



ANNUAL REPORT

July 1, 2017 to June 30, 2018

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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 four affiliated organizations, including the Critical Path Institute, Midwestern University, Northern Arizona University, and the University of Arizona College of Medicine, Phoenix. Established in 1998, the Consortium is intended to make a transformational difference in the scientific fight against AD, 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 Reiman, MD, is the Director of the Consortium and its 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 all internationally recognized for their contributions to and leadership roles in the study of AD and/or related disorders. The external advisors 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 of AD, 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. The Consortium

has introduced new ways for different stakeholders to work together, it has provided data, biological samples, and interested research participants to researchers within Arizona 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. The funds are used to support dozens of research projects each year. Almost all of the projects involve researchers from different scientific disciplines, and about half 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 and was noted for its exceptional track record; productivity and impact; 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 March 2018, the ADCC received highly favorable reviews for the proposed addition of a Brain Imaging and Fluid Biomarker Core (grant pending).

Productivity 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 \$1.5 billion in new investments, including more than half of those investments in the last 5 years.

Consortium researchers have made the pioneering contributions to the study of AD, related disorders, and the aging mind and brain, examples of which are noted here:

- They have helped clarify several 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. They have also provided invaluable public resources of genetic and neuronal gene expression; longitudinal and neuropathological data; high-quality brain tissue. Consortium researchers have introduced new endophenotypic approaches and data-sharing and collaborative paradigms to assist researchers around the world in these endeavors.
- They 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. Consortium researchers have provided invaluable resources of data and volunteers from persons at three levels of genetic risk for AD in the Arizona APOE4 Gene Dose Cohort

and in Colombian early-onset AD-causing mutation carriers from the world's largest autosomal dominant AD kindred. They have introduced new experimental paradigms, image-analysis techniques, and composite cognitive tests to help in this endeavor. Their work anticipated and helped to advance the conceptualization of preclinical AD, has informed the design of prevention trials in persons at increased genetic and/or biomarker risk, and helped to launch a new era in AD prevention research.

- 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. Through the McKnight Brain Institute and other research programs, they have played pioneering roles in studies of the aging mind and brain.
- Consortium researchers have played leadership roles in the use of brain imaging in the unusually early detection, tracking, and scientific study of AD, and they have introduced methods to do so 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, supporting their current or future FDA approval for use in the clinical setting.
- They continue to provide a world-leading resource of longitudinal and neuropathological data, brain and body tissues for the study of AD, Parkinson's disease, and related disorders in its Brain and Body Donation Program.
- With >\$500M in NIA, philanthropic and industry funding, they established the Alzheimer's Prevention Initiative (API). The API launched a new era in AD prevention research and established 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 for AD. The API includes a Colombian prevention trial of an anti-amyloid treatment in the world's largest autosomal dominant AD kindred, an international prevention trial of two other anti-amyloid treatments in persons at highest genetic risk for AD in older persons, and other trials on the way. It includes exceptionally large enrollment registries (e.g., www.endALZnow.org); gene-matching and genetic risk disclosure and impact assessment programs to help support interest and enrollment in prevention trials; and other emerging methods and strategies to help find and support the approval of an AD prevention therapy as soon as possible. The API includes better tests of the amyloid hypothesis (the leading AD theory) than failed trials of anti-amyloid treatments in later stages of the disease and ground-breaking clinical trial data and sample sharing agreements. 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—and they continue to leverage state-supported collaborative research studies to advance new ideas, generate new findings, publications, and grants, and attract outstanding researchers and trainees to Arizona.

The Consortium's organizations and researchers have continued to advance several new scientific and clinical initiatives. For instance, they have begun to generate a public resource of detailed molecular data from different brain cell types and regions from clinically and neuropathologically characterized brain donors with and without AD, recruited big data analysis experts to help in the discovery of disease mechanisms and new treatments, and promote interactions with experimental researchers in ways that are likely to lead to a more promising and diversified portfolio of new treatments. They continue to conduct AD prevention trials and prepare for new trials, and they have begun to develop public resources of data and biological samples to advance the study of AD, further accelerate the evaluation of prevention therapies, and have begun to develop new cerebrospinal fluid and blood biomarkers of AD and related disorders. They and their colleagues have begun to advance the study of chronic traumatic encephalopathy in former football players. They have also begun to develop a shared scientific resource of electronic health record data and biological samples from many thousands of persons, including those from our under-represented Latino and Native American communities in the All of Us Research Program.

Our researchers, organizations, and state officials continue to do everything we can to advance the scientific fight against AD, related disorders, and the aging brain, to serve the needs of affected persons and families, and to include our underserved communities in these endeavors. We seek to establish new standards of dementia care and to find and support the availability of effective AD prevention therapy as soon as possible. To find an effective AD prevention therapy by 2025, one of the promising but unproven prevention therapies needs to work. We now have a chance to find out.

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 future plans. We are determined to make a transformational difference in the fight against AD and to do so together.

Arizona Alzheimer's Consortium
20th Annual Conference – Thursday May 17, 2018
Barrow Neurological Institute (Host Institution)
Goldman Auditorium
350 W Thomas Rd.
Phoenix, AZ 85013

POSTER PRESENTATION SET-UP CONTINENTAL BREAKFAST	7:30 – 8:45AM
WELCOME Michael Lawton, MD President and CEO Barrow Neurological Institute	8:45 – 9:00AM
INTRODUCTION Eric M. Reiman, MD Director, Arizona Alzheimer's Consortium	9:00 – 9:15AM
LEON THAL MEMORIAL LECTURE <i>"Do Lessons from Dominantly Inherited Alzheimer's Disease Extrapolate to Sporadic Late Onset Alzheimer's Disease?"</i> John C. Morris, MD Friedman Distinguished Professor of Neurology Director, Knight Alzheimer's Disease Research Center Washington University School of Medicine	9:15 – 10:30AM
ORAL RESEARCH PRESENTATIONS – SESSION I	10:30 – 11:50AM
POSTER SESSION I & LUNCH	12:00 – 1:00PM
POSTER SESSION II & LUNCH	1:00 – 2:00PM
ORAL RESEARCH PRESENTATIONS – SESSION II	2:00 – 3:30PM
CLOSING REMARKS Eric M. Reiman, MD	3:30 – 3:45PM

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Oral Research Presentations

SESSION I	Moderator: Carol Barnes, PhD
10:30 – 10:42AM	Reduced genomic diversity as a risk factor for non-familial young onset Alzheimer's disease. <u>Richard J. Caselli</u> . Mayo Clinic Arizona; Mayo Clinic Rochester; Translational Genomic Research Institute; Arizona State University; Arizona Alzheimer's Consortium.
10:43 – 10:55AM	Oligomeric amyloid β preferentially targets neuronal and not glial mitochondrial-encoded mRNAs. <u>Diego Mastroeni</u> . Arizona State University; Translational Genomics Institute; Arizona Alzheimer's Consortium.
10:56 – 11:08AM	A public cell-specific Alzheimer's and aging brain resource: evaluation and implementation of single cell transcriptomic analyses. <u>Winnie S. Liang</u> . 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.
11:09 – 11:21AM	Using human induced pluripotent stem cells to investigate the contribution of aging to the onset and progression of Alzheimer's disease. <u>David Brafman</u> , Arizona State University; Arizona Alzheimer's Consortium.
11:22 – 11:34AM	Synaptic deficits in C9ORF72-ALS/FTD patient-derived human stem cell differentiated neurons and in vivo models of C9ORF72. <u>Rita Sattler</u> . Barrow Neurological Institute; Cedars-Sinai Medical Center; Arizona Alzheimer's Consortium.
11:35 – 11:47AM	Flortaucipir paired helical filament tau burden and correlation with cognitive decline in MCI patients without any Aβ. <u>Hillary Protas</u> . Banner Alzheimer's Institute; University of California Berkeley; University of California San Francisco; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Arizona Alzheimer's Consortium

Oral Research Presentations

SESSION II

Moderator: Richard Caselli, MD

2:00 – 2:12PM

Cortical excitability in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis of transcranial magnetic stimulation studies. Ying-hui Chou. University of Arizona; Chang Gung University; Arizona Alzheimer's Consortium.

