegenerative diseases such as Alzheimer's disease. Necroptosis is a programmed form of necrosis that is activated by inflammation or other cellular responses. There are three key regulatory proteins that play a role in activating necroptosis: RIPK1, RIPK3, and MLKL. RIPK1 and RIPK3 are kinases that form the necrosome that phosphorylate MLKL to induce necroptosis. Activated MLKL is known to cause the breakdown of cellular membranes. In order to identify possible compounds that may inhibit necroptosis, we targeted a binding pocket within RIPK3 to disrupt RIPK3-MLKL protein-protein interactions. Mutations of F373 in MLKL have been shown to abolish binding of MLKL to RIPK3 as F373 in MLKL is known to bind within this targeted RIPK3 pocket. Therefore, we performed an in silico docking experiment using the Schrodinger suite of programs with 50,000 drug-like molecules from Chembridge against the RIPK3 binding pocket (pdb: 4m69) in order to disrupt MLKL binding.

Methods: To accurately and quickly quantify TNF- α induced cell death via necroptosis within cell populations and any inhibitory effects from the virtually identified 13 compounds, FACS was used in combination with apoptotic inhibitors (Z-VAD-fmk and SM-164) in HT-29 cells. Cells were stained with Annexin V and Propidium Iodide (PI). HT-29 cells were induced to undergo necroptosis with 25 ng/mL TNF- α , 20 μ M Z-VAD-fmk, and 0.1 μ M SM-164 for 7 hrs while treating cells with 100 μ M of the identified compounds that might inhibit necroptosis. In order to measure target engagement of the compounds that inhibited necroptosis in a cellular context, Cellular Thermal Shift Assay (CETSA) was employed which involves treating cells with 100 μ M compound followed by heating on a temperature gradient to denature and precipitate proteins. Cells were lysed with repeated freezing and thawing cycles (3 times) before centrifugation in order to separate cellular debris and aggregates from soluble proteins. The isolated soluble protein was detected via western blot to quantify the apparent aggregation temperature (Tagg).

Results: Of the 13 compounds identified by in silico docking that could possibly disrupt the protein binding interface, two compounds are decreasing the amount of necroptosis observed in HT-29 cells as measured by flow cytometry. The lead compounds were used to create a dose response curve to identify the Tagg and currently indicate protein stabilization by implying binding of the compounds to RIPK3.

Conclusions: We are further testing necroptosis inhibition with other compounds and will subsequently modify these early leads to improve affinity and necroptosis inhibition. The identification of these small molecules that are showing early signs of inhibiting necroptosis-signaling pathway are promising potential therapeutic leads for Alzheimer's disease.

Poster 60

GENDER DIFFERENCES IN ALZHEIMER'S DISEASE: BRAIN ATROPHY, SYNAPTIC LOSS, HISTOPATHOLOGY BURDEN AND COGNITION. Serrano G, Walker J, Oliver J, Nelson C, Glass M, Arce R, Intorcchia A, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Multiple studies have suggested that females are affected by Alzheimer's disease dementia (ADD) more severely than males. Our previous study showed that, when affected by ADD, females progress more often to severe cognitive dysfunction, associated with more severe neurofibrillary degeneration and greater proportional loss of brain weight. In this study we wanted to investigate if gender differences observed with respect to ADD brain weight loss were due to axonal loss or presynaptic, postsynaptic pruning, and their possible molecular pathways.

Methods: Non-demented controls (ND, n=55) and AD subjects (n=55) from both genders were selected by a database search of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Case selection aimed to avoid differences in age and ADD pathology density between genders. Grey and white matter from frontal and temporal cortex were dissected for protein and RNA extraction. Quantification of presynaptic protein SNAP25, postsynaptic protein PSD95, phosphorylated neurofilament and degraded myelin basic protein complex (dMBP) using enzyme-linked immunosorbent assays (ELISA). Molecular pathways related to synaptic pruning were explored using RT-qPCR for GFAP, IBA1, CX3CR1, CX3CL1 (Fractalkine), SLC1A3 and C1QA.

Results: SNAP25 and PSD95 protein expression were significantly reduced in females with ADD when compared to both their ND control counterpart as well as males with ADD ($p < 0.05$). Additionally, dMBP protein levels were significantly increased in the white matter of females with ADD as compared to their ND control counterparts ($p < 0.05$). Phosphorylated neurofilament protein expression in grey matter was not significantly different between groups, but it was significantly increased in the white matter of ADD subjects ($p < 0.05$); no gender differences were observed. Additionally, GFAP and CX3CL1 RNA expression were significantly reduced in females with ADD when compared to their ND control counterpart. No further differences were observed in any other gene probed in this experiment.

Conclusions: These data together suggest that gender differences in ADD brain weight loss might be largely due to differential presynaptic and postsynaptic terminal loss rather than whole neuronal and/or axonal loss. Previous studies, mainly in animals, suggest that neuronal synaptic loss might be due to pruning deficiencies in microglia and/or astrocytes. Our study only investigated a small set of genes that might be involved in synaptic loss, but our results suggest that astrocytes, and not microglia, might be impaired in females with ADD.

Poster 61

SINGLE-CELL ANALYSIS IN HUMAN BRAIN NEURODEGENERATIVE DISEASE. Serrano G, Intorcchia A, Walker J, Cutler B, Glass M, Arce R, Piras I, Talboom J, Oliver J, Sue L, Lue L, Huentelman MJ, 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.

Methods: In this ongoing project we have investigated multiple methods for the generation of single cell suspensions in fresh human brain. We used various combinations of enzymatic and mechanical dissociation techniques all with the main objective to maximize recovery of morphologically and biochemically intact separated cells. Characterization of the single cell suspensions was done in paraffin-embedded sections stained with H&E, by immunophenotyping with antibodies specific for neurons (MAP2 and/or NeuN), astrocytes (GFAP) and microglia (Iba-1), and also by fluorescence-activated cell sorting (FACS) utilizing the same antibodies. Additionally, we compared extracted RNA from the cell suspensions with RNA from adjacent intact cortical tissue, 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. Delta-delta RT-qPCR analysis suggested that neuronal NEU-N and astrocyte GFAP RNA expression does not seem to be different between dissociated cell suspensions as compared to the whole-tissue homogenates, while IBA1 RNA expression seems to be upregulated in the dissociated cell suspensions. Furthermore, 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). Multiple cell-specific sequenced genes showed up-regulation in the dissociated cell preparations as compared to the whole cortical homogenates, but this was particularly more noticeable in microglia-specific genes, where almost 50% of the sequenced genes showed up-regulation.

Conclusions: Currently we are capable of producing single cell suspensions with full representation of different brain cell types together with RNA quality suitable for use in biochemical analysis. However, our data suggests that our methodology used to generate dissociated cell preparations, despite using hypothermic conditions, probably affects gene expression, especially on cell types that are more reactive to injury such as microglia.

Poster 62

CARDIAC SYMPATHETIC DENERVATION AND SYNUCLEINOPATHY IN ALZHEIMER DISEASE AND LEWY-TYPE-SYNUCLEINOPATHIES. Shprecher DR, Callan M, Cutler B, Serrano G, Adler CH, Shill HA, Caviness JN, Sabbagh MN, Belden CM, Driver-Dunckley E, Mehta SH, Sue LI, Davis KJ, Zamrini E, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Dementia with Lewy Bodies (DLB) Consortium clinical diagnostic consensus criteria have high specificity but low sensitivity. Even in specialist research settings, less than 50% of subjects neuropathologically confirmed as DLB are diagnosed during life, with the most common misdiagnosis reported as Alzheimer's disease (AD). Furthermore, comorbid Lewy body (LB) pathology is very common in AD; up to 60% of AD subjects also have Lewy-type-synucleinopathy (LTS) at autopsy. Some of these are subjects that meet criteria to receive both diagnoses, AD and DLB, but most have LTS that does not meet density and distribution criteria for DLB and are hence termed Alzheimer's disease with Lewy bodies (AD-LB). This is a critical concern for AD clinical trials, as subjects with both AD and LTS may be resistant to therapeutic agents targeting only AD pathology. Clinical and tissue studies have shown cardiac sympathetic denervation in Parkinson disease and dementia with Lewy bodies, potentially making these clinically separable from AD with cardiac nuclear imaging, but this has not been adequately explored in AD-LB.

Methods: In order to determine if AD-LB subjects show sympathetic cardiac denervation, we analyzed epicardial and myocardial tissue from autopsy-confirmed cases using immunostaining for tyrosine hydroxylase (TH) for sympathetic nerve fibers and neurofilament (NF) for total nerve fibers. Subjects included 19 PD, 19 AD-DLB, 20 AD-LB, 12 AD, 12 progressive supranuclear palsy (PSP), 30 incidental Lewy body disease (ILBD) and 22 controls without LTS. We tested the hypothesis that AD-LB will be distinguishable from AD without LB by the loss of cardiac noradrenergic nerve fibers, supporting the feasibility of clinically separating these conditions using cardiac nuclear imaging. Nerve fiber density was graded on a 0-3 point Likert scale, (0=absent, 1=sparse, 2=moderate, 3=numerous).

Results: Kruskal-Wallis analysis of variance between groups indicated a significant difference ($p < 0.01$) of TH staining between the groups and subsequent pair-wise Mann-Whitney analysis showed that PD ($p < 0.05$) and AD-DLB ($p < 0.01$) subjects have significantly reduced TH fiber density as compared to controls; while AD-LB and PSP showed no differences. PD and AD-DLB subjects also showed significant myocardial losses of NF protein-immunoreactive nerve fiber bundles as compared to controls ($p < 0.01$) and both groups showed high LTS densities ($p < 0.0001$). Cardiac LTS densities correlated significantly with brain LTS ($p < 0.001$); while cardiac TH- and NF-immunoreactive nerve fiber densities were negatively correlated with the densities of both brain and cardiac LTS, and UPDRS scores ($p < 0.05$).

Conclusions: The clear separation of AD-DLB from controls, based on cardiac TH fiber density, is the first report of a statistically significant difference between these groups. Our data do not indicate a significant sympathetic cardiac denervation in AD-LB, but strengthen the rationale for using cardiac nuclear imaging with a noradrenergic radioligand, ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) to separate AD from AD with DLB, an important concept as most cases of AD/DLB are not recognized as such during life.

Poster 63

PILOT STUDY COMPARING HOME SLEEP PROFILER TO IN-LABORATORY POLYSOMNOGRAM FOR REM SLEEP BEHAVIOR DISORDER DIAGNOSIS. Shprecher D, Levendowski D, Guevarra C, Lazarz G, Lee-Iannotti J. Banner Sun Health Research Institute; University of Arizona; Advanced Brain Monitoring; Arizona Alzheimer's Consortium.

Background: Diagnosis of REM sleep behavior disorder (RBD) is strongly associated with risk of synucleinopathy, particularly Lewy body dementia and Parkinson disease, but requires PSG for confirmatory diagnosis. Capturing RBD during a one-night PSG opportunity can be challenging due to night-to-night variability of dream enactment behaviors and can be costly to repeat.

Methods: During an overnight PSG (with seizure and four-limb RBD protocol), we simultaneously collected Sleep Profiler data on 6 subjects recruited with recurrent dream enactment behavior but no evidence of neurodegenerative disease. Independent sleep reviewers analyzed the data from each source.

Results: Sleep efficiencies by PSG and SP were 85.3% and 84.6%, respectively, while the median sleep times were identical (358 min). The median sleep onset latency for the PSG was 16 min and 22 min for the SP with a median difference of 5 minutes. The PSG and SP REM percentages were 14.5% and 13%, with a median difference of 1.3%. The SP appeared to under-report N3 sleep and over-report N1 sleep. Of the 6 subjects, four had REM sleep without atonia (RSWA) and concordant dream enactment on both the PSG data and the SP data, but comparisons were not completely blinded. Of the 4 subjects with RSWA, 3 had newly diagnosed obstructive sleep apnea (mean AHI 13.3, range 9.7-16.2/hr).

Conclusions: The Sleep Profiler is worthy of larger scale validation studies to show equivalence with PSG in diagnosis of RBD. We suggest the SP be configured to include capabilities to measure airflow signals to screen for sleep apnea and monitor movement in all four limbs for better detection of RSWA. Such studies should also measure potential benefits in terms of cost and feasibility of recruitment of RBD subjects into neurodegenerative disease research trials.

Poster 64

NEUROANATOMICAL CHANGES OF THE OLFACTORY BULB OF SUBJECTS WITH PARKINSON'S DISEASE. Sinakevitch I, Serrano G, Beach TG, Adler CH, Smith BH. Arizona State University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Olfactory dysfunction is one of the first signs of Parkinson's disease (PD). The aim of this study is to examine and compare the cytoarchitecture of the OB expressing phosphorylated alpha-synuclein (p-syn) in subjects with clinically-manifest PD. The second aim is to study and compare the morphological changes that occur in OB networks (neurons and glia) in three subjects with advance stages of PD. Given that a healthy human olfactory bulb (OB) has a high capacity for regeneration, the objective of this aim was to formulate a hypothesis about how different types of cells might be involved in the possible loss of regenerative abilities of OB during disease progression.

Methods: Paraffin OB sections were obtained from the Arizona Study of Aging and Neurodegenerative Disorders/Brain and Body Donation Program. Sections were stained with a rabbit polyclonal antibody against p-syn to label the pathology associated with PD. Antibodies against glial fibrillary acidic protein (GFAP) and glutamine synthetase were used to label glial cells (oligodendrocyte, astrocyte and olfactory ensheathing cells (OEC)). Anti-doublecortin (DCX) antibodies were used to label a microtubule-associated protein which is characteristic marker of neuronal precursor cells and immature neurons.

Results: We analyzed 22 postmortem olfactory bulbs from patients with PD. We found that PD has p-syn most frequently in the olfactory tract, anterior olfactory nucleus and internal plexiform layer. Other areas are additionally affected in some individual, including the granule cell and mitral cell layers, the external plexiform layer and the most caudal glomeruli. GFAP-positive cell (OEC included) have dramatic changes in morphology in some subjects, with reductions in the extent of processes. The number of immature neurons expressing DCX is often dramatically reduced in some subjects, especially in the mitral cell layer and in the anterior olfactory nucleus, and this may reflect an advanced stage of PD. This pilot study shows that p-syn pathology in the OB is most consistently found in the olfactory tract, the anterior olfactory nucleus of OB and internal plexiform layer. In some subjects, p-syn pathology is also found in additional OB layers and in caudally-located glomeruli.

Conclusions: These neuroanatomical data suggest that the OB slowly might lose capacity for neurodegeneration and repair because of dramatically reduced numbers and morphology of OEC cells, glial cells and newly-born neurons. Our results provide a clear hypothesis for further testing and confirmation on a larger group of subjects, including more clinically normal controls.

Poster 65

AMELIORATION OF NEURODEGENERATIVE CHANGES IN MICE UNDERGOING TRANSVERSE AORTIC CONSTRICTION BY MAS AGONISTS. Soto M, Jadhav S, Butler R, Gaffney K, Rodgers K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is associated with loss of memory and executive function. Several studies have shown a direct correlation between hypertension and an increased incidence of AD like symptoms, including cognitive deficits and increased A β deposition. Most interestingly, individuals who are on anti-hypertensive medications (angiotensin receptor blockers and angiotensin converting enzyme inhibitors) targeting the Renin-Angiotensin System (RAS), have a reduced risk of developing AD. Recently, the protective arm of RAS, angiotensin (1-7)[A(1-7)]/Mas receptor/angiotensin converting enzyme 2, is reduced in AD patients. Mas activation increases cognition and is cardioprotective. Thus, we hypothesized that Mas agonists could help ameliorate AD-like pathology.

Methods: Mice underwent transaortic constriction (TAC), a mouse model of heart failure and hypertension. One week after induction of TAC, mice started treatment with saline or one of three Mas agonists. Seven weeks after surgery, the cardiac function was assessed by echocardiography followed by assessment of their cognitive abilities (8 weeks) using novel object recognition. Upon necropsy, brain, heart, bone marrow and blood were collected.

Results: TAC surgery decreased cognition and increased mitochondrial oxidative stress (OS) in neurons and microglia. Treatment with Mas agonists increased cognition and reduced brain OS. Further, treatment with Mas agonists reduced inflammatory cytokines in the hippocampus

Conclusions: These data support the development of Mas agonist for the treatment of neurodegenerative diseases.

Poster 66

INFLUENCE OF GENISTEIN DIET AND EXERCISE ON WEIGHT LOSS AND MARKERS OF ALZHEIMER'S DISEASE IN HIGH FAT-HIGH SUCROSE-FED MICE. St Aubin C, Fisher A, Oddo S, Caccamo A, Al-Nakkash L. Midwestern University; Arizona State University; Arizona Alzheimer's Consortium.

Background: Chronic consumption of a western diet (high fat with high sugar, HFHS) is associated with metabolic syndrome, insulin resistance, type 2 diabetes, cardiovascular disease, loss of bone mass, inflammation, cognitive decline and increased risk of developing neurodegenerative diseases like Alzheimer's (AD). Genistein, a naturally occurring isoflavone found in soy, improves insulin sensitivity, and exerts anti-inflammatory and neuroprotective properties. 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 and thereby limit progression of AD in C57BL/6J male and female mice.

Methods: C57BL/6J 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 HFD consisted of 60% saturated fat, 20% carbohydrate, 20% protein. Drinking water contained sucrose and fructose. Moderate exercise comprised daily treadmill running for 150 minutes/week for 12 weeks.

Results: In males, body weight was reduced 12-18% ($P<0.05$) in Ex or Gen and reduced 42% ($P<0.05$) by Gen-Ex combined compared to HFHS. In females, body weight was decreased 8% with Gen ($P<0.05$) and reduced 16% by Gen+Ex ($P<0.05$). Total protein expression (evaluated by western blot) determined the following effects ($P<0.05$): Gen reduced CT20 expression in females, Ex reduced CT20 expression in males, Gen reduced CP13 expression in males. We are currently assessing whether total IRS1, mTOR, p-mTOR expression is modified by Gen or Ex to correlate improvements in insulin signaling and energy homeostasis.