2:13 – 2:25PM

The heart of the matter: separating Lewy body dementia from Alzheimer's with tissue from Arizona's brain and body donation program. David R. Shprecher. Barrow Neurological Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

2:26 – 2:38PM

Faster cognitive decline in Alzheimer's disease dementia with clinically-unsuspected Lewy body disease. Thomas G. Beach. Banner Sun Health Research Institute; Banner Alzheimer Institute; Barrow Neurological Institute; Mayo Clinic Arizona; University of Arizona; Arizona Alzheimer's Consortium.

2:39 – 2:51PM

Multiscale analysis of three independent sporadic Alzheimer's cohorts reveals disruption of pathogenic molecular, genetic, and clinical networks by human herpesvirus. Benjamin Readhead. Arizona State University; University of Arizona; Banner Alzheimer's Institute; Icahn School of Medicine at Mount Sinai; Institute for Systems Biology; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

2:52 – 3:04PM

Modeling the Alzheimer's Gut Microbiome-Brain Axis using Next Generation Sequencing – Opportunities and Collaborations at the Pathogen and Microbiome Institute. Emily Cope. Northern Arizona University; Arizona Alzheimer's Consortium.

3:05 – 3:17PM

The potential role of microbes in the development of Alzheimer's disease. Garilyn Jentarra. Midwestern University; Arizona Alzheimer's Consortium.

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Poster Presentations

1. **Network covariance of hippocampal subfield volumes associated with healthy aging and the risk for Alzheimer's disease.** Alexander GE, Bharadwaj PK, Raichlen DA, Klimentidis YC, Fitzhugh MC, Nguyen LA, Haws KA, Hishaw GA, Moeller JR, Habeck CG, Trouard TP. University of Arizona; Columbia University; Arizona Alzheimer's Consortium.
2. **Dementia awareness in hospital settings (DAHS).** Allen A, Snyder N, Long C, Johnson K, Nisson L, Dougherty J, Corley D, Rivas C. Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.
3. **Socioemotional and neural correlates of off-task thinking in young and old adults.** Andrews-Hanna JR, Gardiner CK, Helmuth T, Davis AE, Giordano GR, Bennett G, Banich MT, Bryan AD. University of Arizona; University of Colorado; Arizona Alzheimer's Consortium.
4. **Cell-specific characterization of Alzheimer's disease using single cell RNAseq.** Antone JV, Geiger P, Enriquez D, 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.
5. **The influence of age and ASD on verbal fluency network differences.** Baxter, LC Braden, BB Nespodzany, A Wood, EG Smith, CK. Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona State University; Arizona Alzheimer's Consortium.
6. **Faster cognitive decline in Alzheimer's disease dementia with clinically-unsuspected Lewy body disease.** Beach TG, Malek-Ahmadi M, Zamrini E, Sabbagh MN, Shill HA, Adler CH, Jacobson SA, Belden CM, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta S, Burke AD, Shprecher D, Spann B, Tariot PN, Davis KJ, Long KE, Nicholson LR, Intorcchia A, Glass M, Walker J, Callan M, Curry J, Cutler B, Oliver J, Arce R, Serrano GE, Sue LI, Reiman EM. Banner Sun Health Research Institute; Banner Alzheimer Institute; Barrow Neurological Institute; Mayo Clinic Arizona; University of Arizona; Arizona Alzheimer's Consortium.
7. **Update of a regulatory-endorsed clinical trial simulator for Alzheimer's disease (AD): new data incorporation, statistical modifications, and user-friendly graphical user interface development.** Burton JK, Conrado DJ, Corrigan B, Nicholas T, Chen D, Stone J, Sinha V, Willis B, Wang W, Kern VD, Arnerić SP, Romero K. Critical Path Institute; Pfizer; Merck & Co.; Eli Lilly and Company; Novartis Pharmaceutical Corporation; Arizona Alzheimer's Consortium.

8. **Dissociation of performance in hippocampus- and prefrontal cortical-dependent tasks in aging Fisher 344 rats.** Carey NJ, Zempare MA, Nguyen CJ, Bohne KM, Chawla MK, Sinari S, Huentelman MJ, Billheimer D, Barnes CA. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.
9. **Relationships between mean cortical amyloid burden and regional gray matter reductions in Alzheimer's dementia, mild cognitive impairment and unimpaired older adults.** Chen K, Lee W, Jagust WJ, Weiner M, Reiman EM, the Alzheimer's Disease Neuroimaging Initiative. Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; University of California Berkeley; University of California San Francisco; Arizona Alzheimer's Consortium.
10. **Twelve-month glucose metabolism declines in an empirically pre-defined statistical region-of-interest in amyloid-positive persons with Alzheimer's dementia and mild cognitive impairment: updated ADNI findings.** Chen K, Lee W, Kuang X, Luo J, Devadas V, Thiyyagura P, Chen R, Bauer R, Weiner M, Jagust W, van Dyck C, Reiman EM. Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; University of California Berkeley; University of California San Francisco; Yale University; Arizona Alzheimer's Consortium.
11. **Therapeutic progestin nestorone promotes neurogenesis: implications for sustaining regeneration in female brain.** Chen S, Kumar N, Mao Z, Wang T, Sitruk-Ware R, Brinton RD. University of Arizona; Rockefeller University; Arizona Alzheimer's Consortium.
12. **Cortical excitability in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis of transcranial magnetic stimulation studies.** Chou Y-H, Rapcsak S, Chen N-K, Sundman M, Lim K, Ugonna C, Lindley M, Fuglevand A, Mohler J, Huang Y-Z. University of Arizona; Chang Gung University; Arizona Alzheimer's Consortium.
13. **An iPSC-based platform for investigating idiopathic Parkinson's disease.** Corenblum MJ, Annadurai A, Shrestha K, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.
14. **Multivariate analyses of peripheral blood leukocyte transcripts distinguish Alzheimer's, Parkinson's, control and those at risk for developing Alzheimer's.** Delvaux E, Mastroeni D, Nolz J, Chow N, Sabbagh M, Caselli RJ, Reiman EM, Marshall FJ, Coleman PD. Arizona State University; Banner Sun Health Research Institute; University of Rochester Medical Center; Barrow Neurological Institute; Mayo Clinic, Scottsdale; Arizona Alzheimer's Consortium.
15. **Strategic memory Alzheimer's rehabilitation training (SMART) memory program for amnesic mild cognitive impairment (AMCI): reporting the results of a randomized clinical trial.** DenBoer JW. SMART Brain Aging, Inc.