Conclusions: We conclude that genistein and exercise have sex-dependent effects on HFHS-fed mice: (1) A greater weight loss was noted in males with either Gen or Ex or both, compared to females. (2) Gen reduced CP13 expression, suggestive of Gen's ability to reduce tau phosphorylation in males. We aim to determine mechanistic pathways for these sex-dependent effects and finally to correlate genistein- and exercise-mediated improvements in body weight to markers for AD. Support: Midwestern-Arizona Alzheimer's Consortium.

Poster 67

RELATIONSHIPS BETWEEN BASELINE BRAIN IMAGING BIOMARKER MEASUREMENTS AND AGE IN THE API AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE COLOMBIA TRIAL. Su Y, Romenets SR, Tariot PN, Sink KM, Clayton D, Hu N, Guthrie H, Smith J, Cho W, Langbaum JB, Thomas RG, Giraldo-Chica M, Tobon C, Acosta-Baena N, Navarro A, Piedrahita F, Alvarez S, Chen K, Goradia D, Thiyyagura P, VanGilder PS, Luo J, Ghisays V, Lee W, Malek-Ahmadi MH, Protas HD, Chen Y, Ho C, Suliman S, Quiroz YT, Paul R, Lopera F, Reiman EM, API ADAD Colombia Trial Group. Banner Alzheimer's Institute; Grupo de Neurociencias de Antioquia of Universidad de Antioquia; Genentech Inc.; Roche Products Ltd; University of California; Hospital Pablo Tobon Uribe; Harvard Medical School and Massachusetts General Hospital; Arizona Alzheimer's Consortium.

Background: We previously used data from 54 cognitively unimpaired and impaired 20-59 year-old presenilin 1 (PSEN1) E280A mutation carriers and noncarriers from the world's largest autosomal dominant kindred (median age of 44 at mild cognitive impairment [MCI] onset) to characterize associations with age and estimated ages at onset (AAO) of brain imaging and fluid biomarker abnormalities in the mutation carrier group (Fleisher, 2015). Here, we analyzed baseline brain imaging measurements of amyloid- β ($A\beta$) plaque deposition, precuneus glucose hypometabolism, and hippocampal volume from 242 cognitively unimpaired 30-53 year-old PSEN1 E280A mutation carriers and non-carriers in the Alzheimer's Prevention Initiative (API) ADAD Colombia Trial, characterized their relationships with age, and estimated their AAO in the mutation carrier group.

Methods: Baseline florbetapir PET, fluorodeoxyglucose (FDG) PET, and volumetric MRI images from 167 mutation carriers and 75 age matched noncarriers were analyzed using previously established pipelines (Fleisher, 2015; Su 2015) to characterize 1) $A\beta$ plaque burden using mean-cortical-to-pontine florbetapir standard uptake value ratios (SUVRs), 2) cerebral glucose hypometabolism using precuneus-to-whole brain FDG SUVRs, and 3) neurodegeneration using hippocampal-to-intracranial volume ratios. Linear regression models were used to characterize biomarker associations with age in the two genetic groups. AAOs, defined as the age at which mean biomarker values diverge significantly between the mutation carrier and non-carrier groups, were estimated using both approximate t-tests and the 95% confidence interval (CI) band of age associations.

Results: AAO of mean cortical increases in florbetapir SUVR, decreases in precuneus FDG SUVR, and declines in hippocampal volume were less than 30 years, 36 (95%CI 30-40) years, and 42 (95% CI 37-48) years, respectively.

Conclusions: This study provides information about associations between baseline brain imaging measurements and age in a large number of cognitively unimpaired PSEN1 E280A mutation carriers and non-carriers from the API ADAD Colombia Trial. Findings are roughly consistent with observational studies of ADAD (Bateman, 2012; Fleisher 2015), and the extent to which they support the hypothetical ordering of biomarker changes in preclinical AD (Jack 2018) will be presented.

Poster 68

COGNITION IS ASSOCIATED WITH SEVERAL HEALTH AND LIFESTYLE FACTORS: MINDCROWD FOLLOW-UP SURVEY RESULTS. Talboom JS, Håberg AK, De Both MD, Naymik MA, Schrauwen I, Lewis CR, Bertinelli SF, Hammersland C, Myers AJ, Hay M, Barnes CA, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Norwegian University of Science and Technology; University of Miami; University of Arizona; Arizona State University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Many health and lifestyle factors are thought to alter age-related cognitive decline. Many studies aiming to dissect out these effects are underpowered due to low sample sizes. To overcome this, we asked consenting participants who completed the initial 10-minute MindCrowd test/survey to fill out a 15-minute follow-up survey. This survey asked 119 total questions spanning many health and lifestyle choice areas including: Alzheimer's and cardiovascular (CV) disease history, contraception and menopause, sleep habits, smoking, movement disorders, and diet.

Methods: We developed a web-based paired-associates learning (PAL) and simple visual reaction time (svRT) task and tested over 92,000 individuals between the ages of 18-85. Next, we developed a 215-question follow-up health and lifestyle factor survey. The follow-up survey questions were based on previously validated survey questions wherever possible. Over 10,000 of the 92,000 original MindCrowd participants completed the follow-up survey. Answers to the survey questions served as either 1) single variable or 2) composite variable predictors of PAL and/or svRT scores in statistical models.

Results: Several notable associations between survey questions, PAL, and svRT scores were found. In women, hormonal contraception and menopause choices were associated with both higher and lower PAL scores. Men were associated with lower svRT scores when compared to women. In both men and women, the number of spoken languages was associated with higher PAL scores. Akin to earlier studies, we noted an inverted-U shaped function concerning self-reported stress and PAL performance. Lastly, a composite of five CV variables demonstrated that higher CV was associated with lower PAL scores.

Conclusions: This study suggests that several health and lifestyle factors modify the trajectory of an individual's cognitive performance across their lifespan.

Poster 69

NPTX2 KNOCKOUT RATS: A NOVEL MODEL FOR PROTECTION OF SYNAPTIC FUNCTION IN AGING AND DISEASE. Terrazas A, Zampare M, Carey N, Bohne K, Do L, Trouard T, Worley PF, Pyon W, Barnes CA. University of Arizona; Johns Hopkins School of Medicine; Arizona Alzheimer's Consortium.

Background: Neuronal Pentraxin 2 (NPTX2) is an immediate early gene involved in binding and clustering of AMPA receptors at synapses and mediates homeostatic scaling of circuits. In the hippocampus, this involves the synapses of excitatory pyramidal cells onto inhibitory parvalbumin-containing basket cells. Thus, low NPTX2 levels may tilt the excitatory-inhibitory balance of hippocampal circuits toward excitation. NPTX2 has been proposed to play a role in protection of synaptic function in aging and the progression of Alzheimer's disease (AD; Xiao et al., 2017), and levels of NPTX2 in brain are predictive of whether individuals with pathologically defined brain levels of amyloid plaques and tangles are cognitively symptomatic (demented) or asymptomatic (cognitively normal). That is, if levels of NPTX2 are high in brain, as in the case of normal controls and asymptomatic AD, then cognition is intact – if NPTX2 is low in brain, as in symptomatic AD, the individuals are demented. In fact, NPTX2 levels in CSF are a more sensitive predictor of cognitive status than are markers for amyloid or tau (Xiao et al., 2017).

Methods: To investigate this role of NPTX2, we have begun to examine behavior, brain structural integrity by high resolution MRI, and function with single unit and EEG recordings from area CA1 of the hippocampus in NPTX2 knockout (NPTX2 KO) rats compared to wild-type (WT) controls. The larger study will examine these variables across the lifespan at 6, 12, 18 and 24mo. We report here preliminary data from the young group.

Results: So far, we do not detect overall performance differences between the young NPTX2 KO rats in spatial or working memory versions of the Morris watermaze, in motor behavior on a rotarod, or in anxiety tests using the elevated zero maze. Interestingly, the NPTX2 KO rats exhibited twice as many interruptions of on-going behavior during the spatial and working memory tasks. In the spontaneous object recognition task, the WT animals spent more time than did NPTX2 KO animals with the novel object (mean ratio novel/familiar, KO= 1.26 +/- 0.11, WT = 2.10 +/- 0.05), suggesting poorer overall recognition memory. Additionally, the NPTX2 KO rats explored the objects considerably less than did WT rats (mean number object alternations, KO = 4.1 +/- 3.3; WT = 10.0 +/- 3.0). Hippocampal volume in this young age group of NPTX2 KO rats was not different compared to WT controls (mean normalized hippocampal volume KO = 0.041 +/- 0.0, WT = 0.040 +/- 0.0).

Conclusions: Electrophysiological studies are on-going. The results of these experiments should lead to a better understanding of NPTX2's potential role in the protection of synaptic function during aging and in neurodegenerative disease.

Poster 70

HIPPOCAMPAL MEDIATION OF SUBJECTIVE MEMORY COMPLAINTS DIFFERS BY HYPERTENSION STATUS IN HEALTHY OLDER ADULTS. Van Etten EJ, Bharadwaj PK, Nguyen LA, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Subjective memory complaints may be an important early indicator of cognitive aging. We previously found that in healthy older adults with hypertension, having mild memory complaints was associated with poorer objective memory performance than in those without memory complaints, but this difference was not observed in those without hypertension (Nguyen et al., 2016). In the present study, we sought to investigate whether differences in hippocampal volume underlie subjective memory complaints, if this relationship differs by hypertension status, and how the association is related to objective memory performance in healthy older adults.

Methods: A cohort of 194 older adults [99F/95M, mean \pm sd age = 71.1 \pm 9.7, mean \pm sd Mini-Mental State Exam = 28.9 \pm 1.2, hypertension (yes/no) = 69/125], 50 to 89 years of age, completed a scale of subjective memory complaints and a battery of neuropsychological tests. T1-weighted 3T volumetric MRIs were processed using Freesurfer (v6.0) software to obtain right and left hippocampal volumes. Total intracranial volume (TIV) was computed using T1 scans with SPM12 and white matter hyperintensities (WMH) were computed using T1 and T2 FLAIR scans and a lesion segmentation toolbox. Mediation analyses were performed using PROCESS macro software in SPSS (Hayes, 2012).

Results: Analyses revealed that the mediation of the relation between age and mild subjective memory complaints by right hippocampal volume was moderated by hypertension status (-.03 (SE= .01), 95% CI, [-.06, -.01]). These findings remained significant after including gender, education, hypertension duration, WMH volume, and total recall on word list learning test as covariates. There were no significant mediation effects of the relation between age and memory complaints for left hippocampal volume with or without covariates. Additionally, a sequential mediation model in individuals with hypertension revealed that age predicted right hippocampal volume, which then predicted subjective memory complaints, and in turn predicted objective memory performance (-.16 (SE= .08), 95% CI, [-.40, -.06]). There were no significant sequential mediation models for left hippocampal volume or in individuals without hypertension.

Conclusions: These results indicate that, in healthy older adults, the combination of mild subjective memory complaints and hypertension has an anatomical substrate, reflected by reduced right hippocampal volume, which in turn leads to differences in objective memory performance. Together, these findings suggest that mild memory complaints may provide an early marker of cognitive aging, when observed in the context of hypertension, a common age-related vascular risk factor.

Poster 71

NECROPTOSIS CONTRIBUTES TO TAU MEDIATED NEURODEGENERATION. Vartak RS, Rodin A, De Court B, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Tau accumulation is associated with multiple neurodegenerative disorders including Alzheimer's disease, frontotemporal dementia with Parkinsonism, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Down syndrome, and Pick's disease. Elucidating the mechanisms of tau-mediated neuronal loss is a fundamental step towards unveiling the pathogenic mechanisms of these diseases.

Methods: We used postmortem human tissue and mouse models to show up regulation of necroptosis markers. To probe for a cause-effect link, we injected an adeno-associated virus expressing mutant tau into the brain of wild type mice and necroptosis deficient mice. We also pharmacologically reduced necroptosis and probed its effect on neuronal loss in tau transgenic mice.

Results: We report that tau caused marked neurodegeneration by activating necroptosis. Indeed, genetically and pharmacologically lowering necroptosis activation reduced tau-induced neuronal loss and tau phosphorylation. Mechanistically, we found that inhibiting mTOR activity mitigated tau-induced necroptosis and neuronal loss.

Conclusions: Our findings show that mutant tau activates necroptosis, which in turn contributes to tau-induced neurodegeneration.

Poster 72

HYPOTHERMIA DURING ISOFLURANE ANESTHESIA DOES NOT AGGRAVATE MEMORY IMPAIRMENTS IN AN ALZHEIMER'S DISEASE-LIKE CONDITION INDUCED BY INTRABRAIN STREPTOZOTOCIN IN RATS. Vizin RCL, Harris GT, Almeida MC, Carrettiero DC, Romanovsky AA. St. Joseph's Hospital and Medical Center; Federal University of ABC; Arizona State University; Arizona Alzheimer's Consortium.

Background: Hypothermia and anesthesia are considered risk factors for Alzheimer's disease (AD). This is supported by studies showing that: (1) hypothermia and anesthesia promote tau-protein hyperphosphorylation (a hallmark of AD) and memory impairment in healthy aged rodents; (2) isoflurane promotes tau-protein hyperphosphorylation and memory impairment in some animal models of AD; (3) humans show transient memory impairments after surgery or episodes of hypothermia. We study whether anesthesia-induced hypothermia affects memory in AD-like condition in rats.

Methods: Male Wistar rats (3-month-old) were subjected to hypothermia induced by 1.5-2% isoflurane anesthesia for 3 h without the use of a heating pad (hypothermic groups). Control (normothermic) rats were kept on a heating pad during anesthesia, and their rectal temperature was maintained at $37.5 \pm 0.5^\circ\text{C}$. At 30 min after the onset of anesthesia, rats were subjected to a bilateral intracerebroventricular injection of streptozotocin (STZ, 1 mg/kg) to produce an AD-like condition or to the vehicle (0.05 mol/L citrate buffer, pH 4.5, 2 μL). Spatial working memory was evaluated using the Morris water-maze (days 3-28 postsurgery) and Y-maze (day 30) tests. Recognition memory was evaluated by a novel object-recognition test (day 31).

Results: In the Morris water-maze test, hypothermic and normothermic STZ-injected rats showed similar impairments in spatial working memory, as compared to hypothermic or normothermic vehicle-injected rats, respectively. In the Y-maze test, normothermic STZ-injected rats shown a deficit in spatial working memory, as compared to normothermic vehicle-injected rats, but this effect did not occur in hypothermic STZ-injected rats. In the novel object-recognition test, recognition memory was impaired in normothermic STZ-injected rats compared to normothermic vehicle-injected rats, but no effect was observed in hypothermic STZ-inject rats.

Conclusions: Hypothermia during isoflurane anesthesia does not aggravate the STZ-induced deleterious effects on memory in rats.

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Poster 73

CORRELATION OF PRESYNAPTIC AND POSTSYNAPTIC PROTEINS WITH PATHOLOGY IN ALZHEIMER'S DISEASE. Walker J, Glass M, Arce R, Oliver J, Intorcica A, Nelson C, Papa J, Arce A, Vargas D, Sue L, Beach TG, Serrano G. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Synaptic transmission is essential for nervous system function and its dysfunction is a known major contributor to dementia. The correlation between synaptic loss and Alzheimer's disease dementia (ADD) was established in the late 1980s using electron microscopy (EM) techniques. These methods are precise but are limited by the laborious tissue processing required and by their practical restriction to extremely small tissue samples. In the 1990s, immunochemical quantification became possible and confirmed 30-50% neocortical synaptic protein losses in ADD, but there has not yet been a comprehensive profiling of different synaptic proteins in different brain regions in ADD.

Methods: In this study we quantified densities of two synaptic proteins, the presynaptic protein SNAP25 and the postsynaptic protein PSD95 using enzyme-linked immunosorbent assays (ELISA). Grey matter from cingulate, hippocampus and frontal, visual and entorhinal cortex were dissected for protein extraction from non-demented controls (ND, n=25) and ADD subjects (n=25). Cases were selected by a database search of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Case selection aimed to avoid differences in age and include different levels of ADD pathology.

Results: Our analysis demonstrates that SNAP25 and PSD95 protein expression were significantly reduced in ADD entorhinal cortex as compared to ND controls ($p < 0.0001$). No other brain region showed significant changes in both SNAP25 and PSD95. Significant reductions of presynaptic SNAP25 alone were found in frontal and visual cortex but not in hippocampus and cingulate gyrus. Paradoxically, significant reductions in postsynaptic PSD95 were present in hippocampus and cingulate gyrus but not in frontal and visual cortex.

Conclusions: Caution should be taken in interpreting changes in synaptic protein expression as synaptic loss, but to our knowledge this is the largest set of cases across multiple brain regions used to study synaptic protein expression in ADD. Our results suggest that synaptic transmission in the entorhinal cortex of ADD patients is severely affected, most probably because this brain region is one of the earliest affected areas and by the time of clinically-manifest dementia has very high densities of neurofibrillary tangles. The entorhinal area is the main interface between the hippocampus and neocortex, making this area crucial for memory formation and consolidation.

Poster 74

A SUBSPACE DECOMPOSITION-BASED UNIVARIATE NEURODEGENERATIVE BIOMARKER SYSTEM. Wang G, Su Y, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Ludong University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: A univariate and personalized morphological biomarker based on MRI with strong statistical power will benefit clinical diagnosis and prognosis. Yet, few such biomarkers have been developed, especially those that are accurate to represent the structural features that are associated with the AD disease. To solve this problem, we propose a subspace decomposition method that may be capable of generating a univariate neurodegenerative biomarker reflecting the morphological changes induced by AD related diseases.

Methods: Participants were 119 A β positive AD baseline patients (age: 74.39 \pm 8.26 years, MMSE:23.03 \pm 2.10) and 68 A β negative cognitive unimpaired (CU) baseline subjects (age: 75.80 \pm 5.59, MMSE: 29.01 \pm 0.98). We adopt our hippocampal morphometry system to compute hippocampal morphometry features. We further apply our novel subspace decomposition algorithm to extract low-rank common group structures from the hippocampus radial distance (RD) data of these two groups. Then the group difference analysis is conducted to form the region-of-interest (ROI) based on the permutation t-test method (pvalue< 0.00001). Our subspace decomposition algorithm ensures that the selected areas are connected and smooth. Based on the discovered subregional ROIs, the voxel-wise AD atrophy weights between the A β positive AD group and the A β negative group are computed and the atrophy degrees of a new testing individual subject can be estimated. Further, a univariate neurodegenerative biomarker, Morphological Structure Single Index (MSSI), is defined by the voxel-wise summation across all the voxels on the predefined ROI with the predefined of AD atrophy weights and the atrophy degree of the testing individual.

Results: We find the subspace decomposition-based MSSIs exhibit better classification power than the RD-based MSSIs and the hippocampal volume data. For the left and right hippocampus of the A β positive AD and A β negative CU groups, the maximum areas under the ROC curves are 0.7196, 95% CI [0.6621, 0.7519] and 0.6849, 95% CI [0.6249, 0.7378] based on RD, and 0.8979, 95% CI [0.8570, 0.9286] and 0.8317, 95% CI [0.7867, 0.8760] based on subspace decomposition, 0.6601 and 0.6275 based on volume data. For longitudinal (baseline and 24m) studies, we found the RD-based and volume-based univariate biomarkers carry less statistical power for the estimation of minimal sample size which is required to detect, with 80% power, a 25% reduction in the mean annual change, using a two-sided test and standard significance level alpha-0.05 for a hypothetical two-arm study (treatment vs. placebo, as advocated by the ADNI Biostatistics Core). We call the estimated sample size as an n80 number. In our results, for left and right hippocampus, the n80s of subspace decomposition-based MSSIs are 104 and 127 for AD, 207 and 217 for MCI, 537 and 611 for CTL, respectively. The n80s of RD-based MSSIs are 1047 and 1609 for AD, 1784 and 1907 for MCI, 2680 and 2989 for CTL. And the n80s of volume are 1693 and 2216 for AD, 2257 and 2535 for MCI, 5987 and 8861 for CTL.

Conclusions: We present a low-rank matrix decomposition algorithm combined with the local sparse constraint which can improve the statistical power for in vivo MR image morphological information analysis. The empirical results demonstrated the potential that the data based on our method may generate the more reliable neurodegenerative biomarkers and apply them in our ongoing preclinical AD research.

Poster 75

IMPACT OF REFERENCE REGION USED TO QUANTIFY AMYLOID BURDEN ON INTERPRETING THE RELATIONSHIP BETWEEN AMYLOID BURDEN AND GENETIC RISK FACTORS OF AD. Wang Q, Del-Aguila JL, Cruchaga C, Reiman EM, Su Y, Arizona State University; Washington University in St. Louis; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Using biomarkers as quantitative endophenotype lead to the identification of novel genetic risk factors of Alzheimer's disease and improved the understanding of the mechanisms behind the genetic risk factors. It is previously reported that a SNP in the IL1RAP gene region (rs12053868) is associated with faster amyloid accumulation based on the analysis of longitudinal florbetapir data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). However, we failed to reproduce that observation using the same dataset, therefore we seek to further investigate the potential cause of the discrepancy.

Methods: Processed florbetapir imaging data (cross-sectional N=647; longitudinal N=469) and the ADNI WGS+Omni2.5M genetic dataset were downloaded from the ADNI database. Global amyloid burden was quantified using cerebellar gray matter (CBLG), brainstem (BS), and eroded subcortical white matter (ESWM) as the reference region. Standard uptake value ratio (SUVR) was also assessed for white matter lesions (WML) in additional to typical target and reference regions. Longitudinal rates of amyloid accumulation and SUVR change were assessed using linear regression. The SNP rs12053868 was extracted from the downloaded genetic data for analysis. The relationship between rs12053868, APOE4 status, amyloid burden, regional SUVRs, and the rates of change were assessed using linear effects modeling.

Results: The association between rs12053868 and rate of amyloid accumulation was significant when ESWM ($p=0.004$) and BS ($p=0.014$) were used as the reference region, but not for CBLF referencing ($p=0.164$). ESWM florbetapir binding was strongly correlated with overall amyloid burden ($r=0.83$, $p<0.0001$) and APOE4 status ($p<0.0001$). WML region florbetapir uptake decreased over time ($p<0.0001$) but ESWM did not show significant longitudinal change ($p>0.05$). The rate of change in WML SUVR also associated with rs12053868 ($p<0.05$) regardless of which reference region was used for the quantification.

Conclusions: Conflicting results were obtained when investigating the relationship between amyloid pathology and genetic risk factors of AD. The results suggest image derived amyloid burden measurements may be influenced by signals unrelated to amyloid accumulation. Further investigation is needed to understand the influence of genetic variation on amyloid pathology and its measurement.

Poster 76

INTERPRETING FLORBETAPIR-PET SCAN RESULTS: ASSESSMENT AND ANALYSIS OF DISCORDANT CASES FROM THE IDEAS STUDY. Weidman D, Ghisays V, Protas H, Luo J, Chen Y, Devadas V, Leger J, Sidarous G, Su Y. Banner Alzheimer's Institute; Banner University Medical Center Phoenix; Arizona Alzheimer's Consortium.

Background: Banner dementia specialists participated in the Imaging Dementia--Evidence for Amyloid Scanning (IDEAS) study, which is examining the impact of Amyloid-PET imaging on clinical decision-making in diagnostically uncertain cases of mild cognitive impairment (MCI) and early dementia. The primary aim of our study was to determine the agreement level between the visual (binary) florbetapir-PET results reported to clinicians and a quantitative assessment of cerebral cortical Amyloid-beta deposition.

Methods: The approved binary result (visually positive or negative florbetapir-PET scan) and a recommended standardized quantification (uptake value ratio) were tabulated, with patient age. Regional visual analysis of discordant cases was undertaken.

Results: 10 of 100 cases (10%) were discordant (90% agreement), using a threshold of amyloid burden accurate for moderate to frequent amyloid neuritic plaque (meeting a criterion for pathological Alzheimer's disease) and 7 cases were discordant (93% agreement), using a lower cutoff threshold proposed for any identifiable cerebral amyloid. Regional visual analysis of the discordant cases revealed potential explanations for discordance.

Conclusions: Although a more clinically heterogeneous patient population, the discordance rate of florbetapir-PET imaging in our investigation is comparable to the results reported in a phase1B drug trial, which recruited patients meeting criteria for prodromal or mild AD, and who underwent florbetapir-PET scanning at screening1. A well trained and experienced radiologist reading the PET scans may account for the high agreement between the visual readings and quantitative assessments. Potential reasons for discordance as outlined are useful to consider, and a quantitative measure of cortical amyloid burden—where feasible—may help in interpreting scan images in intermediate or equivocal cases of amyloid-PET positivity.

Poster 77

INTEGRATING GENOMIC AND IMAGING BIOMARKERS FOR EARLY DETECTION OF ALZHEIMER'S DISEASE. Wu J, Wang P, Nyarige V, Caselli RJ, Wang Y, Wang J. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Early detection and prevention of Alzheimer's disease (AD) can significantly impact treatment options, improve quality of life, and save considerable health care costs as the population ages. Brain imaging has been widely used as diagnostic biomarkers for AD, and 70-80% of sporadic AD can be attributed to genetic risk. ApoE SNP is the most established genetic risk factor for AD, but can only explain part of the heredity; effort on new genetic biomarker is needed. Biomarker discoveries have been extensively studied from either brain imaging or genomics (both DNA and transcriptomics), but not sufficiently done by integrating evidences from both fields. Furthermore, it is not well understood whether adding genomic information will improve the early AD detection from pure brain imaging, or vice versa, and whether the genetic features can be used to interpret molecular mechanisms underlying the dynamic change of AD progression, as measured by imaging and transcriptome.

Methods: We developed a novel computational method to integrate genomics with imaging features for an improved AD risk prediction. We apply our novel algorithms on the publicly available Alzheimer Disease Neuroimaging Initiative (ADNI) cohort (over 200 AD and 600 MCIs and controls, with whole genome sequencing, transcriptomics and imaging data).

Results: We found interesting SNP-gene-regulator, and SNP-gene-imaging feature trios. Further experimental validation will illustrate how AD risk SNPs moderate imaging and gene expression relationships, and find the genetic basis of key imaging biomarkers.

Conclusions: Our computational method can integrate genomic, transcriptomic and imaging data to infer gene regulatory logic, and discover genetic basis that responsible for imaging feature changes. This will help us to elucidate the molecular mechanisms of AD associated SNPs and dysregulated genes, and to identify drug targets for important imaging biomarkers.

Poster 78

SIRTUIN 3 MEDIATES TAU DEACETYLATION. Yin J, Li S, Nielsen M, Beach TG, Guo L, Shi J. Barrow Neurological Institute; The Second Hospital of Hebei Medical University; University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Accumulation of hyperphosphorylated microtubule-associated protein tau is a pathological hallmark of Alzheimer's disease (AD). Acetylation at specific sites of tau reduces its stability, alters its structure and function, and leads to tau aggregation. Emerging evidence show tau acetylation has been observed in AD brain at early Braak stages and is involved in regulating tau early accumulation. The NAD-dependent protein deacetylase Sirtuin3 (Sirt3) deacetylates and regulates multiple proteins function. Inhibition of the deacetylase Sirt3 elevates tau acetylation in primary neurons. Our previous studies have shown that Sirt3 is declined significantly in postmortem brains of patients with AD and this decline is strongly associated with poorer cognition and the severity of Tau pathology. However, the effects of deacetylase Sirtuin 3 (Sirt3) on tau acetylation and its aggregations are unclear. In this study, we hypothesize that Sirt3 may be a regulator for tau acetylation and affect tau accumulation.

Methods: We investigated the protein levels of Sirt3 and tangle tau in human postmortem brains slices from AD, mild cognitive impairment and age- and education-matched cognitively normal subjects, and AD model mice. We also measured tau acetylation levels in hippocampal HT22 cells after Sirt3 knockdown or overexpression.

Results: The level of Sirt3 was inversely related with tau protein in brain slices from both human being and AD model mice. Mechanistically, tau acetylation decreased dramatically with Sirt3 overexpression, while tau acetylation increased after Sirt3 knockdown in hippocampal HT22 cells.

Conclusions: Tau acetylation affected tau function and promoted tau aggregation. Tau acetylation was thought as a potential target for delaying tau pathology. Sirt3 reduction was also associated with the severity of tau pathology. This data provided further evidence that Sirt3 played a role in tau acetylation and could be a potential therapy target to order to alleviate tau aggregation. Together with our previous studies, Sirt3 may play an important role in tau acetylation and could be a potential therapy target to alleviate tau aggregation.

STUDENT POSTER PRESENTATIONS

Poster 79

COGNITIVELY NORMAL OLDER ADULTS SHOW ELEVATED SEMANTIC DETAIL GENERATION FOR MULTIPLE FORMS OF AUTOBIOGRAPHICAL MEMORY RETRIEVAL.

Acevedo-Molina MC, Robertson AC, Teposte M, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: In comparison to young adults, cognitively normal older adults generate more semantic details during episodic autobiographical memory retrieval. However, it remains unclear whether this age-related difference persists when the demands of autobiographical memory retrieval promote the generation of semantic details in a more elaborative way. To address this gap in knowledge, we developed a novel "life chapter" task that involved elaborative autobiographical memory retrieval of semantic detail.

Methods: Twenty young and twenty cognitively normal older adults were asked to orally describe remote and recent life chapters in as much detail as possible. Participants were also asked to describe remote and recent episodic autobiographical memories. For both autobiographical tasks, semantic and episodic detail generation was scored using the standard protocol from the Autobiographical Interview (AI; Levine et al., 2002).

Results: In comparison to young adults, older adults generated more detail overall when describing remote and recent life chapters. This was largely driven by their generation of personal and general semantic details, relative to episodic detail. Similar to prior research, in comparison to young adults, older adults also generated more semantic detail accompanied by less episodic detail when recollecting episodic autobiographical memories.

Conclusions: These findings indicate that the elevated generation of semantic details associated with normal aging is present when autobiographical narratives are episodic or semantic in orientation. We suggest that older adults' elevated use of semantic detail during autobiographical memory retrieval may reflect a difference in narrative style and communication goals, as opposed to purely compensation for deficient episodic detail.

Poster 80

AGING, EXPLORATION, AND THEIR NEUROPSYCHOLOGICAL CORRELATES. Alvarado L, Farrell Skupny A, Frisvold A, Mizell JM, Wang S, Keung W, Sundman MH, Franchetti MK, Chou Y, Alexander GE, Wilson RC. University of Arizona; Arizona Alzheimer's Consortium.

Background: Extensive literature has shown that healthy aging causes decline to specific cognitive functions, such as memory and executive functions. However, there is a fascinating dichotomy when it comes to the complexities of decision-making. Older adults tend to outperform young adults in tasks that involve one's ability to delay instant gratification to optimize rewards, but in some economic tasks show higher levels of inconsistency than young adults. Therefore, aging is potentially associated with declines in one cognitive domain while it improves in another. In this study, we investigate whether explore-exploit behavior continues to change in old age and whether an individual's memory abilities (as well as other cognitive abilities) relate to their exploration decisions. Specifically, we are examining the correlations between memory and executive functioning in older adults and how it correlates with their preference of directed exploration (information seeking) or random exploration (error-driven exploration). Our preliminary data from older adults (n = 58, ages 65-74) suggests that explore-exploit behavior continues to change throughout a lifespan, which shows a relationship between their memory abilities and executive abilities. This work has implications not only for healthy older adults, but also older adults at risk for Alzheimer's Disease, as many of our participants show early pre-clinical signs of the disorder. Also, using Transcranial Magnetic Stimulation we were able to temporarily slow down activity within the Frontal Pole of our participants, and preliminary results show that this region is responsible for Directed, but not Random exploration lending further evidence to the idea that these two types of exploration are neurally dissociable.

Methods: Participants completed an MRI/fMRI screening and a battery of complex decision-making tasks as well as cognitive tasks. Decision Making: Decision making tasks included a behavioral task on a computer participants chose between two slot machines to maximize their potential reward. Before adults made their initial decision, they were presented with example plays that revealed equal and unequal data of both slot machines until horizon four. Older adults then made their decision of which slot to play until the end of the horizon. This task was used to examine exploration. Cognitive Tasks: Older adults completed a series of cognitive tasks including a general screening: Montreal Cognitive Assessment (MoCA), memory tasks, verbal tasks, visual spatial tasks and executive tasks. TMS: Using transcranial magnetic stimulation (TMS), neural activity was minimized in the frontal pole of participants while they completed the horizon task. A comparative control condition was also created (pseudo stimulation).

Results: Our preliminary data suggests that older and younger participants show different patterns in both random and directed exploration. In older adults, our data suggests that explore-exploit behavior is related to other cognitive abilities. Directed exploration correlates with declarative memory and random exploration correlates with executive functioning. From the subset of older adults we have also ran through our TMS protocol. In shutting down in the frontal pole, we found a reduction in directed exploration and less information seeking overall. Interestingly, this did not affect older adults random exploration.

Conclusions: Our data shows that older adults show different exploration patterns and these patterns are correlated to their cognitive status. This further reveals the value in examining complex decision making abilities in older adults. We also show that the frontal pole is likely necessary for directed exploration in older adults.

Poster 81

PARO ROBOT INTERVENTION PERSPECTIVES WITH DEMENTIA PATIENTS. Ames L, Andersson E. Midwestern University; Arizona Alzheimer's Consortium.

Background: A qualitative systematic review was conducted to understand the perspectives of caregivers, staff, and residents with dementia concerning interactions with PARO, the social robot.

Methods: An extensive search in databases such as Ebscohost, Medline, and OTseeker was performed. The key words in the search were "PARO," "dementia OR Alzheimer's," and "qualitative OR lived experience."

Results: A total of 4 studies were examined. Perceptions and reactions were categorized by caregiver, staff, or resident with sub-divisions of each category to further divide perspectives between the pros and cons.

Conclusions: Most participants perceived therapeutic benefits of PARO to decrease agitation and increase wellbeing with the barriers. Participants also perceived the barriers to the implementation of PARO as cost and training. Residents reactions varied with over-all positive feedback. Ethical concerns are raised concerning the implementation as a form of therapy.

Poster 82

USING MULTI-METHOD APPROACHES TO CHARACTERIZE MALADAPTIVE REPETITIVE THOUGHT IN OLDER ADULTS. Andrews E, Raffaelli Q, O'Connor M-F, Wilcox R, Mehl M, Matijevic S, Seeley S, Arballo T, Robertson A, Ryan L, Grilli M, Andrews-Hanna J. University of Arizona; Arizona Alzheimer's Consortium.

Background: Existing scientific literature indicates a connection between health-related behaviors and Alzheimer's disease (AD). Historically, these risk-factors have included poor physical and nutritional health, but more recent research has highlighted the role that poor mental health has on the potential development of AD. These findings suggest that therapeutic interventions targeting psychological well-being may reduce the risk for AD, or delay its onset in later life. One target symptom of interest, due to its prevalence and trans-diagnostic nature, is maladaptive repetitive thought (MRT) – a non-deliberate, repetitive form of thinking with problematic consequences. If research efforts accurately characterized MRT in normal and abnormal aging, interventions could be presented at appropriate opportunities and with maximal impact.

Methods: Our current, ongoing, study is assessing MRT using laboratory-based, naturalistic, and neuroimaging methods with cognitively healthy, adult participants who vary in their degree of self-reported MRT and depressive symptomatology. Study aims are to: 1) characterize content, processes, and context-related factors associated with thought in the real world, 2) test novel laboratory-based paradigms to characterize the dynamics of thought and memory in later life, 3) characterize cognitive flexibility as a measure of executive function, and 4) assess how such cognitive measures relate to dynamic functional interactions between brain regions – both at rest and while individuals voice their thoughts aloud. As such, we hope to identify sensitive neurocognitive markers that more accurately indicate how MRT may impact the development and severity of dementia-related symptoms.

Results: Data collection and analyses are currently ongoing, and preliminary findings will be presented. Based on our prior work, we hypothesize that older adults with heightened self-report MRT and depression will display more frequent non-deliberate, task-unrelated, internally-focused thoughts, characterized as more general/abstract, negative, self-focused, past-oriented and rigid. We will also examine contextual predictors of such thoughts, as well as their effect on subsequent mood and other behavioral outcomes. We expect this maladaptive profile of everyday thinking to be accompanied by increased functional connectivity and reduced flexibility of the default mode network.

Conclusions: Through the use of fMRI sequences marked by improved temporal sensitivity and the combination of naturalistic measures of cognition with novel behavioral paradigms sensitive to the dynamic trajectory of thought, our study holds great promise towards uncovering key neurocognitive markers of MRT and depression and possible mechanisms of AD-related risk. These markers can serve as targets of therapeutic intervention to reduce risk factors, highlighting a planned future line of research.