16. **Assessment of dual-task motor function deterioration for detecting cognitive impairment.** Fakhoury S, Gaytan-Jenkins D, Lopez A, Ehsani H, O'Connor K, Zamrini E, Mohler J, Toosizadeh N. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
17. **Longitudinal depressive symptoms and cortical amyloid are associated with cognitive decline in older adults.** Gatchel JR, Rabin JS, Buckley RF, Locascio JJ, Quiroz YT, Vannini P, Amariglio RE, Rentz DM, Johnson KA, Blacker D, Donovan NJ, Sperling RA, Marshall GA. Harvard Medical School; Arizona Alzheimer's Consortium.
18. **The safe and effective applications of essential oils in Alzheimer's dementia.** Geiger, JL. Banner Health; Arizona Alzheimer's Consortium.
19. **The role of nicotinic acetylcholine receptor (nAChRs) in mediating amyloid beta-induced alterations in basal forebrain cholinergic intrinsic excitability.** George AA, Bimonte-Nelson HA, Lukas RJ, Whiteaker P. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.
20. **Improved diagnosis of Parkinson's disease from a detailed olfactory phenotype.** Gerkin RG, Adler CH, Hentz JG, Shill HA, Driver-Dunckley E, Mehta SH, Sabbagh MN, Caviness JN, Dugger BN, Serrano G, Belden C, Smith BH, Sue L, Davis KJ, Zamrini E, Beach TG. Arizona State University; Mayo Clinic College of Medicine; Barrow Neurological Institute; Banner Sun Health Research Institute; University of California San Francisco; Arizona Alzheimer's Consortium.
21. **Comparing cerebral white matter, cerebellar, and pontine reference regions to characterize florbetapir PET measurements of fibrillar amyloid- β burden in PSEN1 E280A mutation carriers and noncarriers from the Colombian autosomal dominant Alzheimer's disease kindred.** Ghisays V, Protas H, Yinghua C, DeMarco E, Tariot PN, Langbaum JB, Quiroz YT, Lopera F, Reiman EM, Chen K. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona State University; Universidad de Antioquia; Massachusetts General Hospital, Harvard Medical School; Arizona Alzheimer's Consortium.
22. **The Alzheimer's Prevention Registry's Genematch program: update on progress and lessons learned in helping to accelerate enrollment into Alzheimer's prevention studies.** Gordon D, Graf H, Walsh T, High N, Nichols J, Reiman EM, Tariot PM, Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Institute.
23. **Measuring pre-clinical cognitive and functional decline over time: separating and combining Alzheimer's specific decline and cognitive and functional decline related to aging in cognitive composite scores.** Hendrix S, Ellison N, Langbaum JB, Chen K, Bennett DA. Pentara Corporation; Banner Alzheimer's Institute; University of Arizona; Rush University; Arizona Alzheimer's Consortium.

24. **Pharmacokinetics and safety profile of intravenous administration of allopregnanolone in patients with early Alzheimer's disease.** Hernandez GD, Lopez CM, Desai M, Kono N, Irwin R, Rodgers KE, Mack WJ, Schneider LS, Brinton RD. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.
25. **Pharmacokinetics and safety profile of single-dose administration of an estrogen receptor β -selective phytoestrogenic (phytoestrogen) formulation in women with cognitive deficits and menopausal symptoms.** Hernandez GD, Zhao L, Chen YL, Franke A, Mack WJ, Schneider LS, Brinton RD. University of Arizona; University of Kansas; University of Southern California; University of Hawaii; Arizona Alzheimer's Consortium.
26. **Evaluation of cardiovascular structure and function in young and aged female APOE3 and APOE4 mice.** Hoxha B, Jones C, Vallejo-Elias J, Powell J, Virden T, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.
27. **Cardiovascular characterization of young and aged, female and male APOE4 mice.** Hoxha B, Vallejo-Elias J, Jones C, Powell J, Virden T, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.
28. **Amelioration of neurodegenerative changes in mice undergoing transverse aortic constriction by Mas agonists.** Jadhav SS, Gaffney KG, Rodgers KE. University of Arizona; Arizona Alzheimer's Consortium.
29. **Identification of a wide variety of bacteria in the brain tissue of individuals with either mild cognitive impairment (MCI) or Alzheimer's disease.** Jentarra G, Chu P, Jones TB, Kaufman J, Vallejo J, Jones D, Tullot T, Potter P. Midwestern University; Arizona Alzheimer's Consortium.
30. **Effects of candida albicans infection in 3X-Tg-AD mice.** Jones TB, Vallejo J, Gonzalez F, Kaufman J, Jentarra G, Kerry-Gnazzo A, Potter P, Tullot T, Jones D. Midwestern University; Arizona Alzheimer's Consortium.
31. **Temporal contiguity predicts reward association learning in bonnet macaques.** Kyle C, Smith AC, Gray DT, Burke SN, Barnes CA. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.
32. **Early diagnosis of Alzheimer's disease with voxel-based features: a deep learning approach.** Lee D, Pan R, Chen K. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
33. **Protecting DNA: Are individuals with autism spectrum disorder at risk for accelerated cognitive aging?** Lewis CR, Agrawal K, Walker N, Taguinod F, Smith C, Ringenbach S, Huentelman M, Braden BB. Translational Genomics Research Institute; Arizona State University; Southwest Autism Research and Resource Center; Arizona Alzheimer's Consortium.

34. **Age stratification corrects bias in estimated hazard of APOE genotype for Alzheimer's disease.** Liu L, Caselli RJ. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
35. **Neuropsychological comparison of incident mild cognitive impairment and prevalent mild cognitive impairment.** Locke DEC, Hansen A, Golafshar MA, Dueck AC, Woodruff BK, Stonnington CM, Geda YE, Caselli RJ. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
36. **Patient and partner perception of the impact of the Mayo Clinic HABIT Healthy Action to benefit independence & thinking program for mild cognitive impairment.** Locke DEC; Cuc AV, Eilertsen J, Lucas P, Hurst D, Khayoun R, Morris M, Chandler M. Mayo Clinic Arizona; Mayo Clinic Florida; Arizona Alzheimer's Consortium.
37. **Comparative effectiveness of behavioral interventions to prevent or delay dementia: preliminary outcomes.** Locke DEC, Chandler M, Cuc AV, Eilertsen J, Lucas P, Caselli M, Hoffman-Snyder C, Wethe J, Hurst D, Francone A, Smith GE. Mayo Clinic Arizona; Mayo Clinic Florida; University of Florida; Arizona Alzheimer's Consortium.
38. **Synaptic deficits in C9ORF72-ALS/FTD patient-derived human stem cell differentiated neurons and in vivo models of C9ORF72.** Lorenzini I, Ghaffari L, Levy J, Burciu C, Shenoy D, Twishime N, Bhatia D, Lall D, Baloh R, Sattler R. Barrow Neurological Institute; Cedars-Sinai Medical Center; Arizona Alzheimer's Consortium.
39. **Performance of IMR-based assays in measuring Alzheimer's disease core biomarkers in plasma and potentials for clinical use.** Lue LF, Guerra A, Sabbagh MN. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
40. **Cerebral amyloid angiopathy with neuritic plaque pathology correlates with cognitive decline in preclinical AD.** Malek-Ahmadi M, Chen K, Perez SE, Mufson EJ. Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
41. **A separable state-space model of learning across trials and days in an aging study in macaque monkeys.** Malem-Shinitski N, Zhang Y, Gray DT, Burke SN, Smith AC, Barnes CA. University of Berlin; Harvard University; University of Arizona; University of Florida; Arizona Alzheimer's Consortium.
42. **Response to hormonal intervention in aging female brain is endocrine status dependent: implications for Alzheimer's disease.** Mao Z, Yin F, Yao J, Brinton R. University of Arizona; Arizona Alzheimer's Consortium.
43. **Oligomeric amyloid β preferentially targets neuronal and not glial mitochondrial-encoded mRNAs.** Mastroeni D, Nolz J, Khdour OM, Sekar S, Delvaux E, Cuyugan L, Liang WS, Hecht SM, Coleman PD. Arizona State University; Translational Genomics Institute; Arizona Alzheimer's Consortium.

44. **Intervention development for caregivers of people with ADRD and Down syndrome/ID: An update.** Montague R, Carll P, Goldman J, Gomez Morales A, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.
45. **Planning and efficiency on the Tower of London test in ASD.** Nespodzany A, Braden BB, Baxter LC, Smith CK. Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona State University; Arizona Alzheimer's Consortium.
46. **Alzheimer's Prevention Registry: can email interaction predict study interest in cognitively healthy, prospective volunteers?** Nichols JB, High NM, Gordon DJ, Graf HP, Malek-Ahmadi MH, Chen K, Reiman EM, Tariot PN, Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
47. **Predictive network modeling identified novel targets in AD.** Petyuk VA, Chang RR, Ramirez-Restrepo M, Beckmann ND, Henrion MYR, Piehowski PD, Zhu K, Wang S, Clarke J, Huentelman MJ, Xie F, Andreev V, Engel A, Guettoche T, Navarro L, De Jager P, Schneider JA, Morris CM, McKeith IG, Perry RH, Lovestone S, Woltjer RL, Beach TG, Sue LI, Serrano GE, Lieberman AP, Albin RL, Ferrer I, Mash DC, Huette CM, Ervin JF, Reiman EM, Hardy JA, Bennett DA, Schadt E, Smith RD, Myers AJ. Pacific Northwest National Laboratory; Icahn School of Medicine at Mount Sinai; University of Miami Miller School of Medicine; University of Nebraska-Lincoln; Translational Genomics Research Institute; Arbor Research Collaborative for Health; Children's Hospital of Philadelphia; Brigham and Women's Hospital; Harvard Medical School; Broad Institute; Rush University Medical Center; Newcastle University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
48. **Classification of differentially expressed genes from Alzheimer's disease brain homogenates according to cell specific expression.** Piras IS, Coleman PD, Huentelman MJ. Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.
49. **Decreased levels of beta-arrestin 1 in brains of patients with Alzheimer's disease.** Potter PE, Choi S, Jones D, Beach T. Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.
50. **Flortaucipir paired helical filament tau burden and correlation with cognitive decline in MCI patients without any AB.** Protas HD, Ghisays V, Luo J, DeMarco EL, Thiyyagura P, Devadas V, Bauer III R, Landau SM, Weiner M, Jagust WJ, Reiman EM, Chen K. Banner Alzheimer's Institute; University of California Berkeley; University of California San Francisco; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
51. **An alternative to dye-based approaches to remove lipofuscin-induced background autofluorescence from primate brain tissue.** Pyon W, Gray DT, Chawla MK, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

52. **In vivo measurements of cortical thickness, amyloid and tau pathology, and episodic memory in preclinical autosomal dominant Alzheimer's disease.** Quiroz YT, Agüero C, Lopera F, Norton D, Aguirre-Acevedo D, Chen, K, Baena A, Guzman-Velez E, Paredilla-Delgado E, Alvarez S, Dickerson BC, Sperling RA, Reiman EM, Johnson KA. Universidad de Antioquia; Massachusetts General Hospital; Harvard Medical School; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
53. **Sex differences in aging with injury: the use of remote ischemic conditioning as an anti-inflammatory treatment for brain injury induced peripheral inflammation.** Saber M, Rowe R, Lifshitz J. University of Arizona; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; Arizona Alzheimer's Consortium.
54. **Single-cell analysis in human brain neurodegenerative disease: a pilot study.** Serrano G, Lue L-F, Brafman D, Huentelman M, Intorcía A, Guerra A, Walker J, Cutler B, Curry J, Callan M, Glass M, Arce R, Oliver J, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
55. **Prevalence of REM sleep behavior disorder in Sun City, Arizona.** Shprecher DR, Intorcía A, Glass M, Curry J, Walker J, Cutler B, Callan M, Serrano G, Zhang N, Sue LI, Davis KJ, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
56. **Predicting alpha-synuclein pathology by REM sleep behavior disorder diagnosis.** Shprecher DR, Adler CH, Zhang N, Hentz JG, Serrano GE, Dugger BN, Shill HA, Savica R, Caviness JN, Sabbagh MN, Belden CM, Driver-Dunckley E, Mehta SH, Sue LI, Davis KJ, Zamrini E, Beach TD. Banner Sun Health Research Institute; Mayo Clinic Arizona; University of California Davis; Barrow Neurological Institute; University of Arizona; Mayo Clinic; Arizona Alzheimer's Consortium.
57. **Are Lewy bodies associated with sympathetic pathology in dementia subjects?** 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. Barrow Neurological Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
58. **An integrated biomanufacturing platform for the large-scale expansion and neuronal differentiation of human pluripotent stem cell-derived neural progenitor cells.** Srinivasan G, Morgan D, Varun D, Brookhouser N, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
59. **Sex-dependent differences in genistein- and exercise-induced weight loss in high fat-high sucrose-fed mice.** St. Aubin C, Fisher A, Plochocki J, Broderick T, Al-Nakkash L. Midwestern University; Arizona Alzheimer's Consortium.

60. **Longitudinal assessment of advanced multi-parametric MRI biomarkers of Alzheimer's disease.** Stokes AM, Baxter LC, Nespodzany A, Caselli RJ, Sabbagh MN, Li Z, Pipe JG. Barrow Neurological Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
61. **Brain derived neurotrophic factor and apolipoprotein e4: their association with glucose metabolism, beta-amyloid and cognitive decline in cognitively unimpaired adults.** Stonnington CM, Shariieff S, Thiyyagura P, DeMarco E, Caselli RJ, Locke DEC, Lu B, Reiman EM, Chen K. Mayo Clinic Arizona; Midwestern University; Banner Alzheimer's Institute; Tsinghua University; Arizona Alzheimer's Consortium.
62. **Improved prediction of imminent progression to clinically significant memory decline using multivariate surface morphometry of MRI biomarkers and patch-based sparse coding.** Stonnington CM, Zhang J, Li Q, Shi J, Bauer RJ, Reiman EM, Caselli RJ, Chen K, Wang Y. Mayo Clinic Arizona; Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
63. **Web-based testing shows effect of family history of Alzheimer's disease on learning, memory, and reaction time specifically modified by diabetes and apolipoprotein E genotype.** Talboom JS, Håberg AK, DeBoth M, Siniard AL, Ryan L, Glisky E, Huentelman MJ. Translational Genomics Research Institute; University of Arizona; Norwegian University of Science and Technology; Arizona Alzheimer's Consortium.
64. **Comparison of collateral circulation (leptomeningeal arteriole) function in cognitively normal, mild cognitive impairment, Alzheimer's disease and vascular dementia.** Truran S, Karamanova N, Beach T, Serrano G, Madrigal C, Madine J, Davies H, Reaven P, Migrino RQ. Phoenix Veteran's Association; Banner Sun Health Research Institute; Banner University Medical Center; University of Liverpool; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.
65. **Intermittent fasting rescues necroptosis-mediated neuronal loss in a mouse model of Alzheimer's disease.** Turner EC, Branca C, Ferreira E, Velazquez R, Belfiore R, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
66. **Tau induces neurodegeneration by activating necroptosis.** Vartak RS, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
67. **Acute tau knockdown in the hippocampus of adult mice causes learning and memory deficits.** Velazquez R, Ferreira E, Tran A, Turner EC, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
68. **Intracerebroventricular injection of streptozotocin promotes increase in body temperature: implications for Alzheimer's disease.** Vizin RCL, Harris G, Kunstetter AC, Almeida MC, Carrettiero DC, Romanovsky AA. St. Joseph's Hospital and Medical Center; Universidade Federal do ABC; University of Wisconsin-Madison; Universidade Federal de Minas Gerais; Arizona Alzheimer's Consortium.