Poster 83

CONVERGENT BIOLOGICAL MECHANISMS REVEALED BY SNP'S LINKED TO ALZHEIMER'S DISEASE. Baldwin E, Fang J, Han J, Li J, Yin F, Lussier YA, Li H. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is a chronic neurodegenerative disease affecting tens of millions of people worldwide and is the leading cause of dementia. A significant amount of risk is attributed to genetics, but it is believed that lifestyle and environmental factors also play a role over time. In the pathogenesis of AD, brain proteins fail to function normally; neurons become damaged, eventually lose their connections and die. Toxic proteins exist primarily in two formations: plaques and tangles. Plaques occur due to the buildup of beta-amyloid, which disrupts cell-to-cell communication between neurons, while tangles occur after disrupted tau proteins self-organize into fibrils that become toxic to neurons. Despite a significant amount of research, the interplay between the environment, biological mechanisms and the genetics of AD is yet to be understood.

Methods: In this study, we hypothesized that the convergence of mechanisms with distinct genetic variance may provide unique insight into the pathogenesis of AD. We investigated 93 AD-associated single nucleotide polymorphisms (SNPs) that had both genome-wide association to AD and expression quantitative trait association through the GTEx project. We quantified the eQTL similarity scores between SNP's by their semantic similarity of the annotated gene ontology terms of downstream genes [1]. The significance levels were determined by deep permutations of an eQTL-derived multiscale network consisting of eQTL SNPs, mRNA targets, and gene ontology terms [2]. Furthermore, we prioritized molecular mechanisms that converged between distinct SNPs with a false discovery rate (FDR) <0.05.

Results: Among our prioritized genetics-specific molecular targets, several eQTL elements were identified that corresponded to convergent downstream mechanisms. For instance, three independent intergenic SNP's on chromosome 17 were prioritized because of their convergence and related biological processes by the downstream genes of microtubule associated protein tau (MAPT), WNT3 and PLEKHM1, which each have roles in cell growth, axonogenesis, and autophagy. MAPT itself is known to regulate axon extension and has been implicated in other neurodegenerative diseases. More importantly, cross-chromosome relationships were prioritized and revealed convergent downstream mechanisms from distinct trans-eQTL's. For example, SNP's on chromosomes 17 and 19 were identified near genes that regulate synaptic transmission, which when deteriorates, is a known cause of memory loss in AD patients. Further, a pair of SNP's associated with antigen processing and cell signaling were linked to the high density of human leukocyte antigen (HLA) genes on chromosome 6, and cytokine genes on chromosome 1. This suggests a strong genetic involvement of convergent mechanisms in the immune system during the pathogenesis of AD.

Conclusions: This study demonstrates a new methodology for connecting AD-related intergenic SNP's with risk-identified genes, and their convergent downstream biological mechanisms. Identifying variants correlated to underlying cellular processes associated in pathogenesis of diseases provides a new route of investigation in personalized medicine, genetic targeting and molecular pathologies.

[1] Li, H., et al. npj Genomic Medicine 1:16006, 2016.

[2] Han, J., et al. PSB, 2018, pp. 524-535.

Poster 84

RELATION OF WHITE MATTER LESION LOAD TO CORTICAL GRAY MATTER THICKNESS IN HEALTHY AGING. Bharadwaj PK, Nguyen LA, Hishaw GA, Trouard, TP, Moeller JR, Habeck CG, Alexander GE. University of Arizona; Columbia University; Columbia University Medical Center; Arizona Alzheimer's Consortium.

Background: Cerebral white matter hyperintensities (WMH) measured by magnetic resonance imaging (MRI) are associated with vascular risk factors and are thought to reflect small vessel disease. Recently, Kern et al. (2017) used a multivariate technique, the Scaled Subprofile Model (SSM; Alexander & Moeller, 1994) to identify a WMH-related covariance network of regional gray matter volume related to differences in blood pressure control. Here, we sought to extend this multimodal multivariate approach, by deriving a covariance network of WMH-related cortical thickness (WMH-CTh), and to evaluate its relation to age and vascular risk in a cohort of community-dwelling, healthy older adults, 50 to 89 years of age.

Methods: Volumetric T1 and T2-FLAIR MRI scans were acquired in 182 older adults (mean Age = 69.7 ± 10.4 , 90F/92M, hypertension = 122N/60Y). Systolic blood pressure (SBP) was computed from average ambulatory blood pressure over 24 hours. T1 scans were processed using FreeSurfer v5.3 to extract cortical thickness values from 68 regions. Global WMH maps were generated from T1 and T2-FLAIR scans using the Lesion Segmentation Toolbox (Schmidt et al., 2012). The SSM was applied to regional cortical thickness measures to derive the covariance pattern related to total WMH load.

Results: The WMH-CTh pattern accounted for 15.1% of the variance in WMH load and was characterized by cortical thickness reductions bilaterally in superior temporal and right precentral regions, with relative increases bilaterally in the caudal anterior cingulate region, and in the left mid-frontal and rostral anterior cingulate regions. Greater expression of the WMH-CTh pattern was associated with increasing age (variance=36%, $p \leq 4.72E-19$) and hypertension (variance=3%, $p \leq 1.98E-2$), but was not related to SBP ($p = 0.15$). After we controlled for gender, hypertension, diabetes, smoking history, and SBP, the relation between WMH-CTh and age remained significant (change in variance=31%, $p \leq 2.49E-17$).

Conclusions: These results suggest that, in healthy older adults, aging is associated with an increasing relation between WMH lesion load and regional cortical thickness that is distinct from common vascular risk factors. Together, these findings support the use of multimodal network covariance methods to advance understanding of the relation between gray and white matter differences in the context of brain aging.

Poster 85

HISTOPATHOLOGICAL RESPONSES TO CANDIDA ALBICANS INFECTION IN 3xTG-AD MICE. Brown C, Vallejo-Elias J, Gonzalez F, Jentarra G, Potter P, Kaufman J, Tullo T, Jones D, Jones TB. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a neurodegenerative condition of unknown etiology characterized by amyloid plaques comprised of amyloid- β proteins (A β). Chronic inflammation, amplified microglial activation, as well as several microorganisms (Spirochetes¹, HSV-12,3, Candida^{4,5}) have been correlated with AD, therefore chronic infection may contribute to the histopathology associated with AD. The purpose of this project is to compare the ability of 3xTG-AD mice to clear a Candida Albicans infection to similarly infected C57/BL6 wild type mice. The systemic response to infection, including amyloid deposition and histopathological effects, were quantitatively and qualitatively evaluated in peripheral tissues (kidney and spleen) of infected 3xTG-AD and C57/BL6 mice, and uninfected controls. We hypothesized that fungal infection would exacerbate the deposition of amyloid in 3xTG-AD mice and induce it in infected C57/BL6 mice, in an age-dependent manner. Because A β is comparable to antimicrobial peptides, i.e., it is induced by pro-inflammatory cytokines, forms channels that disrupt calcium homeostasis, and polymerizes into fibrils capable of entangling microbial cells^{6,7}, we hypothesized that 3xTG-AD mice would clear Candida more efficiently than C57/BL6 mice.

Methods: Tissues were collected at 1, 4, 7, or 14 days post-infection and processed for routine histology. Following cryosectioning at 10 μ m, renal and splenic sections were stained with Congo Red (Abcam) to identify amyloid species or Periodic Acid Schiff (PAS; Sigma Aldrich) to identify C. albicans. Images were digitized and evaluated by an experimenter blinded to genotype and treatment protocol.

Results: In agreement with previous data from our laboratory showing age-dependent deficits in fungal clearance in 3xTG-AD mice, we demonstrated the presence of Candida yeast and branching hyphae in the spleen and kidney, respectively, of 3xTG-AD, but not C57/BL6 mice at 12 months of age. We also observed abnormal splenic cellular architecture in infected 3xTG-AD mice as evidenced by the presence of numerous multi-nucleated, Congo red-negative, but PAS-positive (i.e., glycogen-rich) cells with loosely organized chromatin. Polarized microscopy revealed fatty oval casts and Maltese crosses with apple green birefringence in infected C57/BL6 and 3xTG-AD mice, suggesting an amyloid-induced nephrotic syndrome. Kidney sections with amyloid also demonstrated erythrocyte deposits indicating increased friability of the renal vasculature with amyloid deposition. Qualitative evaluation of amyloid in the kidney demonstrated the induction of amyloid in response to infection in C57/BL6 mice and a reduction in amyloid in 3xTG-AD mice when compared to non-infected controls.

Conclusions: We show here that systemic infection with C. albicans can induce amyloid in peripheral tissues of C57/BL6 mice. This was associated with reduced fungal burden in these mice. We also demonstrate that 3xTG-AD mice that would be expected to accumulate amyloid, have reduced amyloid deposition compared to non-infected mice. This was associated with increased fungal burden. Collectively these data support our hypothesis that amyloid is induced in the periphery by inflammation and potentially plays an antimicrobial role in infection, demonstrating that amyloid has widespread systemic effects, specifically on the kidney and spleen.

Poster 86

THE INTELLICAGE: AN AUTOMATED SYSTEM FOR ASSESSING COGNITION IN TRANSGENIC MOUSE MODELS OF ALZHEIMER'S DISEASE. Bustos L, Velazquez R, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Cognitive deficits are a central feature of Alzheimer's disease (AD). Transgenic animal models of AD were developed to better understand the pathogenic mechanisms associated with this insidious disease. To assess cognitive deficits associated with AD pathologies in these mice, behavioral assessments are performed using tasks, such as the Morris Water Maze. However, these tasks impose stressful and socially impoverished environments that can alter an animal's performance. The Intellicage was designed to circumvent the issues of traditional behavioral tests. The system allows for the implementation of programmable tests, while collecting continuous data about each animal's performance. Behavioral paradigms are implemented with minimal human interaction, thereby producing data not confounded by stress. Additionally, up to 16 mice are housed in each testing cage, thereby reducing social impoverishment. Various cognitive facets can be tested in the Intellicage, including sensorimotor, attention, impulsivity, behavioral flexibility, and spatial learning and memory.

Methods: The intellicage has four corners each containing an operant chamber controlling access to water. Entry into a corner responds to an individual radiofrequency identification (RFID) transponder subcutaneously implanted in each animal. We used 12-month-old APP/PS1 mouse mice, which develop Amyloid- β pathology at this age, and non-transgenics (NonTg) mice (n = 8 per genotype). The animals underwent a three-part adaptation phase in order to acclimate to their new environment. Then, all animals were tested in a place preference learning, reversal learning, and serial reaction time task, which taps into spatial learning, behavioral flexibility, and attention, respectively. Output includes visits to an assigned "correct" and "incorrect" corner, nose-pokes into ports, and licks at an accessed water-bottle.

Results: For the place preference learning experiment, where each animal is assigned a designated "correct corner", we found a significant effect of day after 6 days of testing (>80% correct visits by Day 6). During the reversal learning tasks, where the animal's "correct corner" is now the opposite corner of the cage, we found a significant drop in performance in Day 1 (40% correct visits). By Day 6, all animals had reached above 80% correct performance.

Conclusions: We were able to detect differences in spatial learning, memory and behavioral flexibility in our transgenic mice. In conclusion, automated testing of socially kept mice is a powerful and efficient tool for dissecting complex features and behavioral profiles while removing confounds caused by stress and human interaction.

Poster 87

DEEP LEARNING ALGORITHMS FOR BRAIN IMAGE CLASSIFICATION. Champaneria H, Luo J, Su Y, Pan R. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by memory loss and cognitive impairment. It is associated with significant structural changes of the brain, which can be measured using magnetic resonance imaging (MRI) scans. Early diagnosis of AD plays an important role in delaying the progress of cognitive decline, and using advanced deep learning (DL) algorithms, such as convolutional neural networks (CNNs), to detect subtle brain structure changes can provide an opportunity for early AD detection. However, currently, most medical image studies with deep learning algorithms are hampered by the small sample size. In this research, we explore several transfer learning techniques, which borrow some existing CNN models with minor adjustments on their final layers, to overcome the limitation of sample size. Our algorithms read the MRI raw image data to classify AD group versus cognitively unimpaired (CU) group.

Methods: In this study, the classification of the brain MRI data from Alzheimer's Disease Neuroimaging Initiative (ADNI) study is investigated. Training an entire DL model from scratch is impractical because it is relatively rare to have a dataset of sufficient size. An alternative is to pre-train a DL model with a very large dataset (e.g., natural images on ImageNet) and then use this model as a fixed feature extractor for the task of classifying medical images of interest. We utilize the AlexNet and ResNet architectures, which are pre-trained on ImageNet, and take their model specifications, except the last fully connected layer, as the image feature extractor for our applications. The support vector machine (SVM) algorithms are then applied to these features to classify brain images. The results of the deep learning models are validated by the output of the image processing using Freesurfer software.

Results: Using a pre-trained AlexNet we are able to obtain 70% accuracy in AD classification. This model can be further fine-tuned by modifying pre-training images. We are currently testing ResNet for AD classification. Because the ResNet architecture is much deeper (over 100 layers) we plan to use ASU's GPU cluster to train and test ResNet.

Conclusions: Our preliminary study shows that transfer learning of DL algorithms is a promising approach to AD prediction with a limited number of training examples. This study has the potential to establish an automated image-based early AD detection method, which will benefit both AD research and clinical applications.

Poster 88

CHALLENGES OF PAIN MANAGEMENT FOR LONG TERM CARE RESIDENTS WITH DEMENTIA. Conant RA, Uriri-Glover J. Arizona State University; Arizona Alzheimer's Consortium.

Background: An evidence-based project was implemented to demonstrate validity of the delivery of focused pain management training and education in improving the quality of life for residents and staff through an increased ability to assess for and identify pain in residents with dementia and other cognitive impairments. Approximately 50% of elderly adults in the long-term care setting who have dementia experience chronic pain (Achterberg et al., 2013). The role of the certified nursing assistant in the daily life of residents of long-term care puts them in a position where often they are the first to recognize and report pain, and potentially play a role in bridging the communication gap. However, they may not take the time to adequately assess a patient's pain, or a lack of proper training and knowledge may be detrimental to their ability to properly recognize pain and/or assess degree of discomfort (Achterberg et al., 2013; Jansen et al., 2016). Research has been done on the role of certified nursing assistants and other frontline caregiving staff who work with elderly long-term care residents with dementia regarding the recognition and assessment of pain, concluding that delivery of focused pain management training and education results in improvement of quality of life for residents and staff (Petyaeva et al., 2017).

Methods: The project site was the memory care unit of a long-term care facility in Arizona. Participants were any consenting nurses, lpns, and nursing assistants. A 39-minute interactive education intervention was completed using pre and posttests and a PowerPoint presentation on dementia and use of the PAINAD scale, followed by a question and answer session to obtain feedback from staff. Content validity was established for pre/post-tests via face validity, as the test has not been already formally validated, as it is unique to this project. The PAINAD scale has well documented validity and reliability and is widely recognized as an effective tool for assessing pain in patients with dementia, particularly those with impaired verbal communication ability. Goal participation: 15+ staff members.

Results: Basic demographic data including education, job position, and years of experience will be collected. The responses to seven questions on a Likert Scale on the content of the presentation will be analyzed via paired t-test analysis to determine what if any effect the intervention had on the knowledge level of the participants. Mean difference, median value, and standard deviation calculations will also be performed for further analysis of the results. All these statistical tests will be performed with the purpose of determining if the educational intervention was successful. Findings will be presented at the AAC annual conference.

Conclusions: The hypothesis for this project is; can targeted pain assessment education improve the ability of staff who care for patients with dementia to identify pain, thus allowing it to be treated sooner, resulting in less disruptive behaviors and a higher quality of life for staff and patients. Implementation of this project will lead to accurate pain assessment of LTC residents with dementia. In the clinical setting this enables prompt pain control measures to be utilized, ultimately leading to better management of residents' pain. Disruptive behaviors by residents will decrease, lowering the caregiving burden on staff. Staff participation, knowledge, and satisfaction will increase as they feel more equipped to assess and provide care for the residents. IHI Triple Aim goals will be met, improving the healthcare experience and overall health of the residents, and reducing per capita cost of care.

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IN VIVO CHARACTERIZATION OF CARDIAC AND AORTIC FUNCTION & STRUCTURE IN THE HUMAN APOLIPOPROTEIN E MOUSE MODEL OF ALZHEIMER'S DISEASE. Curry T, Dickman R, Hoxha B, Gadaqkar S, Vallejo-Elias J, Jones TB, Esfandiarei M. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease and the leading cause of dementia worldwide. The $\epsilon 4$ isoform of Apolipoprotein E (APOE4) has been associated with an increased likelihood of late onset AD and has also been associated with an increased risk of cardiovascular disease (CVD). It has been observed that cardiovascular disease increases the risk of developing AD and that those with AD have cerebral vascular abnormalities. This association has led to the hypothesis that cardiovascular dysfunction may precede the onset of AD. Currently, little is known about the pathological consequences associated with the APOE isoforms in the heart and major peripheral arteries, and what effect this may have on the probability of developing late onset AD. In this study we have assessed and characterized cardiovascular parameters in a well-established targeted replacement murine model for AD.

Methods: In vivo analysis of biophysical properties, including aortic root diameter, aortic stiffness, and cardiac parameters in 3- and 6- month old wild-type C57BL/6, targeted replacement APOE3, and targeted replacement APOE4 mice was performed using the Vevo 2100 high-resolution ultrasound imaging system (FUJIFILM VisualSonics).

Results: Our study indicated that aortic root diameter at the sinotubular junction was significantly increased in APOE4 mice at 3 & 6 months of age when compared to APOE3 group, with no significant difference observed at the regions of aortic anulus or sinus of Valsalva. Pulse wave velocity, a reliable index of aortic wall stiffness, was comparable amongst genotypes. Cardiac stroke volume was significantly increased in APOE4 mice when compared to wild type at 3 months of age. There was no significance in heart rate, cardiac output, ejection fraction, MV E/A ratio, and fractional shortening at 3 and 6 months of age. Interventricular septum (IVS) depth at diastole was significantly decreased in APOE4 mice when compared to APOE3 at 6 months of age. The left ventricular mass (LVM), when corrected for weight, of the 6-month-old APOE4 mice was significantly decreased when compared to APOE3 and wildtype.