69. **Gender differences in Alzheimer's disease: brain atrophy, synaptic loss, histopathology burden and cognition.** Walker J, Curry J, Oliver J, Intorcchia AJ, Callan M, Glass M, Cutler B, Arce R, Sue LI, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
70. **Mitochondrial haplogroup in combination with APOE genotype as potential predictive biomarker to identify responders to regenerative therapeutic allopregnanolone for Alzheimer's disease.** Wang Y, Solinsky C, Hernandez G, Schneider L, Brinton RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.
71. **How does apolipoprotein E regulate energy metabolism in Alzheimer's disease?** Yin J, Reiman EM, Nielsen M, Carcione T, Beach TG, Caselli RJ, Shi J. Barrow Neurological Institute; Banner Alzheimer's Institute; University of Arizona; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
72. **Membrane-mediated mechanisms of neurotoxicity induced by mixtures of amyloidogenic proteins in neurodegenerative diseases.** Younger S, Johnson NM, Downs CA, Morrison HW, Yuan JX-J, Saavedra SS, Arce FT. University of Arizona; Arizona Alzheimer's Consortium.
73. **Feasibility of quantifying amyloid burden using volumetric MRI data: preliminary findings based on the deep learning 3D convolutional neural network approach.** Yuan Y, Wang Z, Lee W, Thiyyagura P, Reiman EM, Chen K. Texas A&M University; Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
74. **Quantification of amyloid burden from florbetapir PET images without using target and reference regions: preliminary findings based on the deep learning 3D convolutional neural network approach.** Yuan Y, Wang Z, Lee W, VanGilder P, Chen Y, Reiman EM, Chen K. Texas A&M University; Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
75. **Correlations between Rey auditory verbal learning test (AVLT) and upper extremity dual task function in detecting cognitive impairment.** Zamrini E, Fakhoury S, Gaytan-Jenkins D, Lopez A, Ehsani H, Belden C, O'Connor K, Mohler J, Toosizadeh N. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

STUDENT POSTER PRESENTATIONS

76. **Clinical reasoning: a 75-year-old woman with rapidly progressive dementia.** Aslam S, Fritz M, Sabbagh M. Barrow Neurological Institute; Earlham College; St. Joseph's Hospital and Medical Center; Arizona Alzheimer's Consortium.
77. **S6K1 activity: role and implications in AD brains.** Belfiore R, Caccamo A, Oddo S. Arizona State University; University of Catania; Arizona Alzheimer's Institute.

78. **Multimodal neuroimaging reveals white matter microstructure related covariance networks of subcortical gray matter volumes in healthy aging.** Bharadwaj PK, Fitzhugh MC, Nguyen LA, Haws KA, Hishaw GA, Trouard TP, Moeller JR, Habeck CG, Alexander GE. University of Arizona; Columbia University; Columbia University Medical Center; Arizona Alzheimer's Consortium.
79. **Using human induced pluripotent stem cells to investigate the contribution of APOE risk variants and aging to the onset and progression of Alzheimer's disease.** Brookhouser N, Brafman, DA. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.
80. **Age-associated changes in awake hippocampal sharp-wave ripples during spatial eyeblink conditioning.** Cowen SL, Gray DT, Wiegand JL, Schimanski LA, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
81. **Investigating the mechanisms of a multi-state model of Wnt signaling.** Cutts J, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
82. **Advanced techniques in diffusion MR image analysis for characterizing neurological changes with age.** Do L, Bernstein A, Bharadwaj P, Lindley M, Wheeler G, Alexander G, Barnes C, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.
83. **Dynamic expression of RNA stress granule components in aging brains: from flies to rats.** Eck R, Siddegowda B, Chawla MK, Yao S, Barnes CA, Zarnescu DC. University of Arizona; Arizona Alzheimer's Consortium.
84. **Functional connectivity changes and hearing loss in older adults.** Fitzhugh MC, Baxter LC, Rogalsky C. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
85. **Relation of physical sport activity to regional white matter integrity in older adults.** Franchetti MK, Bharadwaj PK, Nguyen LA, Klimentidis YC, Haws KA, Fitzhugh MC, Hishaw GA, Trouard TP, Raichlen DA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.
86. **Interactive effects of family history of Alzheimer's disease and gender on brain volumes among cognitively healthy older adults.** Gallegos N, Stickel A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
87. **The impact of depressive symptoms on cognition among Hispanics compared with non-Hispanic whites.** Gregolynskyj A, Stickel, A, McKinnon A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
88. **The importance of physical activity among the elderly.** Hindosh Z, Stipho F, Tirambulo C, Sutherland-Mills C, Sween A, Golden T, Toosizadeh N, Mohler J. University of Arizona; Arizona Alzheimer's Consortium.

89. **Rare ABCC1 gene mutation is associated with altered amyloid precursor protein processing in a familial case of late-onset Alzheimer's disease.** Jepsen WM, De Both M, Siniard AL, Henderson-Smith A, Ramsey K, Caselli RJ, Serrano G, Beach TG, Huentelman M. Translational Genomics Research Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
90. **Deficits in aged rats on the w-track continuous spatial alternation task suggest impaired hippocampal-prefrontal interactions.** Kapellusch AJ, Lester AW, Schwartz BA, Brewster JR, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
91. **Maze complexity and task learning order affects memory performance in estrogen-treated rats.** Koebele SV, Quihuis AM, Lavery CN, Plumley ZMT, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.
92. **Impact of $\alpha 5$ nicotinic receptor subunit in alcohol-induced alterations of hippocampal structure and function.** Li S, Gao M, Shen J, Wu J. Shantou University Medical College; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
93. **Effects of aging and APOE E4 on the relationship between white matter integrity and cognition.** Matijevic S, Walther K, Huentelman M, Ryan L. University of Arizona; University of Erlangen; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
94. **Cerebral amyloid angiopathy correlates with semantic memory in non-cognitively impaired older adults.** Methuku V, Malek-Ahmadi M, Chen K, Perez SE, Mufson EJ. BASIS Peoria; Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
95. **Sex differences in metabolic and inflammatory aging of the brain in humanized APOE- $\epsilon 4$ knock-in rats.** Mishra A, Yin F, Mao Z, Shang Y, Do L, Trouard TP, Brinton RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.
96. **Explore-exploit behavior in older adults.** Mizell J-M, Wang S, Franchiotti M-K, Keung J, Alexander G, Wilson RC. University of Arizona; Arizona Alzheimer's Consortium.
97. **Efficient differentiation of human pluripotent stem cell derived astrocytes on a defined substrate.** Morgan D, Brookhouser N, Brafman DA. Arizona State University; Arizona Alzheimer's Consortium.
98. **Regional covariance patterns of white matter microstructure in healthy aging.** Nguyen LA, Bharadwaj PK, Fitzhugh MC, Haws KA, Hishaw GA, Moeller JR, Habeck CG, Trouard TP, Alexander GE. University of Arizona; Columbia University; Arizona Alzheimer's Consortium.
99. **An evaluation of short-term and long-term ovarian hormone deprivation in the APP/PS1 mouse model of Alzheimer's disease: impacts of spatial working and reference memory.** Palmer JM, Strouse IM, Koebele SV, Woner VE, Willeman M, Peña V, Winslow W, Oddo S, Bimonte-Nelson HA. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

100. **Together, but not for better? Evaluating the cognitive effects of ethinyl estradiol and drospirenone given individually and in combination in surgically menopausal rats.** Peña VP, Poisson ML, Koebele SV, Croft C, Patel S, Strouse IM, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.
101. **Memory impairments from 17 β -estradiol plus levonorgestrel hormone therapy are dependent on their ratio.** Prakapenka AV, Berns-Leone C, Peña VL, Northup-Smith S, Melikian R, Patel S, Ladwig DS, Hiroi R, Mann AL, Valenzuela-Sanchez MJ, Sirianni RW, Bimonte-Nelson HA. Arizona State University; Red Mountain High School; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
102. **Cognitive decline and its relationship to perceived quality of life in Parkinson's disease.** Pulaski S, Ponce F, Hanson K, Troster AI. Barrow Neurological Institute; Arizona Alzheimer's Consortium.
103. **Developing a clinically relevant in vitro model of Alzheimer's disease using progerin induced aging.** Raman S, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
104. **Aging hippocampal neural stem cell function and NRF2.** Reed A, Ray S, Corenblum MJ, Anandhan A, Ortiz F, Zhang DD, Barnes CA, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.
105. **Elucidating the effects of PRAS40 on learning and memory.** Sarette P, Velazquez R, Rodin A, Caccamo A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
106. **Circular RNAs in functionally distinct regions of healthy aged human brain.** Sekar S, Geiger P, Serrano GE, Sue LI, Beach TG, Liang WS. Translational Genomics Research Institute; Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
107. **A new link between arthritis and Alzheimer's disease?** Squire M, Alkouli MF, Anderson M, Castro M, Al-Nakkash L, Broderick TL, Plochocki JH. Midwestern University; Arizona Alzheimer's Consortium.
108. **Memory and processing speed predict functional independence differentially in non-Hispanic and Hispanic white middle aged and older adults.** Stickel A, McKinnon A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
109. **Pathologically confirmed AD in APOE ϵ 2 homozygotes is rare but does occur.** Stipho F, Jackson R, Sabbagh MN. University of Arizona; Arizona Alzheimer's Consortium.
110. **Tick-tock, don't forget the clock: why frequency of 17 β -estradiol treatment matters for working memory and spatial accuracy during menopause.** Strouse IM, Valenzuela-Sanchez MJ, Prakapenka AV, Quihuis AM, Sirianni RW, Bimonte-Nelson HA. Arizona State University; Barrow Neurological Institute; Red Mountain High School; Arizona Alzheimer's Consortium.

111. **Cognitive-upper-extremity function dual task challenge in healthy adults using fMRI.** Tirambulo C*, Sutherland-Mills C*, Toosizadeh N, Lindley M, Golden T, Chen N-K, Mohler J, Chou Y-H. University of Arizona; Arizona Alzheimer's Consortium.
112. **Movement of molecules through gap-junction channels: an alternative mechanism for the spreading of Alzheimer's disease pathology?** Tran L, Chu P, Murthy A, Weidang L, and Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.
113. **Diagnostic and therapeutic potential of antibody fragments selective for human AD brain derived tau variants.** Venkataraman L, He P, Beach TG, Peltz C, Yaffe K, Sierks MR. Arizona State University; Banner Sun Health Research Institute; University of California San Francisco; Arizona Alzheimer's Consortium.
114. **Age-related differences in executive network functional connectivity and relationships with social communication impairments in autism spectrum disorder.** Walsh MJM, Baxter LC, Smith CJ, Braden BB. Arizona State University; Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona Alzheimer's Consortium.
115. **The efficiency of generative and direct retrieval of episodic autobiographical memories in healthy aging.** Wank, AA, Andrews-Hanna, J, Grilli, MD. University of Arizona; Arizona Alzheimer's Consortium.
116. **Hippocampus morphometry study on pathology-confirmed Alzheimer's disease patients with surface multivariate morphometry statistics.** Wu J, Zhang J, Shi J, Chen K, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
117. **Proximity-aware longitudinal order preserving dictionary learning for prognosis of subjective cognitive impairment.** Zhang J, Wu J, Chen K, Reiman EM, Caselli RJ, Wang. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

2018 Oral Research Presentation

Abstracts

REDUCED GENOMIC DIVERSITY AS A RISK FACTOR FOR NONFAMILIAL YOUNG ONSET ALZHEIMER'S DISEASE. Caselli RJ, Woodruff BK, Lindor NM, Wieben ED, Piras I, Huentelman MJ, Liu L. Mayo Clinic Arizona; Mayo Clinic Rochester; Translational Genomic Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Genomic diversity, reflected by relative heterozygosity, affects our ability to cope with physiological stresses. Inbreeding reduces this ability due to excess homozygosity of deleterious recessive mutations. We hypothesized that inbreeding depression (reduced heterozygosity) might be a risk factor for nonfamilial onset Alzheimer's disease (YOAD).

Methods: Whole exome sequencing (WES) was performed in two clinical series of consecutively evaluated patients diagnosed with AD prior to age 60 years. Cohort 1, accrued in 2013 included 10 patients and 13 controls-consenting unaffected first-degree relatives (6 parents, 7 siblings). Cohort 2, accrued in 2016 included 14 patients, 11 cognitively normal octogenarian controls (NOC) and 10 late onset AD (LOAD) controls (n=10). Genetic diversity was based on the excess of heterozygotes score (SH; Gillespie JH, 2004). Lower SH indicates higher diversity. Using the Panther database, we grouped genes by their common biological pathways and computed the false discovery rate (FDR). Pathways with $FDR < 0.1$ were regarded as significant.

Results: In cohort 1, we examined 139,332 biallelic positions harboring single nucleotide variants (SNVs). Excess heterozygosity of the YOAD group was lower than controls across all mean allele frequencies (MAF) save for private SNVs (in only one subject). A Kaplan-Meier plot showed low diversity was a risk factor for YOAD (Chi-square test $p=0.02$). In cohort 2 we examined 198,974 biallelic positions harboring SNVs. Across all MAF categories, the diversity of the YOAD group was significantly lower than the other two groups. A Kaplan-Meier plot showed low diversity was a risk factor for YOAD (Chi-square test $p=0.04$). After adjusting for APOE genotypes and gender, high SH (i.e., low heterozygosity) remained a significant risk factor for AD (p -value=0.04; O.R.=5.1 for every 1% increase of SH). Two pathways with $FDR < 0.1$ were the Heterotrimeric G-protein signaling pathway (p -value=0.0017) and the Notch signaling pathway (p -value=0.0038), but genetic diversity of these two classical AD pathways was not associated with age of onset (p -value=0.33 and 0.70, respectively).

Conclusions: Lower genomic heterozygosity was associated with enhanced risk for nonfamilial YOAD.

OLIGOMERIC AMYLOID β PREFERENTIALLY TARGETS NEURONAL AND NOT GLIAL MITOCHONDRIAL-ENCODED MRNAS. Mastroeni D, Nolz J, Khdour OM, Sekar S, Delvaux E, Cuyugan L, Liang WS, Hecht SM, Coleman PD. Arizona State University; Translational Genomics Institute; Arizona Alzheimer's Consortium.

Background: Our laboratories have demonstrated that accumulation of oligomeric amyloid β (O β) in neurons is an essential step leading to O β -mediated mitochondrial dysfunction.

Methods: Alzheimer's disease (AD) and matching control hippocampal neurons, astrocytes, and microglia were isolated by laser-captured microdissection from the same subjects, followed by whole-transcriptome sequencing. Complementary in vitro work was performed in O β -treated differentiated SH-SY5Y, followed by the use of a novel CoQ10 analogue for protection. This compound is believed to be effective both in suppressing reactive oxygen species and also functioning in mitochondrial electron transport.

Results: We report decreases in the same mitochondrial-encoded mRNAs in Alzheimer's disease laser-captured CA1 neurons and in O β -treated SH-SY5Y cells, but not in laser-captured microglia and astrocytes. Pretreatment with a novel CoQ10 analogue, protects neuronal mitochondria from O β -induced mitochondrial changes.