Conclusions: Our current data suggests that the introduction of human APOE4 into the murine model results in an increase in aortic root diameter at the area of the sinotubular junction, which is associated with signs of cardiac abnormalities, when compared to APOE3 and wild type experimental groups.

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EVALUATION OF AORTIC WALL CONTRACTILITY & STRUCTURAL INTEGRITY IN THE HUMAN APOLIPOPROTEIN E MOUSE MODEL OF ALZHEIMER'S DISEASE. Dickman R, Talley N, Hoxha B, Curry T, Alexander T, Johnson N, Gadagkar S, Vallejo-Elias J, Jones TB, Esfandiarei M. Midwestern University; Arizona Alzheimer's Consortium.

Background: Apolipoprotein E (APOE) is a multifunctional protein with three isoforms (epsilon 2, epsilon 3, and epsilon 4) that correspond with diverse functional and pathological manifestations. Most notably, the epsilon 4 allele has been associated with an increased risk of cardiovascular disease, and is considered a prominent risk factor for the development of late onset Alzheimer's disease (AD). AD is a progressive neurodegenerative disease and the leading cause of dementia. Although research in AD has been ongoing, the pathogenesis of the disease remains elusive. The discovery of cerebral vascular abnormalities in AD patients and the association of APOE epsilon 4 (APOE4) with cardiovascular disease has led to the hypothesis that the condition may initially arise from peripheral vascular dysfunction. However, little is known about the pathological consequences associated with the apolipoprotein isoforms in major peripheral arteries, such as the aorta.

Methods: In this study, we aimed to characterize the functional (vasoconstriction and vasodilation) and structural (aortic wall elasticity and integrity) characteristics of the thoracic aorta in wild type C57BL/6, targeted replacement APOE3, and targeted replacement APOE4 mice, at 9, 12, and 18 months of age, using small chamber myography.

Results: Our data showed a significant increase in phenylephrine-induced contraction in APOE4 mice when compared to APOE3 at 9 months of age, however, this difference was not shown at 12 or 18 months of age. There was no evident difference in acetylcholine-induced relaxation between experimental groups at any age group. The rupture point was significantly reduced in aortic segments isolated from APOE3 and APOE4 mice when compared to wild type mice at 9 and 12 months of age. Significance amongst the rupture points was lost at 18 months of age, which could be due to the effects of natural aging in all experimental groups.

Conclusions: This study provides the first preliminary evidence of peripheral vascular dysfunction in the well-established mouse model of AD (APOE). Our data demonstrates an early decrease in aortic wall integrity in both APOE3 and APOE4 mice when compared to wild type. This could indicate that the introduction of the human apolipoprotein E gene into the murine model is causing weakening of the aortic wall. At 9 months of age APOE4 mice show an increase in phenylephrine-induced contraction when compared to APOE3, indicating a role for APOE4 in vascular smooth muscle dysfunction.

Poster 91

DIFFUSION WEIGHTED MRI CHARACTERIZATION OF APOE4 EFFECTS ON SEX AND GENOTYPE IN MOUSE MODEL. Do L, Bernstein A, Mishra A, Desai M, Lindley MD, Ugonna C, Chen NK, Brinton R, Trouard TP. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: The Apolipoprotein E (ApoE) protein is integral for lipid shuttling and is expressed in the brain. The ApoE4 allele is a major risk factor for Alzheimer's Disease (AD). Diffusion weighted magnetic resonance imaging (dMRI) has the potential to characterize sex and genotype effects in a mouse model containing a targeted replacement of mouse APOE gene with human ApoE3 or ApoE4. The ApoE4 allele is a major risk factor for Alzheimer's Disease (AD). The purpose of the study was to use MRI to characterize sex and genotype effects in mice using volumetric and dMRI measures, and validating them with cognition and transcriptomics.

Methods: Male and female mice (C57BL/6, n=11, 16 months) with a targeted replacement of the mouse APOE gene with humanized ApoE3 (ApoE3) or ApoE4 (ApoE4) underwent cognitive tests, transcriptomics followed by euthanasia and fixation of the brain. The brains were imaged using a 7T Bruker Biospec MRI scanner with a high-resolution 3D T2-weighted sequence 75 μ m isotropic resolution. 3 sets of diffusion-weighted MRI (dMRI) were collected using 32 directions and diffusion weighting of b=1000s/mm², in plane resolution of 150 μ m, and slice thickness of 450 μ m. Image Analysis- The structural MR images were brain extracted followed by bias field-correction. The data was then registered to a T2-weighted reference image and atlas with 356 regions of interest (ROIs) to each animal using ANTs. Volumes of 30 regions of the brain were compared across 4 groups (male and female; ApoE3 and ApoE4) using multiple t-tests. Raw, low-resolution, dMRI data were motion and eddy-current corrected and denoised. The three shifted datasets were reconstructed using in-house software to generate 150 μ m isotropic images followed by brain extraction, bias field correction and run through a two-step SyN registration in ANTs to create a labeled atlas in individual diffusion space. The dMRI data were then analyzed to obtain fractional anisotropy (FA). Parameter maps were analyzed by registering the mouse atlas to each fixed mouse brain dMRI data, and then comparing mean value of the top quartile of FA.

Results: Grey matter volumes showed significant sex effect in both genotypes. White matter areas larger in the ApoE4 animals, and the effect was significant in males. Sexual dimorphism in white matter tracts was only observed in ApoE3, with the females showing larger volumes than the males. Assessment of FA revealed that ApoE3 males had significantly higher FA in several white matter tracts, while ApoE4 females trended towards lower FA. Cognitive studies indicate ApoE3 males have higher scores compared with ApoE4 females and males. Hippocampal transcriptomics suggests that ApoE4 animals have reduced oxidative phosphorylation compared with ApoE3. But, only ApoE4 females showed coincident increased ketogenesis.

Conclusions: Structural MRI data reveal genotype and sex differences on regional brain volumes. Lower FA values in ApoE4 males and females could indicate changes in white matter compared with ApoE3. Evidence from cognitive and hippocampal transcriptomics show ApoE4 animals have reduced cognition and oxidative phosphorylation. ApoE4 females show a bioenergetic shift in fuel utilization, from glucose to fatty acids derived from white matter catabolism.

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MRI ASSESSMENT OF SEX DIFFERENCES IN APOE4 KNOCK-IN IN RODENT BRAINS. Do L, Mishra A, Bernstein A, Lindley MD, Ugonna C, Chen NK, Brinton R, Trouard TP. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: Diffusion magnetic resonance imaging (dMRI) can be used to help characterize neurological degenerative processes, such as Alzheimer's disease (AD). Carriers of the $\epsilon 4$ allele of the apolipoprotein E gene (APOE $\epsilon 4$) have been shown to undergo faster rates of cognitive decline from Mild Cognitive Impairment (MCI) to AD compared to carriers with the $\epsilon 3$ allele. Using a humanized APOE $\epsilon 4$ gene knock-in rat model, the individual and combined impact of sex and APOE $\epsilon 4$ genotype on white matter microstructure was measured using dMRI.

Methods: Wildtype (WT), and with a humanized APOE $\epsilon 4$ knock-in, male and female rats (Sprague Dawley, n=8, 2 per group,) were used in this study. At 16 months old, metabolomic studies were conducted to investigate sex and APOE $\epsilon 4$ genotype effects. Intact skulls containing the fixed brains underwent MRI on a 7T Bruker Biospec MRI scanner. Anatomical 3D T2-weighted RARE images were collected with 100 μ m isotropic resolution. In addition, three sets of dMRI were collected using 8-shot echo planar imaging with 32 directions and a diffusion weighting of $b=1000$ s/mm², and 4 $b=0$ images. In plane resolution was 200 μ m and slice thickness was 600 μ m. Image Analysis- High-resolution anatomical MRI images were semi-automatically brain extracted using MRIcron and Mango and bias field-corrected using ANTs. The data was further analyzed by registering a T2-weighted reference image and atlas with 115 regions of interest (ROIs) ANTs. Volumes of specific regions of the brain, inclusive of white matter and grey matter areas, were compared across the 4 groups (male and female; WT and APOE $\epsilon 4$) using pair-wise t-tests. Three low resolution datasets were reconstructed using in-house super-resolution reconstruction software, to generate 200 μ m isotropic dMRI data. The brain was then semi-automatically extracted from non-brain tissue and bias field corrected and two SyN registrations were performed in ANTs to create a labeled atlas in individual diffusion space. The high-resolution dMRI data were then fit to the diffusion tensor imaging (DTI) model. From the DTI fit, fractional anisotropy (FA), and mean diffusivity (MD) were calculated on a voxel-by-voxel basis using MRTrix and directionally encoded color maps were generated. Parameter maps were analyzed by registering the labeled rat atlas to each individual fixed rat brain dMRI data, and then comparing the mean value of the top quartile of FA in white matter ROIs.

Results: Total brain volumes showed a significant sexual dimorphism in WT as well as APOE $\epsilon 4$ animals, with the females having significantly lower volumes. Grey matter regions – such as, the neocortex and hippocampus proper trended to be larger in APOE $\epsilon 4$ males whereas white matter areas- such as anterior commissure, fimbria of the hippocampus and hippocampal commissure trended to be larger in the APOE $\epsilon 4$ females. Microstructural analysis revealed that there is a sex difference in FA in males and females, in which APOE $\epsilon 4$ females trended to have lower FA values. Cortical metabolomics analyses suggested a reduction in glucose utilization as evidenced by a reduction in metabolites of the TCA cycle and reduced fatty acid oxidation in APOE $\epsilon 4$ females with respect to the APOE $\epsilon 4$ male.

Conclusions: Both volumetric and dMRI measures were able to show trends of sexual dimorphism as well as genotype effect. These findings were supported with metabolomic data suggesting reduction in glucose utilization and possible shift to fatty acids derived from white matter catabolism as a fuel source possibly indicating an energy deprived state especially in APOE $\epsilon 4$ females with respect to the APOE $\epsilon 4$ male. These findings are pending ultrastructural imaging analyses, i.e. electron microscopy, to corroborate the microstructural assessment.

Poster 93

INTERACTIVE EFFECT OF SEX AND BDNF MET ALLELE ON MEMORY IN OLDER ADULTS.

Elias M, Matijevic S, Ryan L, Huentelman MJ. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Brain-derived neurotrophic factor (BDNF) plays a critical role in hippocampal-dependent memory and plasticity, promoting both synaptogenesis and neurogenesis. The BDNF gene Met allele, which is associated with abnormal BDNF expression, has been shown to negatively influence hippocampal volume, stress reactivity, and cortisol levels in a manner resulting in poorer memory ability. This has implications for cognitive aging, given the susceptibility of the hippocampus to age-related damage and dysfunction, and indeed the Met allele has been linked to memory deficits in older adults. However, evidence from the literature on the Met allele and stress indicate that the effects of the Met allele may be modulated by sex through estrogen induced BDNF synthesis in the brain, which may have an additional impact on memory. Therefore, the present study aims to characterize the interactions between age, gender and the BDNF met allele, and their effects on memory performance in older adults.

Methods: The neuropsychological and genetic data analyzed in this study ($n = 268$) were collected from cognitively normal older adults ($M = 72.27$, $SD = 6.42$, age 60-90) living in the Tucson area. Male ($n = 81$) and female ($n = 187$) participant data was assigned to one of two BDNF groups, Non-Met carrier ($n = 131$) or Met carrier ($n = 137$). Decreases in memory performance was the primary outcome measure, as defined by a composite memory score (Glisky & Kong 2008). A Univariate ANOVA was run to assess interactions and main effects of age, sex and BDNF Met carrier status, and t-tests and Pearson's correlations were ran as follow-up tests.

Results: In the UANOVA, a significant main effect was found for Age ($F = 22.726$, $p < 0.000$) but not for Sex ($F = 0.909$, $p = 0.341$) nor Carrier status ($F = 1.323$, $p = 0.251$). A three way interaction between Sex, Carrier status, and Age was found ($F = 5.038$, $p = 0.026$), along with a significant two way interaction between Sex and Carrier status ($F = 4.392$, $p = 0.037$). Non-carrier females scored better than carrier females ($t = 9.08$, $p < 0.001$), whereas carrier males scored better than non-carrier males ($t = -2.10$, $p = 0.039$), and the only significant correlations between age and memory scores were exhibited for carrier females ($r = -0.33$, $p = 0.001$) and non-carrier males ($r = -0.51$, $p = 0.002$). Sex and Age ($F = 2.220$, $p = 0.137$) and Carrier status and Age ($F = 1.378$, $p = 0.241$) were not found to have significant interactions.

Conclusions: BDNF carrier status is shown to have a statistically significant impact on memory performance, though in a sex-specific manner moderated by age. Specifically, met carrier status in females shows a significant, negative impact on memory, while the effect is reversed for males. These results suggest that the presence of the met allele may be less detrimental for males' memory performance than for females. These results may be skewed because of the uneven distribution of male and female participant data, prompting further exploration of this finding.

Poster 94

THE DEVELOPMENT OF A HIGHLY SELECTIVE AND ORALLY BIOAVAILABLE INHIBITOR OF DYRK1A FOR TREATMENT OF ALZHEIMER'S DISEASE. Foley C, Dunckley T, Hulme C. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Targeting Alzheimer's disease (AD) pathology at single components is clearly 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. The hyperphosphorylation of the microtubule stabilizing protein tau contributes to tau dysfunction and aggregation into NFTs, which are highly correlated to dementia severity in AD.

Methods: Medicinal Chemistry

Results: A highly selective and orally bioavailable inhibitor of DYRK1A has been developed. Analogues with lower clearance and higher brain/plasma ratios are being developed.

Conclusions: DYRK1A inhibition offers a promising approach toward the treatment of Alzheimer's and other neurodegenerative disease.

Poster 95

RELATION BETWEEN PHYSICAL SPORT ACTIVITY AND WHITE MATTER HYPERINTENSITY VOLUME IN OLDER ADULTS. Franchetti MK, Bharadwaj PK, Nguyen LA, Klimentidis YC, Hishaw GA, Trouard TP, Raichlen DA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Cerebral white matter lesion load, as measured by white matter hyperintensities (WMHs) on MRI, have been associated with cardiovascular risk factors like hypertension as well as increasing age and poorer cognitive performance. Physical activity (PA) may play an important role in maintaining cerebral white matter (WM) in the context of healthy aging. We sought to determine whether high levels of self-reported physical sport activity are associated with lower WMH volume.

Methods: Self-report ratings of physical sport activity were obtained from 196 healthy older adults (mean \pm SD age = 69.8 \pm 10.6 years). Participants reporting high sport activity (n=36) were compared to those with low sport activity (n=160). MRI scans were acquired at 3T, including volumetric T1 and T2 FLAIR scans. Total WMH volume was computed with a multispectral, automated lesion segmentation method to produce probability maps using Statistical Parametric Mapping (SPM12) and the lesion segmentation toolbox (LST; Schmidt et al., 2012). ANCOVA tested age group (young-old (YO) = 50-69 years; old-old (OO) = 70-89 years), PA group, and age by PA group interaction effects after controlling for gender and hypertension status.

Results: Main effect of PA shows a strong trend for significance ($p = 0.0503$). We found a significant main effect for age group ($p = 0.005$) and an age by PA group interaction ($p = 0.005$). Simple effects analyses indicated that total WMH volume for the high PA group is comparable between the YO and OO. In addition, the OO with low PA had a significantly greater WMH volume than both the YO with low PA ($p = 2.72E-10$) and the OO with high PA ($p = 0.00038$). These findings remained significant after correcting for total intracranial volume (TIV).

Conclusions: In this community-dwelling sample of healthy older adults, we observed a main effect of age with the older group having greater total WMH volume, as well as an age by PA interaction. Among the low PA groups, total WMH volume is greater in the OO than YO groups, indicating an age group difference that was not observed in the high PA groups. The age groups did not differ in total WMH volume for the high PA groups suggesting diminished age differences with greater physical sport activity. Together, these results suggest that reporting high levels of physical sport activity may be associated with lower WMH volume in the context of healthy aging. Engaging in high levels of physical sport activity may be an important lifestyle factor that can help to maintain the integrity of white matter in old age.

Poster 96

ELEMENTAL AND CONFIGURAL ODOR DISCRIMINATION IN APP/PS1 MICE. Gupta TA, Sanabria F, Oddo S, Smith BH. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) involves marked cell loss and tau pathology in the olfactory bulb, leading to diverse deficits in olfactory identification and discrimination (Ohm & Braak, 1987; Doty & Reyes, 1987). Further research suggests that olfactory bulb pathology appears in early stages of AD (Kovacs, Cairns, & Lantos, 2001) and that olfactory dysfunction is correlated with the level of amyloid-beta pathology in AD mouse models. Olfactory deficits are accompanied by amyloid pathology in the hippocampus, as well as deficits in hippocampus-dependent cognition such as spatial memory tasks (Caccamo, De Pinto, Messina, Branca, & Oddo, 2014). The hippocampus is also involved in configural learning (learning involving stimulus compounds) using stimuli from different modalities (Gallagher & Holland, 1992). The current study investigates potential deficits in the elemental and configural learning in the APP/PS1 mouse model of Alzheimer's disease, using a novel olfactory patterning paradigm.

Methods: Wild-type and mutant APP/PS1 mice (ages 4-months, 7-months, and 11-months) were trained on an olfactory instrumental patterning task. In an operant chamber fitted with olfactometers, mice were trained with 6 trial types, four of which involved presentation of a single binary mixture, and two of which involved presentation of a double binary mixture. In single binary mixture trials mice may receive mixture A, B, C, or D. In a compound trial, they may receive compound AB or compound CD. Importantly the reinforced response for a given set of elements (e.g. element A or element B = left head entry) is the opposite of that for its compound (compound AB = right head entry). This design ensures that the mice cannot use their knowledge of the elements to learn the responses associated with the compounds. Mice were first trained with only elemental trials for 42 sessions, followed by 42 sessions with both elemental and compound trials.

Results: Despite the apparent role of the hippocampus in configural learning using multiple stimulus modalities and the presence of amyloid pathology in the hippocampi of APP/PS1 mice (Puolvali et al., 2002), our analyses to date indicate no significant deficits in elemental or configural olfactory discrimination in mutant APP/PS1 mice across age cohorts.