Conclusions: Similarity of expression changes in neurons from Alzheimer's disease brain and neuronal cells treated with O β , and the effect of a CoQ10 analogue on the latter, suggests a pretreatment option to prevent O β toxicity, long before the damage is apparent.

A PUBLIC CELL-SPECIFIC ALZHEIMER'S AND AGING BRAIN RESOURCE: EVALUATION AND IMPLEMENTATION OF SINGLE CELL TRANSCRIPTOMIC ANALYSES. Liang WS, Beach TG, Antone JV, Geiger P, Enriquez D, Serrano G, Mastroeni D, Readhead B, Dudley J, Reiman EM. 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: There is a critical need to clarify molecular mechanisms involved in the development of Alzheimer's disease (AD) at both the cellular and regional level in the brain and use them to discover new opportunities in the diagnosis, early detection, and tracking of AD, as well as to provide a more diversified portfolio of promising treatments.

Methods: We will analyze 100 subjects including 50 expired brain donors with clinical and neuropathological evidence of dementia due to AD and 50 expired brain donors without cognitive impairment, neuropathological criteria for AD, or other comorbidities. Fresh frozen brain tissue for all donors will be provided by the Banner Brain and Body Tissue Bank. For this four year study, three complementary arms of analyses will be performed: (a) laser capture microdissection (LCM) and RNA sequencing (RNAseq) of astrocytes, microglia, tangle-bearing neurons, and non-tangle bearing neurons from differentially impacted brain regions in AD, including the entorhinal cortex, hippocampal CA1, posterior cingulate cortex, superior frontal gyrus (SFG), and primary visual cortex; (b) single cell library preparation (nuclei and whole cell) on the 10x Genomics Chromium platform and RNAseq of the SFG for all subjects (scRNAseq), and (c) whole genome sequencing (WGS) of the SFG for all subjects. Data from (a) and (b) will be integrated to generate a cell-specific transcriptomic reference, and data from (a-c) will be integrated for multi-scale network analysis.

Results: As scRNAseq is a relatively new area, we have been working on protocol optimization of tissue dissociation and sample preparation, as well as comparison of nuclei versus whole cell approaches using the 10x platform. Preliminary analyses show that preparation and sequencing of single nuclei from fresh frozen tissue yields data for the highest number of genes and that nuclei and whole cell preparations from fresh frozen tissue yield complementary expression data. Ongoing efforts include WGS of the SFG for 50 donors as well as LCMing of cells for RNAseq analysis.

Conclusions: While there are both apparent advantages and disadvantages to scRNAseq, comparing and integrating data generated using this approach with that from LCM and RNAseq will both provide valuable insight into cell-specific transcriptomics as well as improve our understanding of the differences across the two tools. Overall, construction of this complementary, cell and region-specific, public resource will offer the chance to inform on experimental studies in animal, cellular and other laboratory models and clarify the extent to which their findings are relevant to AD, a fundamentally human disease.

USING HUMAN INDUCED PLURIPOTENT STEM CELLS TO INVESTIGATE THE CONTRIBUTION AGING TO THE ONSET AND PROGRESSION OF ALZHEIMER'S DISEASE. David Brafman, PhD. School of Biological and Health Systems Engineering, Arizona State University; Arizona Alzheimer's Consortium.

Alzheimer's disease (AD) affects over 120,000 individuals in Arizona and has a direct cost to Arizona that is estimated in excess of \$5 billion/year. Although the pathological hallmarks of AD, such as axonal transport defects, synaptic loss, and selective neuronal death, are well-characterized, the underlying mechanisms that cause AD onset and age-related progression are largely unknown, thereby making it difficult to design effective therapies. With hiPSC technology it is possible to obtain a fully differentiated cell type (such as a skin cell) from an AD patient and reprogram it back into a cell type that is capable of differentiating into all of the cell types of the mature, adult body (such as cortical neurons). Therefore, with hiPSC-based technologies we have the potential to probe AD disease mechanisms and design molecularly targeted therapies. Although we and others have used AD hiPSC-derived neurons to study this disease in a simplified and accessible system, these models have been limited by the (i) absence of phenotypes and pathological hallmarks associated with later stages of the disease in aging humans and (ii) inability to consistently model the sporadic form of AD. Based on extensive characterization of hiPSC-derived neurons, we contend that these cells are too immature to accurately mimic the degenerative phase of AD that is observed in aging adults. To that end, we are using our collective experience in stem cell bioengineering, neurodegenerative disease modeling, and computation modeling to develop an inducible model of cortical aging that allows for the real-time tracking of AD phenotypes in an age-dependent manner. Ongoing detailed phenotypic analysis of control and AD-cortical neuronal cultures of various 'ages' has revealed genetic, biochemical, and signaling pathways that are independently influenced by age and disease status. Overall, the new insights gained from this project will have significant impact on our understanding of the genetic, biochemical, and cellular events that lead to AD onset and age-related progression.

SYNAPTIC DEFICITS IN C9ORF72-ALS/FTD PATIENT-DERIVED HUMAN STEM CELL DIFFERENTIATED NEURONS AND IN VIVO MODELS OF C9ORF72. Lorenzini I, Ghaffari L, Levy J, Burciu C, Shenoy D, Twishime N, Bhatia D, Lall D, Baloh R, Sattler R. Barrow Neurological Institute; Cedars-Sinai Medical Center; Arizona Alzheimer's Consortium.

Background: The hexanucleotide repeat expansion GGGGCC (G4C2) found in the non-coding region of the C9orf72 (C9) gene represents the most common genetic abnormality in amyotrophic lateral sclerosis (ALS) (40-50%) and frontotemporal dementia (FTD) (10-30%). ALS and FTD patients have genetic, pathologic and symptomatic overlap. Therefore, understanding the molecular mechanisms of disease pathogenesis in this ALS/FTD disease spectrum could lead to the development of novel therapeutic strategies. Cognitive decline as seen in normal ageing or Alzheimer's disease (AD) is characterized by changes in neuronal morphology, spine density and progressive synapse loss. We hypothesize that similar mechanisms are responsible for the dementia symptoms caused by the C9 mutation and that these events arise early during disease progression before any neurodegeneration has occurred. Based on recent findings in AD and FTD, we hypothesize that this synaptic dysfunction might involve the neural-immune complement pathway.

Methods: Here we present preliminary data supporting this hypothesis using C9-ALS/FTD patient-derived human induced pluripotent stem cells differentiated into motor neurons (hiPSC-MNs) and cortical neurons (hiPSC-CNs), in addition to C9 mouse models.

Results: We found significant changes in dendritic branching, dendritic length, spine density and detected alterations in the expression pattern of synaptic proteins in hiPSC neurons. We also observed changes in neuronal excitability using longitudinal micro-electrode array analysis. Similar changes in dendritic arborization and dendritic length were observed in homozygous C9orf72 $-/-$ knockout mice. In addition, increased complement pathway activation and decreased gene expression of pre-synaptic markers were observed in this C9 mouse model.

Conclusions: Our data suggest that synaptic deficits are present in C9 ALS/FTD which are likely to be triggered by aberrant neural-immune interactions. These synaptic dysfunctions are hypothesized to contribute to cognitive impairment and neuronal cell death found in C9orf72 patients.