Conclusions: Results of the current study suggest that discrimination of olfactory mixtures may not be subject to the same hippocampal dependence as configural learning in other stimulus modalities. Future research may investigate the role of other structures, such as the piriform cortex, which receives the majority of olfactory bulb projections. These results also indicate that deficits in olfaction in AD patients might not be due to effects of the pathology on the hippocampus.

Poster 97

INDIVIDUAL COGNITIVE STIMULATION THERAPY EFFECT ON CAREGIVERS OF PERSONS WITH DEMENTIA. Hershkowitz AB, Uriri-Glover J, Buchanan BL. Arizona State University; A.T. Still University; Arizona Alzheimer's Consortium.

Background: Persons with dementia require specialized care because it is a slow progressing neurological disorder, impacting the physical ability, cognition, and behaviors of individuals. Globally, there are over 47 million persons with dementia and the number is projected to double every 20 years. Many caregivers lack the training, education, and experience to care for persons with dementia, which may alter their attitude of caring for this population. Cognitive stimulation therapy (CST) is an evidence-based intervention that can improve short-term cognition for individuals with dementia and can improve the quality of the relationship between the caregiver and care recipient. Historically, health care professionals proctored CST group sessions; however evidence suggests caregivers can successfully deliver one on one individual cognitive stimulation therapy (ICST) with proper training. ICST offers structured, stimulating activities for caregiver use, to engage persons with mild to moderate dementia. The Transtheoretical Model conceptual framework guided this ICST intervention for caregivers. The purpose of the evidence-based project was to evaluate the ability to improve the attitudes of caregivers toward persons with dementia by providing an educational intervention that engaged persons with dementia in stimulating activities together with a caregiver.

Methods: An educational training session was conducted at a large not-for-profit Christian-centered, senior assisted living facility in Maricopa County. "Making a Difference Individual Cognitive Stimulation Therapy Vol. 3" was the manual/workbook caregivers utilized, which offers 75 structured activities to complete with persons with dementia. The facility assisted in identifying the caregiver participants and then each caregiver chose a person with dementia to engage in activity. Informed consent by the caregiver was included and there was no identifying personal information from the data; rather the caregiver was assigned a numerical identifier. The sample size was 5 female formal caregivers who participated in the project. The caregiver implemented activities with the care recipient, two sessions per week for a period of four weeks. Pre and posttest data was collected using the Dementia Attitude Scale (DAS). Caregivers maintained a weekly participation log, including the activity performed, time spent on activity, and notes for next session. Included in the posttest were three open-ended exit questions about the caregivers experience with ICST. The DAS consisted of twenty questions evaluating attitudes toward dementia and was scored on a seven-point Likert-scale. A higher the score equates to a more positive attitude by caregivers toward persons with dementia. The DAS has solid psychometrics and has validity $r=0.21$; an analysis of reliability using Cronbach's Alpha ranged from 0.83-0.85. Results: Descriptive statistics were used to describe the sample and outcome variable and inferential statistics was used to analyze the data. The data collected was analyzed using the software SPSS @v.25. Wilcoxon signed-rank test was used to compare the average scores of the sample pre and post intervention and a two-tale test was ran with the critical value set at $p < .05$ ($z = -1.214$, $p = .225$).

Conclusions: Participation logs demonstrated the care recipients engaged in several stimulating activities that were meaningful to the caregiver and the care recipient. This finding does not support the quantitative results, which showed no significant improvement in the attitudes of caregivers. The caregivers' ratings of 'social comfort and dementia knowledge' did not improve as a result of the intervention. Although the literature suggests that ICST can have a positive impact on caregivers' engagement with people with dementia, this study did not produce similar findings. Further research is needed due to the small sample size included in this study.

Poster 98

ABCC1 MUTATION IS ASSOCIATED WITH ALTERED APP PROCESSING IN A FAMILIAL CASE OF LATE-ONSET ALZHEIMER'S DISEASE. Jepsen WM, De Both M, Piras IS, Siniard AL, Henderson-Smith A, Ramsey K, Serrano G, Caselli RJ, Beach TG, Huentelman MJ. Translational Genomics Research Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Genome wide association studies (GWAS) have provided valuable insight into the complexities of the common polymorphic variants associated with Alzheimer's disease (AD). However, GWAS has failed to completely describe the heritable risk for AD; therefore, approaches utilizing genome sequencing are now necessary in order to characterize the remaining rare variants and genes that may alter AD risk.

Methods: The investigated family consisted of 10 siblings, 6 of whom were diagnosed with dementia, most frequently with a behavioral variant suggestive of frontotemporal dementia (FTD). However, a recent autopsy of an affected sibling revealed a high level of AD neuropathological change with no evidence of FTD. Whole exome sequencing analysis was utilized to identify the top genetic variants associated with dementia diagnosis. The identified variant was studied in vitro to confirm modulation of hallmark AD-associated peptides and transcripts via ELISA, flow cytometry, RNA-seq, and qRT-PCR.

Results: We identified a germline mutation in the ABCC1 gene (chr16:16216007 A>G, p.Y1189C) associated with increased extracellular Abeta1-40,1-42, and Abeta/sAPPalpha peptide ratios, in vitro. Further analysis revealed that the effect is most likely due to modulation of TIMP3, a metallopeptidase inhibitor capable of altering alpha-secretase cleavage of APP. ABCC1 is also shown to influence the expression of PLXNA4, KCNIP4, and MEGF10, all of which are associated with AD pathology.

Conclusions: This serves as strong evidence for the association of ABCC1 in the pathogenesis of AD, thereby adding further human genetic support to the "amyloid hypothesis", and is – to the best of our knowledge – the first germline mutation in ABCC1 to be associated with human disease. Modulation of ABCC1 is predicted to be a novel way to therapeutically alter Abeta processing in humans via its multimodal influence on AD pathology and amyloidogenesis.

Poster 99

PIM1 INHIBITION AS A NOVEL THERAPEUTIC STRATEGY FOR ALZHEIMER'S DISEASE.

Knowles S, Velazquez R, Caccamo A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Accumulation of amyloid- β ($A\beta$) and neurofibrillary tangles are the prominent neuropathologies in patients with Alzheimer's disease (AD). Strong evidence indicates that an imbalance between production and degradation of key proteins contributes to the pathogenesis of AD. The mammalian target of rapamycin (mTOR) plays a key role in maintaining protein homeostasis as it regulates both protein synthesis and degradation. A key regulator of mTOR activity is the proline-rich AKT substrate 40 kDa (PRAS40), which directly binds to mTOR and reduces its activity. Notably, AD patients have elevated levels of phosphorylated PRAS40 (pPRAS40), which correlate with $A\beta$ and tau levels as well as cognitive deficits. Physiologically, pPRAS40 is regulated by Pim1, a protein kinases of the protooncogene family.

Methods: We have identified a Pim1 inhibitor (Pim1i) that crosses the blood brain barrier and reduces pPRAS40. Here, we tested the effects of a selective Pim1i, on spatial reference and working memory and AD-like pathology in 3xTg-AD mice.

Results: Pim1i-treated 3xTg-AD mice performed significantly better than their vehicle treated counterparts and as well as non-transgenic mice in a spatial reference memory task after 4 weeks of treatment. Additionally, 3xTg-AD Pim1i-treated mice showed a reduction in soluble and insoluble $A\beta$ 40 and $A\beta$ 42 levels, as well as a 45.2% reduction in $A\beta$ 42 plaques within the hippocampus. Furthermore, phosphorylated tau immunoreactivity was reduced in the hippocampus of Pim1i-treated 3xTg-AD mice by 38%. Mechanistically, these changes were linked to a significant increase in proteasome activity.

Conclusions: These data strongly suggest that Pim1i might be a valid therapeutic target for AD. Notably, there were peripheral side effects with the Pim1i, evident by splenomegaly at autopsy. In light of these side effects, we next proposed a series of experiments in order to reduce peripheral side effects and extend our findings. We are currently developing a strategy to increase the amount of Pim1i absorbed by the brain while reducing the concentration in the periphery. Additionally, we plan to examine the Pim1i effects on neuronal cell loss in the 5xFAD mouse model of AD. Completion of the proposed work may springboard the use of the Pim1i for AD to clinical trials.

Poster 100

HYSTERECTOMY WITH OVARIAN CONSERVATION UNIQUELY IMPACTS COGNITION AND SERUM HORMONE PROFILES IN A RAT MODEL. Koebele SV, Palmer JM, Hadder B, Melikian R, Fox C, Strouse IM, DeNardo D, George C, Daunis E, Bimonte-Nelson HA. Arizona State University; Senestech, Inc.; Arizona Alzheimer's Consortium.

Background: Hysterectomy (surgical removal of the uterus) is the second most common gynecological surgery following only cesarean section (CDC, 2010; Carlson et al., 1993). The majority of hysterectomies are performed in women prior to age 51 (Wright et al., 2013), which is the average age for natural menopause onset, and prior observations suggest that surgical removal of the ovaries before natural menopause onset may be detrimental to cognition. Thus, ovaries are preserved in about half of hysterectomy procedures. In the last decade, these findings have been extended, such that hysterectomy itself prior to natural menopause onset has also been implicated in an increased relative risk of developing dementia compared to women who did not undergo gynecological surgery (Rocca et al., 2007, 2012; Phung et al., 2010). The factors underlying cognitive and brain changes with variations in surgical menopause remain unclear and warrant further evaluation.

Methods: We examined spatial learning and memory using a rat model of variations in surgical menopause, including a novel model of hysterectomy with ovarian conservation. Adult Fischer-344-CDF female rats underwent sham, ovariectomy, hysterectomy, or ovariectomy plus hysterectomy surgery. Six weeks after surgery, subjects were tested on the water radial-arm maze, a spatial working and reference memory task. Serum hormone profiles and ovarian follicle counts were also obtained.

Results: Results indicate that hysterectomy impaired spatial working memory performance when working memory load was taxed compared to the control group as well as to the other variations in surgical menopause. Serum ovarian hormone profiles were altered in rats with hysterectomy compared to sham-operated rats, while histological analyses of the ovarian tissue suggested that surgical intervention did not alter ovarian morphology itself, at least at the time point assessed.

Conclusions: This is the first systematic pre-clinical evaluation of the cognitive effects of hysterectomy with and without ovarian conservation. These results underscore the critical need to further study the contribution of the uterus to the female phenotype, including effects of hysterectomy with and without ovarian conservation, on the trajectory of brain and endocrine aging to decipher the impact of common variations in gynecological surgery in women. Moreover, findings demonstrate that the nonpregnant uterus is not dormant, and indicate that there is an ovarian-uterus-brain system that becomes interrupted when the reproductive tract has been disrupted, leading to alterations in brain functioning.

Poster 101

FMRI EXAMINATION OF CONTEXTUAL EFFECTS ON PATTERN SEPARATION IN YOUNGER AND OLDER ADULTS. Lawrence A. Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Pattern separation is the neural ability to store two very similar representations as distinctive, allowing behaviorally for recognition discrimination among stimuli with highly overlapping features. Pattern separation is a proposed function of the hippocampus (Kirwan et al., 2012), and impaired pattern separation may contribute to age related memory changes (Burke and Barnes, 2006; Burke et al., 2010; Holden & Gilbert, 2012). Older adults tend to perform more poorly than younger adults at recognition discrimination tasks, making more errors falsely identifying a similar but not previously seen object as one they have seen before (Holden & Gilbert, 2012; Holden, Hoebel, Loftis, & Gilbert, 2012; Stark, Stevenson, Wu, Rutledge, & Stark, 2015). In functional MRI studies, hippocampal hyperactivity and changes to the co-activation patterns of the hippocampus, perirhinal cortex, and parahippocampal gyrus are associated with age-related deficits in pattern separation performance (Reagh et al., 2018). Burke et al. (2018) described changes to medial temporal lobe anatomical circuitry which may lead older adults to be unable to utilize detailed information necessary for pattern separation and instead rely on global or holistic information in the environment. This may make it more difficult for older adults to distinguish between highly overlapping similar representations which requires an analysis of fine detail. This bias toward holistic information processing may explain why older adults are particularly sensitive to contextual cues during memory tasks (Gutchess et al, 2007; Craik & Schloerscheidt, 2015; Memel and Ryan, 2017).

Methods: This study tests whether contextual information provided by repeated background scenes contributes to poor pattern separation performance among older adults using a task modelled after the classic object mnemonic discrimination task (Kirwan & Stark, 2007; Stark, Yassa, Lacy, & Stark, 2013a) but which manipulates contextual information by placing objects in naturalistic scenes that are either repeated or novel between the first and second presentation.

Results: We examine how hyperactivation in the hippocampus and differential patterns of activation among the perirhinal cortex, parahippocampal gyrus, and hippocampus are related to poorer pattern separation in younger and older adults.

Conclusions: This study integrates findings from both object recognition literature and pattern separation literature which have typically operated independently. The contextual effects on memory for older adults observed in object recognition literature has important implications for our understanding of pattern separation. Indeed, typical methods of studying pattern separation does so using single isolated units of information, such as a single object on a white background. Although a white background is also a context (Hayes, Nadel, & Ryan, 2007) it is important to consider the effects of more naturalistic contexts on pattern separation because information in the natural world is not processed in isolation but within a rich environmental context. This study provides an account of how the influence of context on pattern separation may change as individuals age.

Poster 102

ROLE OF WHITE MATTER INTEGRITY IN AGE-RELATED DIFFERENCES IN AUTOBIOGRAPHICAL MEMORY. Matijevic S, Grilli M, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Consistent findings from the literature indicate that older adults describe events from memory with less episodic detail (spatio-temporally defined and event-specific) than younger adults. This episodic deficit has been attributed to age-related damage to the medial temporal lobe (MTL), specifically the hippocampus. However, a variety of cortical regions also play a role in autobiographical memory retrieval, and communication between these cortical regions and MTL areas may be crucial for successfully generating episodic information during event narration. In the present study, we aim to explore how MTL-cortical connectivity impacts the retrieval of episodic details by analyzing the relationship between the integrity of relevant white matter tracts and the generation of different types of episodic detail during an autobiographical memory narration task. Furthermore, we intend to examine what role MTL-cortical tracts play in the age-associated impairment of episodic retrieval.

Methods: Diffusion weighted images were acquired for 22 younger adults (mean age 26) and 41 older adults (mean age 67). All participants received a modified version of the Autobiographical Interview (Levine et al., 2002), in which they were asked to describe 3 specific events from their personal past. Descriptions of the 3 events were coded for episodic and semantic details, as well as 'other' extraneous comments. Episodic details were further categorized as either event information (ex. objects or thoughts-emotions) or spatiotemporal context. Deterministic tractography will be used to extract fractional anisotropy (FA) values, a measure of overall white matter integrity, from the uncinate fasciculus, fornix and cingulum.

Results: We expect to see strong relationships between uncinate fasciculus FA and event information, and cingulum FA and spatio-temporal information. We also expect fornix FA to predict both episodic detail types. In regards to age differences, we hypothesize that lower FA in older adults compared to younger adults for all three tracts will moderate the negative relationship between age and episodic details.

Conclusions: Understanding the structural underpinnings of autobiographical memory will help illuminate how age-related changes in autobiographical memory retrieval are induced. The results from this study will not only clarify the neural substrates of episodic retrieval, but will help us understand the impact of aging on brain-behavior relationships.

Poster 103

THE PERCEIVED BENEFIT OF NATURE ON THE WELL-BEING OF SKILLED NURSING FACILITY RESIDENTS. O'Neil L, Sokoloski M, Andersson E. Midwestern University; Arizona Alzheimer's Consortium.

Background: A systematic review was performed to examine the effectiveness of nature on the perceived well-being of residents living in skilled nursing facilities.

Methods: Five databases were searched up to 2018. Titles, abstracts, and full articles were screened by the researchers and discussed with a third reviewer when necessary. Level of trustworthiness was assessed. Thematic analysis was utilized to synthesize results.

Results: Four studies with strong trustworthiness, including one systematic review, were included. Three themes and eight key concepts were identified. Views and experiences of nature are discussed in relation to how themes are thought to have an effect on the perceived well-being of residents.

Conclusions: Participation in both nature and nature simulated environments was shown to improve residents' perceived well-being while living in skilled nursing facilities. Future research should focus on the experience of residents without dementia and on universal designs for nature components in facilities.

Poster 104

CONTEXT-DEPENDENT MEMORY IN COGNITIVELY-NORMAL OLDER E4 CARRIERS AND NON-CARRIERS. Palmer JM, Lawrence A, Grilli M, Talboom J, Huentelman MJ, Ryan L. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The ability to distinguish between items, such as objects, that are highly similar to one another requires the use of pattern separation or orthogonalizing information into distinct representations in the brain. Older adults generally perform worse on pattern separation tasks compared to younger adults. Specifically, older adults are less likely to correctly identify similar objects and more likely to incorrectly identify a similar object as one that they have seen before. This suggests that older adults may have a decreased ability to create distinctive neural representations of objects with multiple overlapping features, compared to younger adults.

Context also plays an integral role in visual perception and recognition memory for objects, and the context in which an object is viewed can lead older adults to make even more similarity judgment errors. Older adults are more likely to make pattern separation errors (i.e. falsely recognizing similar objects as "old") when these similar objects are embedded in a context that was observed previously. Age-related impairment in pattern separation may therefore be a combination of a lack of utilizing details along with an over-reliance on the familiarity of the context in which an object is placed. Previous evidence suggests that changes in perirhinal cortex functioning may be the neural mechanism underlying older adults' bias toward context familiarity. In contrast, recent preliminary data from our laboratory suggest that older adults who carry the APOE e4 allele are less likely to be influenced by the scene context during object recognition compared to older non-carriers. The e4 allele may confer a memory benefit that moderates older adults' susceptibility to rely on contextual familiarity, rather than object details.

Methods: Participants were recruited from an existing pool in our laboratory. Older adults were carefully screened to exclude neuropathological conditions. Genetic status was determined from saliva by the Translational Genomics Institute (Tgen) in Phoenix, Arizona. For the behavioral task, objects were embedded in semantically-related scenes and presented one at a time on a computer screen. Participants indicated whether each presented object was "new", "similar", or "different" compared to objects seen previously. Each object was either embedded in a context that was previously presented, a new context that had not been seen before, or on a white background. Behavioral performance was compared between e4 carriers and noncarriers, using age as a continuous covariate.

Results: Our results indicate that carriers and noncarriers do not differ on traditional recognition (i.e. correctly identifying an old object as old). However, consistent with our preliminary data, older e4 carriers made fewer pattern separation errors than non-carriers, and were less susceptible to the influence of repeated contexts.

Conclusions: The results suggest that the presence of the e4 allele may provide a memory benefit to older adults because e4 carriers may not be biased toward relying on context over detail during object recognition.

Poster 105

CEREBRAL ARTERY REACTIVITY IN ADULT APOE3 AND APOE4 MICE. Patel RG, Souders L, Hoxha B, Ion E, Vallejo-Elias J, Jones CB, Powell J, Virden T, Struthers J, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common form of dementia, and is the 6th leading cause of death in the US. Growing evidence supports a link between AD and cardiovascular disease (CVD). Variant isoforms of apolipoprotein E (APOE) are risk factors for both AD and CVD. The most common APOE isoform, APOE3, has neutral risk for developing AD, whereas APOE4 increases AD risk. In order to study APOE-mediated processes, cerebral vessels were isolated from mice expressing human-ApoE targeted replacement of APOE3 (B6.129P2-Apoetm2(APOE*3)Mae N8) and APOE4 (B6.129P2-Apoetm3(APOE*4)Mae N8)(Taconic Labs). Our objective was to characterize vascular function by assessing myogenic tone (MT) and mechanical characteristics in the posterior cerebral artery (PCA) isolated from APOE3 and APOE4, male and female mice. We hypothesize that APOE4 expression in female mice alters vascular smooth muscle function, leading to vascular remodeling and altered cerebrovascular structure/function in PCAs compared to PCAs isolated from age matched control (APOE3) mice.

Methods: PCAs were rapidly isolated from adult (12 month), male and female, APOE3 and APOE4 mice, cleaned of connective tissue, cut into 5mm segments, and cannulated in an arteriograph chamber to assess mechanical characteristics and myogenic tone (MT). Upon equilibration, vessels were challenged with 60mM [K+]o at an intraluminal pressure of 60mm Hg. Vessels not responding to elevated [K+]o were not used in the study. Active/passive wall tension, wall thickness, distensibility, stress/strain and MT was measured with step-wise increases in intraluminal pressure (10mm Hg to 140mm Hg).

Results: PCAs from female APOE3 mice showed greater MT than PCAs from male APOE3 mice ($P<0.05$). In addition, female APOE4 mice showed greater MT than male APOE4 mice ($P<0.05$). When challenged with 60mM [K+]o, all groups showed similar % constriction. Passive wall tension was lower in female APOE4 compared to male APOE4 mice ($P<0.05$). Male APOE4 mice showed greater wall thickness than female APOE4 mice and male APOE3 mice ($P<0.05$). Preliminary data suggests a difference in distensibility between male and female APOE4 mice but no differences in stress/strain throughout the groups.

Conclusions: Our data suggests PCA structure and function are altered in APOE4 mice compared to age matched APOE3 mice. Increased MT in female APOE3 and APOE4 mice compared to males indicates sex differences in the PCA's. Elevated MT observed in APOE4 female mice may be a result of vascular remodeling. Our data suggests differences in mechanical characteristics between male and female APOE3 and APOE4 mice. We continue to collect data to better understand these differences.

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Poster 106

AN ASSESSMENT OF THE TRANSITION TO MENOPAUSE IN THE RAT IN THE TGF344-AD MODEL OF ALZHEIMER'S DISEASE. Peña, VL, Northup-Smith S, Woner VE, Bulen HL, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: In the United States, Alzheimer's Disease (AD) is known to be the sixth leading cause of death with over 5.7 million Americans currently diagnosed. Of those diagnosed, roughly two-thirds are women. It is clear that as our population is aging and AD diagnoses are increasing, we need to further investigate this increased risk of AD in women. One possible reason for this increased risk is that women undergo a transition to reproductive senescence which is not as extreme as that experienced by men. Previous preclinical assessments of menopause and AD have been primarily limited to methods of surgical menopause, usually via ovariectomy (the surgical removal of the ovaries). The current project utilized 4-vinylcyclohexene diepoxide (VCD) to model follicular depletion and transitional menopause in the ovary-intact TgF344-AD transgenic rat model of AD expressing two human genes: human amyloid precursor protein (APPSW) and presenilin 1 (PS1E9). This model displays A plaque-like and neurofibrillary tangle-like pathology in addition to neuronal loss, as well as some behavioral impairments. The goal of this experiment was to investigate the relationship between follicular depletion and transitional menopause, and AD-like behavior and pathology.

Methods: Young adult female rats were utilized. Four treatment groups were evaluated: wild type (WT) VCD (n=9), WT Sham (n=10), transgenic (TG) VCD (n=10), and TG Sham (n=10). Rats received either VCD injections or Sham injections, followed by a behavioral battery that included the Water Radial Arm Maze (WRAM) to assess spatial working and reference memory, the Morris Water Maze (MWM) to assess spatial reference memory, the Open Field Task to assess locomotor activity and anxiety-like behavior, as well as the Visible Platform Task as a control test to assess motor and visual acuity and to confirm ability to perform the procedural components of a water-escape maze task. After the behavioral battery, rats were sacrificed and brains, blood serum, uterine horn weight, and ovaries were collected.

Results: Results indicated that TG rats were impaired compared to WT rats during learning on the WRAM. The data also indicated that menopause induction had a negative cognitive impact on the WT rats, but not the TG rats, for WRAM performance. There were no group differences on the control task. Data are still being analyzed for the MWM and Open Field tasks.

Conclusions: Initial data analyses suggest that the TG animals are impaired while learning a complex task involving both working and reference memory in the TgF344-AD model, and that whether transitional menopause influences these outcomes might depend on TG status. Further analysis of AD-like pathology, ovarian histology, and hormone levels are underway for these behaviorally-tested rats so that relationships between transitional menopause status, behavioral outcomes, and AD-like pathology can be better understood.

Poster 107

LET'S TALK ABOUT SEX (HORMONES): COGNITIVE CHARACTERIZATION AND EVALUATION OF GONADAL HORMONE DEPRIVATION IN A RAT MODEL OF ALZHEIMER'S DISEASE. Peña, VL, Bulen HL, Northup-Smith S, Barker C, Woner VE, Prakapenka AV, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: As of 2018, the Alzheimer's Association estimates that in the United States alone, 5.7 million individuals are living with Alzheimer's Disease (AD), with almost two thirds of those individuals women. As the population continues to age, it is increasingly imperative to make advancements in our understanding of AD progression and treatment, while additionally focusing on why women have a potential increased risk of developing the disease. In recent years, the TgF344-AD transgenic rat model of AD expressing mutant human amyloid precursor protein (APPSW) and presenilin 1 (PS1 Δ E9) genes has been developed. This model exhibits A β plaque-like pathology, tau-like pathology leading to neurofibrillary tangles, and neuronal loss; although it has been less studied, behavioral impairment has also been observed.

Methods: The current project utilized the TgF344-AD rat model to systematically characterize cognition in male and female rats with or without gonadectomy (the surgical removal of the gonads, Gdx). The goal of this experiment was to delineate the role of hormone deprivation in this TgF344-AD model to elucidate whether Gdx in both males and females plays a role in behavioral impairments and AD-like pathology. Eight treatment groups were included in this study: male wild type (WT) Sham (n=10), female WT Sham (n=10), male WT Gdx (n=10), female WT Gdx (n=10), male TG Sham (n=10), female TG Sham (n=10), male TG Gdx (n=10), female TG Gdx (n=10), for a total of 80 rats. In adulthood, all animals received surgery and underwent a behavioral battery including cognition, a test of locomotor activity and anxiety-like behavior, and a control task to evaluate motor and visual acuity.

Results: For both sexes, animals with the TG genotype were impaired during learning compared to WT animals. Additionally, males that were of the TG genotype were particularly sensitive to the negative effects of gonadal hormone deprivation during learning. During the latter asymptotic portion of testing, both sexes showed improvements in handling an increasing working memory load after their respective gonadal organs were surgically removed. There were no genotype or hormone differences on the control task. The data for the task measuring locomotor activity and anxiety-like behaviors are still being scored and analyzed.

Conclusions: The data analyzed thus far from this study testing the TgF344-AD rat model of AD indicate that TG animals of both sexes exhibit learning impairments compared to their respective WT counterparts. Additionally, the data indicate that hormone loss is also impacting behavioral outcomes, particularly in males. Pathology assessments are ongoing in these behaviorally-tested animals to allow study of relationships between pathology and behavioral outcomes. We hope this work will allow a better understanding of the interactions between sex, hormones, and AD-associated behavior and pathology.

Poster 108

INVESTIGATING GENETIC SEX DIFFERENCES TO EXPLAIN ALZHEIMER'S DISEASE MECHANISMS. Peters M, Natri H, Evanovich A, Wilson MA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease is a form of dementia that causes irreversible brain tissue damage that affects an estimated 5.4 million Americans. Alzheimer's disease disproportionately affects women: women at the age of 65 have a 1 in 6 chance of developing the disease while men of the same age have a 1 in 11 chance. Evidence is emerging that the severity and progression of Alzheimer's disease are affected by the immune system. Notably, women are four times more susceptible to autoimmune diseases than men, and the X chromosome is enriched for genes expressed in the immune system. Sex differences in gene expression in the brain could be due to genetic differences (genetic females have two X chromosomes while males have one X and one Y), hormonal differences (gonadal hormones such as testosterone, progesterone, and estrogen are notably different between the sexes), or a combination of the two. Genetic sex differences in gene content and expression have been shaped by millions of years of evolution. Here we describe the landscape of genetic sex differences in RNAseq data across 13 regions of healthy brains.

Methods: In this study, to minimize artifacts due to different methodological assumptions, we employed multiple approaches for gene expression quantification and inference of differential expression. Transcript and gene expression levels were quantified using an alignment based method (HISAT2 and featureCounts) as well as a quasi-mapping based method (Salmon). The resulting count data were used to test for differential gene and isoform expression using four different popular approaches (EdgeR, LimmaVoom, DESeq2, and IsoformSwitchAnalyzeR). We quantified how different statistical assumptions and the algorithms themselves affected sex-differential expression analysis of RNAseq data derived from thirteen different types of brain tissue.

Results: Preliminarily, we find that there are substantial variations in the magnitude of sex differences across the brain, regardless of which methods are implemented. The code is available at: https://github.com/SexChrLab/GTEx_Brains.

Conclusions: Our results emphasize the need for future studies to carefully consider the regions of the brain sampled, and the sex of the samples in cases and controls.

Poster 109

THE EFFECTS OF FAMILY HISTORY OF ALZHEIMER'S DISEASE AND APOLIPOPROTEIN E4 STATUS ON COGNITIVE FUNCTIONS. Sangam S. Stickel A. Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Epidemiologic research indicates that a first-degree family history of Alzheimer's Disease (AD) increases risk of developing the disease (Cupples et al., 2014). Persons with a family history of AD perform worse on measures of verbal learning and memory compared to persons without a family history of AD (Jonaitis et al., 2013). Presence of another risk factor for AD, the apolipoprotein (APOE) E4 allele, is also associated with poorer verbal memory before the onset of the disease. However, the interaction of family history of AD and the apolipoprotein E4 allele on verbal learning and memory is relatively understudied. The present study aimed to determine how family history of AD and the interaction between family history and APOE genotype affect memory and other cognitive functions in cognitively healthy older adults.

Methods: Forty individuals with a family history of AD (mean age = 69 years) were matched on age, gender, education and APOE status to 41 individuals without a family history (mean age = 70 years). All participants completed a neuropsychological battery. Tests of interest included the California Verbal Learning Test and Wechsler Memory Scale- III Logical Memory and Digit Span Backward subtests. The latter test was a measure of working memory. In SPSS, general linear models tested the main effects of family history and APOE E4 status on cognitive measures, controlling for age, gender, and education. We also tested the interactions between family history and APOE E4 status.

Results: Family history groups did not differ on any cognitive measure. APOE E4 carriers had poorer learning, short delay free recall, long delay free recall, and recognition on the CVLT as well as poorer delayed story recall on Logical Memory compared to non-carriers. APOE groups did not differ on Logical Memory immediate recall nor Digit Span Backward. There was a significant interaction between family history of AD and E4 status on Digit Span Backward such that those with both risk factors performed worse than E4 carriers without a family history. E4 non-carriers did not differ from each other based on family history status. The interaction did not predict performance on any other cognitive task.

Conclusions: Taken together, APOE E4 status, but not family history of AD, independently predicts learning and memory in our sample of cognitively healthy older adults. Surprisingly, the two risk factors interacted to impact working memory performance but not memory performance.

Poster 110

SEX DIFFERENCES IN COGNITIVE AND SYMPTOM PROFILES OF OLDER ADULTS WITH AUTISM SPECTRUM DISORDER. Stoeckmann M, Baxter LC, Smith CJ, Foldes E, Webb C, Gonzales A, Braden BB. Arizona State University; Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona Alzheimer's Consortium.

Background: Theories have suggested that females with autism spectrum disorder (ASD) demonstrate higher levels of symptom masking relative to males, and a proposed masking mechanism is executive functioning. Declines in executive functioning are a hallmark of normal aging and are also observed in aging adults with ASD, suggesting that aging may reduce masking abilities. Furthermore, if females with ASD are preferentially engaging executive function strategies for symptom masking, aging may have a greater effect on age-related symptom exacerbation. However, no studies have characterized executive function sex differences in an older adult sample and its relationship with ASD symptoms. We aimed to provide a preliminary characterization of sex differences on two measures of executive functioning in mid-to-older adult men and women with ASD and its association with ASD traits.

Methods: Participants were mid-to-older (40-70 years) adult men or women of average intellectual functioning with ASD or NT development (female ASD: n=11; female NT: n=12; male ASD: n=29; male NT: n=23). Sex, diagnosis, and sex by diagnosis interactions were examined using Analysis of Variance for behavioral regulation (Wisconsin Card Sorting Task; WCST) and a metacognitive (Tower of London; ToL) measures of executive functioning. Relationships between executive functioning and ASD traits were examined using the Social Responsiveness Scale – 2nd Edition (SRS-2) Social Cognition Subscale and the Adult Repetitive Behaviors Scale (RBQ-2A). IQ was included as a covariate in all analyses.

Results: For WCST, there was a significant main effect of diagnosis ($F_{1,71}=12.878$, $p=0.001$) and a significant diagnosis by sex interaction ($F_{1,71}=4.030$, $p=0.049$). Both women and men with ASD made more errors than their NT counterpart (women: $p=0.004$, novel finding; men: $p=0.044$, one-tailed replication); but, the magnitude of difference was greater for women with ASD (women: $d=0.972$; men: $d=0.48$; Fig. 1a). No significant main effects or interaction were observed for the ToL. However, exploratory post hoc analysis showed that females with ASD demonstrated more planning errors than males with a moderate effect size ($d=0.46$) that approached significance ($p=0.107$; Fig. 1b). In male and female ASD groups, correlations were observed between the SRS-2 Social Cognition Subscale and ToL performance, such that worse ToL performance was associated with increased ASD-related social behavior (female ASD: $r_7=0.70$, $p=0.036$; male ASD: $r_{27}=0.39$, $p=0.045$; Fig. 2a). Alternatively, the RBQ-2A showed a significant correlation with WCST performance in females with ASD but not males (female ASD: $r_8=0.70$, $p=0.026$; male ASD: $r_{21}=-0.09$, $p=0.686$), such that more errors were associated with increased repetitive behaviors (Fig. 2b).

Conclusions: In one of the first investigations of sex differences in mid-to-older adults with ASD, this study shows a tendency toward greater executive function difficulties in females with ASD compared to males with ASD. Furthermore, women with ASD show a stronger association between ASD traits and executive functioning than men. This suggests that older adult women with ASD may capitalize even further on executive functioning for symptom masking relative to men with ASD. Longitudinal research on sex differences in age-related cognitive and symptom changes are warranted.

Poster 111

EFFECTS OF EXPRESSION OF HUMAN APOE3 AND APOE4 ON ELASTIC PROPERTIES OF MURINE AORTAE. Strange T, Dickman R, Pascual A, Esfandiarei M, Jones C, Jentarra G, Vallejo-Elias J, Jones TB. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer disease (AD) is a chronic, progressive neurodegenerative disorder of uncertain etiology that affects millions of individuals worldwide. Although aging is the predominant risk factor for late-onset forms of this disease (LOAD), carriers of the ϵ 4 isoform of apolipoprotein E (ApoE4) are at greater than expected risk for development of LOAD. ApoE is a lipid-binding protein that plays a major role in cholesterol metabolism in the brain and periphery and ApoE4 is associated with increased prevalence of various cardiovascular disorders, including atherosclerosis. Because cardiovascular disease is a common comorbidity in AD patients, it is possible that peripheral vascular dysfunction contributes to Alzheimer pathogenesis. Vascular risk factors such as hypertension and hypoglycemia, common in AD patients, cause blood-brain barrier dysfunction and damage to the neurovascular unit. Whether ApoE4 contributes to these vascular risk factors in AD is unknown. Studies have shown that elastin and other proteins of elastic fibers may contribute to hypertension and other cardiovascular diseases including atherosclerosis, thus disruption of elastic fibers may contribute to the vascular dysfunction associated with AD. The purpose of this project is to determine whether ApoE4 affects the structural integrity of the aorta by disrupting elastic fibers which are a prominent component of big non-resistance peripheral arteries.

Methods: In this study, we compared the structural characteristics (elastin fiber fragmentation and organization) of the aorta in wild type C57BL/6, human targeted replacement APOE3, and human targeted replaced APOE4 mice. Mice were euthanized at 12 months of age, the aorta dissected, and processed for routine histology. Paraffin-embedded aortic sections were mounted on slides and elastic fibers were stained using modified Verhoeff Van Gieson staining. Images of aortic rings were captured at 40X magnification and analyzed in Image J (NIH). Elastic fibers were manually traced using the freehand line tool in Image J and the number and length of each fragment recorded. A total of 3 sections were analyzed from each sample.

Results: Aortae from ApoE4 mice demonstrated a significantly increased number of elastin fiber fragments (one-way ANOVA; $p = 0.03$) compared with C57/BL6 mice. The number of fragments from ApoE3 and C57/BL6 samples were not different, nor did ApoE3 significantly differ from ApoE4. The average length of fibers was significantly decreased in both ApoE3 and ApoE4 groups when compared to the C57/BL6 group (one-way ANOVA followed by Tukey post-hoc for multiple comparisons; $p = 0.01$). In addition, the frequency of aortae displaying webbing, or the interlinking of elastic fibers between concentric layers, appeared to be increased in both groups of ApoE mice compared with C57/BL6 mice, although to a greater extent in ApoE4 aortae.

Conclusions: The main finding of this study is that aortae of ApoE4 mice have increased fragmentation, as evidenced by an increase in the number of elastic fiber fragments and the decreased length of the fibers. This was associated with enhanced webbing, which indicates a lack of overall organization of the elastic fibers. Collectively these data suggest a role for the human ApoE4 allele in disruption of aortic wall integrity which may have implications for peripheral vascular dysfunction in AD.

Poster 112

AN EVALUATION OF THE LEVONORGESTREL-RELEASING INTRAUTERINE DEVICE AND ITS IMPACT ON COGNITIVE FUNCTION IN A RAT MODEL. Strouse IM, Prakapenka AV, Northup-Smith SN, Woner VE, Peña VL, Koebele SV, DeNardo D, Sirianni RW, Bimonte-Nelson HA. Arizona State University; Barrow Neurological Institute; University of Texas Health Science Center at Houston; Arizona Alzheimer's Consortium.

Background: It is claimed clinically that Levonorgestrel (Levo)-releasing intrauterine devices (Levo IUDs), such as Mirena, administer the synthetic hormone Levo in a localized fashion. While some research supports this claim, other scientific evidence suggests that Levo released by Levo IUDs also enters into systemic circulation. Given that Levo can positively impact memory when administered subcutaneously in the rat model (Prakapenka et al., 2018) and a recent marked increase in IUD use, it is crucial to evaluate whether Levo IUD use impacts cognitive function. This study aimed to determine whether the presence of IUDs, either containing or not containing Levo, impacts cognition in a rat model, where the ovaries were either removed or kept intact.

Methods: Rats received either Sham or Ovariectomy (Ovx) surgery (removal of the ovaries), plus an additional surgical manipulation of either no IUDs, Blank IUDs (without Levo), or Levo IUDs, enabling us to evaluate the effects of IUD administration alone or in concert with circulating ovarian hormones. After surgery, all treatment groups were tested on the Water Radial Arm Maze (WRAM) to evaluate spatial working and reference memory.

Results: At sacrifice, upon investigation of the uteri, it was determined that some of the IUDs were expelled and no longer present in animals from the following groups: Sham–Blank IUD, Ovx–Blank IUD, and Sham–Levo IUD. Results from the remaining three groups showed that, compared to Sham–no IUD animals, Ovx–no IUD animals had marginally impaired working memory performance, and that Ovx–Levo IUD animals had marginally enhanced memory performance, not specific to a particular memory type, compared to Ovx–no IUD animals. Ovx–Levo IUD animals also had increased uterine horn weights and qualitatively more cells present in their vaginal smears relative to Ovx–no IUD animals, confirming local uterine stimulation by presence of the Levo IUDs.

Conclusions: Overall, these results indicate that a Levo-containing IUD may impact memory, although these findings are marginal and preliminary, and must be expanded upon and replicated with an alternative IUD implantation procedure. The potential for the Levo IUD to exert effects on cognition suggests a need for future research on how contraceptive use impacts women's health globally, as well as specifically to memory, across the lifespan.

ISOMETRY INVARIANT SHAPE DESCRIPTORS FOR BRAIN SURFACES: APPLICATIONS TO ALZHEIMER'S DISEASE. Tu Y, Wen C, Wu J, Caselli RJ, Chen K, Reiman EM, Lepore N, Gu X, Wang Y. Arizona State University; Stony Brook University; Mayo Clinic Arizona; Banner Alzheimer's Institute; Children's Hospital, Los Angeles; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD), an irreversible neurological degeneration, is the most common cause of dementia among older adults. It is commonly believed that treatment could have great benefits if it is started during the earliest stages of AD. Therefore, there is a need to develop sensitive AD biomarkers for evaluating AD burden, progression and response to interventions. Comparing to other measurement, imaging features extracted from magnetic resonance imaging (MRI), which may identify subtle shape alterations, have great potential as valid imaging biomarkers. However, the complex geometry of cortical surfaces poses a major challenge to defining such a feature that is sensitive in qualification, robust in analysis, and intuitive in visualization. Among various the surface-based biomarkers, isometry invariant shape descriptors, which have the same value independent of the surface representation and surface location, are of great interest in depicting the intrinsic shape properties.

Methods: We propose an isometry invariant shape descriptor with the proposed spherical area preserving mapping of cortical surfaces. For each subject, we acquire the anatomical MRI scan. Then we adopt Freesurfer to extract cortical surfaces. Further, we map cortical surfaces to the unit sphere, in a sense of preserving area around each vertex. Based on the area preserving mapping, we extract shape descriptors to quantify the shape dilation comparing to the registration map. We use Beltrami coefficient to quantify the shape dilation. For comparisons between subjects, our shape descriptors is resampled with same topology across subjects.

Results: The spherical area-preserving algorithm is achieved. The algorithm can map cortical surface to unit sphere within minutes for the whole mesh with more than 160,000 vertices. This is the first time globally optimized area-preserving mapping is proposed. Besides, a virtual zoom can be easily incorporated to help zoom regions for visual inspection. With the shape descriptors, we detected specific regions, e.g. medial temporal lobe areas, that reflect the emerging of AD. Lastly, we trained an SVM classifier, which can predict subject's clinical status (AD or cognitively unimpaired) with an accuracy of 94%. Our shape descriptors outperform some popular isometry invariants, e.g. cortex volume (accuracy 54%), spherical harmonic coefficients (accuracy 77%).

Conclusions: The proposed Beltrami coefficient, extracted from area-preserving map and alignment map, is efficient in abnormal detection, intuitive in geometry and automatic in process. Besides, the spherical area-preserving provides a fast and stable embedding for genus zero cortical surface.

Poster 114

USING DIFFUSION TENSOR IMAGING TO IDENTIFY STRUCTURAL NEURAL CORRELATES OF MOTOR LEARNING AND VISUOSPATIAL PROCESSES IN COGNITIVELY-INTACT OLDER ADULTS. VanGilder JL, Fitzhugh MC, Rogalsky C, Schaefer Y. Arizona State University; Arizona Alzheimer's Consortium.

Background: We have recently shown that by testing older adults' visuospatial function, we can predict their motor learning capacity. In fact, our studies show that older adults with above-normal visuospatial scores retained up to four times as much skill as those with below-normal visuospatial scores, regardless of baseline upper extremity motor function, age, and other impairments in language, attention, or delayed memory. We hypothesize that visuospatial tests have predictive value because they probe the health of critical neural structures for motor skill learning. Classic neuropsychological studies have long supported the role of parietal cortex in visuospatial function and more recent neuroimaging studies have shown that the structural integrity of white matter tracts between parietal and frontal cortices is related to motor skill learning. More specifically, our preliminary data suggest that the right superior longitudinal fasciculus (SLF), a frontoparietal white matter tract, may be a candidate neural pathway for explaining our previous behavioral findings and for predicting motor skill learning in older adults. Although the parietal cortex has long been linked to visuospatial function, there are conflicting reports on the relationship between the structural integrity of neural pathways emerging from the parietal cortex (i.e., the right SLF) and different visuospatial abilities. Thus, the purpose of this ongoing study is to address the gap in knowledge of the relationship between right SLF structure and visuospatial function.

Methods: Cognitively-intact older adults (n=10, age>65) completed the Rey Complex Figure Test and Recognition Trial (RCFT), an age-adjusted visuospatial exam that assesses visual construction and memory. Participants also underwent diffusion-weighted magnetic resonance imaging, and a tensor model was applied to quantify right SLF fractional anisotropy (FA), a measure of white matter structural integrity. Participant RCFT test scores were entered into a linear regression model as a predictor of right SLF FA.

Results: Results indicate that right SLF FA positively correlated with RCFT overall score ($R\text{-sqr}=0.394$, $p=0.0519$), where higher right SLF FA values predict better RCFT scores.

Conclusions: These preliminary data serve as proof-of-concept and support our hypothesis that visuospatial processes may be integrated in the right SLF such that clinical visuospatial testing may predict right SLF structural integrity. The results of this study may indicate that paper-and-pencil visuospatial tests currently used in clinical settings could be used as a cost-effective proxy for neuroimaging, particularly in cases of contraindication or lack of imaging resources.

Poster 115

OUT OF THE LAB, INTO THE REAL-WORLD: PRELIMINARY EVIDENCE THAT MEASURING AUTOBIOGRAPHICAL MEMORY RETRIEVAL IN A NATURALISTIC SETTING REPLICATES LABORATORY-BASED FINDINGS. Wank AA, Moseley S, Polsinelli AJ, Glisky EL, Mehl MR, Grilli MD. University of Arizona; Minnesota Epilepsy Group; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: Autobiographical memory interviews allow us to study the complex recollection of specific "real-life" events in a controlled laboratory setting. Such research has revealed that alterations in episodic autobiographical memories (EAMs) is characteristic of many neuropsychological populations. The ability to capture EAMs in everyday life would create opportunities to evaluate how EAM manifests in naturalistic contexts and evaluate the validity of in-lab/clinic EAM assessments. The Electronically Activated Recorder (EAR; Mehl et al., 2001) is a promising candidate to study these everyday EAMs. Participants wear the EAR while it samples 30-second blocks of ambient noise, including conversation, from their environment. The aim of the present study was to examine the content of participants' EAMs detected by the EAR to shed light on the ecological validity of EAM laboratory findings.

Methods: Secondary data analysis of EAMs was conducted on a sample of 102 cognitively normal older adults who wore the EAR. The Autobiographical Interview scoring procedure (Levine et al., 2001) was used to identify episodic and semantic details of autobiographical memories and future thoughts within the content captured by the EAR. We analyzed the scored details for degree of episodic specificity and its relations with demographic and neuropsychological factors.

Results: Null hypothesis significance testing and Bayesian estimation analyses revealed that, similar to lab-based AM interviews, naturalistic EAMs contained mostly episodic details and episodic specificity of one's past events was related to episodic specificity of one's future events. Furthermore, EAM episodic specificity was weakly related to performance on a standardized list-learning measure of episodic memory. Other effects observed in the lab were not replicated, such as episodic specificity differences between men and women and its relationship with working memory.

Conclusions: Using the EAR to gather EAMs in naturalistic settings replicate some findings presented in the laboratory-based EAM literature. Clinically, our results support the use of EAM tasks as measures of real-world cognitive functioning. We also suggest that the EAR could be a useful research tool for better understanding EAM content in everyday life.

Poster 116

THE COGNITIVE EFFECTS OF THE HIGHLY SELECTIVE PROGESTIN NESTORONE IN A RAT MODEL OF SURGICAL MENOPAUSE. Woner VE, Koebele SV, Northup-Smith S, Willeman M, Barker C, Schatzki-Lumpkin A, Valenzuela Sanchez M, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Progestins, synthetic hormones that mimic some of the effects of endogenous progesterone, are prescribed for a myriad of health reasons to women across their reproductive and menopausal years, most commonly in combination with an estrogen to oppose estrogen-induced uterine hyperplasia. Some research has shown that administration of several different progestogens, including progesterone, is detrimental to cognition; however, the potential mechanisms behind these cognitive outcomes are unknown. One possible explanation is that the parent molecules from which progestins are derived yield biological activities and affinities beyond the progesterone receptor that in turn modulate cognitive outcomes. These findings, along with research demonstrating the role of some progestogens with strong affinities for the progesterone receptor (PR) in neurogenesis and neuroprotection, suggest that a 'purely- progestational' molecule that maximizes PR affinity and minimizes affinities to other receptors may be cognitively beneficial.

Methods: We evaluated the cognitive effects of a daily regimen of Nestorone (segesterone acetate), a 19-norprogesterone derivative with a strong and pointed PR affinity and no androgenic or estrogenic receptor affinity, in a rat model of surgical menopause. Middle aged Fischer-344 rats were given either Sham surgery or Ovariectomy (Ovx), which is the surgical removal of the ovaries. Animals then received daily administration of either medroxyprogesterone acetate (MPA), which has previously been shown in our laboratory to induce cognitive deficits, Nestorone, given at a low or high dose, or the Vehicle (given to the Sham group and one Ovx group). Next, animals were tested on a behavioral battery involving spatial working and reference memory tasks including the Water-Radial Arm Maze (WRAM) and the Morris Maze, as well as the Visible Platform (VP) control task, and the Open Field Test (OFT) to measure activity and anxiety-like behavior.

Results: Findings demonstrate that animals receiving the low dose of Nestorone demonstrated impaired spatial working memory performance compared to Ovx-Vehicle treated rats on the WRAM, and that Ovx-Vehicle rats, along with Ovx rats treated with the high dose of Nestorone, exhibited deficits in delay-induced memory retention on the WRAM. We additionally found delay-induced memory retention impairments for MPA-treated animals on the WRAM, replicating our previous findings of MPA-induced memory compromise. On the Morris Maze, MPA-treated rats and rats treated with the high dose of Nestorone were impaired relative to Ovx-Vehicle rats.

Conclusions: The cognitive and brain effects of Nestorone merit further study, as previous literature has framed Nestorone as being neuroprotective, whereas the current study found memory deficits with long-term administration at both the low and high doses used herein. Through further neurobiological evaluations, we seek to understand the relationship between Nestorone's biological activity and subsequent behavioral outcomes in the hopes of finding a progestin that improves cognitive and brain health, and can be paired with an estrogen to create a hormone formulation that promotes positive health outcomes for women across the lifespan.

ADDITIONAL POSTER PRESENTATIONS

Poster 117

OVARIAN HORMONES MEDIATE ACQUISITION OF NICOTINE SELF-ADMINISTRATION AND ACCUMBENS GLUTAMATERGIC PLASTICITY. Leyrer-Jackson JM, Pina J, Ulangkaya, J, Bimonte-Nelson H, Gipson CD. Arizona State University; Arizona Alzheimer's Consortium.

Background: Nicotine addiction in women remains a significant public health liability. Women report greater craving during certain phases of the menstrual cycle, and as such, pharmacotherapies for smoking may be less efficacious in women compared to men, possibly due to interactions with ovarian hormones. Mechanistically, 17- β -estradiol (E2) receptors are located on GABAergic medium spiny neurons (MSNs) within the nucleus accumbens core (NAcore). Synapses on NAcore MSNs undergo rapid, transient plasticity during nicotine seeking due to increased extracellular glutamate during nicotine seeking. We hypothesized that ovarian hormones play an important role in the acquisition of nicotine self-administration as well as NAcore glutamatergic plasticity.

Methods: Female Sprague-Dawley rats were left intact or Ovariectomized (OVX), followed by intravenous jugular catheter implantation. Animals underwent nicotine self-administration, where the active lever yielded one infusion (0.02 mg/kg/infusion, i.v.) paired with a compound stimulus (lights + tone). A subset of OVX females received E2 supplementation for the last 4 days of self-administration. Animals were then sacrificed for electrophysiological recordings.

Results: OVX females did not readily acquire nicotine self-administration compared to intact females ($p < 0.05$). E2-treatment increased self-administration to levels similar to intact females. Additionally, deprivation of ovarian hormones due to OVX potentiated NAcore MSNs following nicotine self-administration, which was reversed by E2-treatment in OVX females (ANOVA, $p < 0.05$).

Conclusions: These results suggest that ovarian hormones mediate nicotine reinforcement. As well, these results indicate that following nicotine self-administration in intact females, NAcore synapses rest in a depotentiated state, which may increase nicotine use vulnerability. Finally, cessation of ovarian hormones may induce metaplasticity in NAcore synapses, which is reversed by E2-treatment. Taken together, these studies reveal control of ovarian hormones on nicotine addiction and underlying NAcore glutamatergic plasticity. The next study will focus on middle aged-females to determine neurobiological underpinnings of age-related changes in nicotine motivation and reward circuitry.

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Poster 118

AN ADAPTIVE SAMPLING FRAMEWORK FOR PARTIAL VOLUME CORRECTION OF β -AMYLOID PET. VanGilder P, Luo J, Goradia DD, Ghisays V, Protas H, Thiyyagura P, Malek-Ahmadi M, Lee W, Chen Y, Devadas V, Reiman EM, Su Y. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Positron emission tomography (PET) provides important in vivo measurement of brain pathology such as amyloid deposition in the studies of neurodegenerative disease and clinical trials. However, PET images suffer from partial volume effects due to their low spatial resolution, which complicate the measurement of amyloid plaques. To compensate for these effects, several partial volume correction (PVC) approaches have been investigated, although limited work has been done to investigate and validate voxel-wise approaches.

Methods: Here, an adaptive sampling partial volume correction (ASPVC) technique was used to generate partial volume corrected amyloid burden images and surface maps using a maximum likelihood approach. Nineteen participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) data base with baseline and follow-up florbetapir PET scans were included in this study. All the subjects were amyloid positive and had evidence of cognitive impairment at baseline, and the mean time interval between scans was 1.97 years. Amyloid burden was quantified using mean-cortical standard uptake value ratio (SUVR) that had undergone ASPVC, as well as uncorrected and regional spread function (RSF) corrected SUVRs. Sensitivity to longitudinal changes in amyloid burden were compared by examining sample size estimates for a hypothetical interventional clinical trial. Annualized mean and standard deviation were calculated for each subject, and sample sizes were estimated assuming a 25% treatment effect at a power of 80% and significance level of 5% (two-sided t-distribution).

Results: SUVR values obtained using ASPVC were highly correlated with values obtained without PVC and with RSF PVC ($R^2=0.86$ and 0.95 , respectively), as was the annualized change in SUVR between baseline and follow-up ($R^2=0.86$, 0.82). When looking at estimated sample sizes, using uncorrected SUVR would require the greatest number of subjects ($n=2008$). Both PVC methods reduced this number greatly, though ASPVC yielded a smaller required sample size ($n=520$) than RSF PVC ($n=867$).

Conclusions: ASPVC outperforms non-corrected and RSF PVC for sensitivity to longitudinal changes in amyloid burden when using mean-cortical SUVR and may be useful for reducing sample sizes need for clinical trial applications or tracking changes in amyloid burden. This approach may also improve quantification of tau and other PET modalities as well.