FLORTAUCIPIR PAIRED HELICAL FILAMENT TAU BURDEN AND CORRELATION WITH COGNITIVE DECLINE IN MCI PATIENTS WITHOUT ANY AB. Protas HD, Ghisays V, Luo J, DeMarco EL, Thiyyagura P, Devadas V, Bauer III R, Landau SM, Weiner M, Jagust WJ, Reiman EM, Chen K. Banner Alzheimer's Institute; University of California Berkeley; University of California San Francisco; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: We previously investigated flortaucipir PET measurements paired helical filament (PHF) tau burden in MCI patients with and without florbetapir PET criteria of moderate to frequent amyloid plaques (SUVR>1.18), and we found tau burden even in those who did not meet this criteria for any amyloid positivity. We now extend this study to MCI patients who did or did not meet florbetapir PET criteria for any amyloid (Fleisher 2011) (SUVR>1.08) to investigate the relationship of cognitive decline and higher tau burden in MCI patients even in the absence of any amyloid.

Methods: Flortaucipir PET scans were acquired in 27 A β ⁺ and 32 A β ⁻ persons with MCI and in 50 A β ⁻ cognitively unimpaired adults from ADNI-3. A β positivity was defined using mean cerebral-to-cerebellar florbetapir SUVRs>1.08 (Fleisher 2011). We compared regional flortaucipir SUVRs in a voxel-based approach and also in pre-specified regions, precuneus, parahippocampal and inferior temporal regions, among these groups. The same pre-specified regions were used to characterize relationships between regional flortaucipir SUVRs and cognitive impairment assessed with MMSE, ADAS-cog, CDR-SB and AVLT long-term memory (LTM) in the A β ⁺ and/or A β ⁻ MCI groups.

Results: In comparison with the A β ⁻ unimpaired controls, the A β ⁺ and A β ⁻ MCI groups had significantly higher flortaucipir SUVRs in a number of locations, including in the Braak ROIs that are preferentially affected by AD. In comparison with the A β ⁻ MCI group, the A β ⁺ MCI had significantly higher flortaucipir SUVRs in the same locations. In A β ⁻ MCI group, higher entorhinal, parahippocampal, and inferior temporal flortaucipir SUVRs were associated with CDR-SB measure. Correlation of MMSE with inferior temporal flortaucipir SUVR was also significant. With the more liberal A β ⁺ threshold, we found significant correlation of CDR-SB with entorhinal, parahippocampal, inferior temporal, and precuneus flortaucipir SUVRs and also between MMSE and precuneus and entorhinal flortaucipir SUVR in A β ⁺ MCI.

Conclusions: Even when we limited our analysis to people who did not have any plaques, we observed elevated tau burden and correlation with cognition raising the possibility that tau pathology in this population not depend on amyloid pathology in relationship to cognitive impairment.

CORTICAL EXCITABILITY IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS OF TRANSCRANIAL MAGNETIC STIMULATION STUDIES. Chou Y-H, Rapcsak S, Chen N-K, Sundman M, Lim K, Ugonna C, Lindley M, Fuglevand A, Mohler J, Huang Y-Z. University of Arizona; Chang Gung University; Arizona Alzheimer's Consortium.

Background: Transcranial magnetic stimulation (TMS) is a safe and painless brain stimulation technique that has been used to measure in vivo cortical excitability in diverse disease states including Alzheimer's disease (AD) and mild cognitive impairment (MCI). The utility of TMS measures in characterizing excitatory and inhibitory properties of neurotransmitter systems and the integrity of corticospinal pathway has been substantially supported by numerous pharmacological TMS studies. Recently, neuropathological studies have suggested early-stage motor cortex involvement in AD, despite a lack of motor dysfunction. Thus, motor cortical excitability measures be sensitive enough to detect dementia in the incipient stage of disease. The purpose of this meta-analysis is to quantify alterations in cortical excitability associated with Alzheimer's disease and mild cognitive impairment.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods were utilized. Databases were searched using combinations of the following terms: (transcranial magnetic stimulation, theta burst stimulation, or TMS), and (Alzheimer's disease or mild cognitive impairment) and (cortical excitability).

Results: Ten studies (N = 418) were included in the meta-analysis. Patients with AD exhibited significantly (1) lower resting motor threshold (RMT), effect size $d = 1.61$, $z = 4$, $p < .0001$, (2) lower active motor threshold (AMT), effect size $d = 0.74$, $z = 1.98$, $p < .05$, (3) reduced short-latency afferent inhibition (SAI), $d = 1.14$, $z = 4.04$, $p < .0001$, and (4) reduced short-interval intracortical inhibition (SICI), $d = 6.91$, $z = 11.16$, $p < .0001$, compared to healthy controls. Patients with MCI also showed significantly lower RMT relative to healthy controls, $d = 0.63$, $z = 3.13$, $p < .002$. No significant group differences were observed in cortical silent period and central motor conduction time.

Conclusions: The pooled evidence suggests the existence of cortical hyper-excitability as documented by the reduced RMT and AMT in AD and MCI, as well as reduced inhibition as measured by the SAI and SICI in AD. First, hyper-excitability is associated with severity of dementia. For example, Sakura et al. (2007) reported that AD patients exhibited the lowest RMT, followed by the MCI, and then the healthy controls. Khedr et al. (2011) divided AD patients into mild, moderate and severe groups and found that dementia severity was significantly correlated with the reduction of RMT and AMT. Second, the level of SAI reflects the integrity of central acetylcholinergic pathways. The acetylcholine (ACh) is a neurotransmitter essential for processing memory and learning. Consistent with the cholinergic hypothesis, our meta-analysis also supports a reduction in levels of ACh in AD. Previous studies have shown that the reduced SAI in AD could be normalized by AChE inhibitors. Finally, intracortical inhibition as measured by SICI is decreased in AD and the reduced inhibition is related to cognitive deterioration. Future studies will be needed to examine whether these cortical excitability measures are reliable and accurate biomarkers that can be used to differentiate prodromal dementia from normal healthy aging prior to the disease progressing to a more clinically evident phase.

THE HEART OF THE MATTER: SEPARATING LEWY BODY DEMENTIA FROM ALZHEIMER'S WITH TISSUE FROM ARIZONA'S BRAIN AND BODY DONATION PROGRAM. 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. Barrow Neurological Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Comorbid Lewy body (LB) pathology is very common in Alzheimer disease (AD) and confound clinical trial design- yet there is no in-vivo test to identify it. Tissue studies have shown cardiac sympathetic denervation in Parkinson disease and dementia with Lewy bodies, but have not been explored in mixed AD/LB cases.

Methods: In order to determine if Alzheimer subjects with Lewy bodies show sympathetic cardiac denervation, we analyzed 30 cases with autopsy-confirmed AD/DLB, 30 AD/LB not meeting DLB criteria, 30 AD-no LB, 22 controls- no LB, 30 control/LB (ILBD). Using tyrosine hydroxylase (TH) staining of epicardial and myocardial tissue, 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. Staining 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 ($p = 0.008$) between the groups, and subsequent pair-wise Mann-Whitney analysis showed that PD ($p = 0.014$) and DLB ($p = 0.008$) subjects have significantly reduced TH fiber density as compared to controls. The TH density in ILBD hearts was midway between the control and PD or DLB groups but the difference was too small for this to reach significance ($p = 0.16$).

Conclusions: The clear separation of DLB from controls based on cardiac TH fiber density is the first report of a statistical difference between these groups. Our data therefore strengthen the rationale for using cardiac nuclear imaging with a nor-adrenergic nuclear imaging ligand, meta-iodobenzylguanidine (MIBG) to separate DLB from AD with DLB, an important concept as most cases of AD/DLB are not recognized as such during life. Our results indicate that MIBG would not be likely to clinically separate the AD/LB from AD subjects without LB.

FASTER COGNITIVE DECLINE IN ALZHEIMER'S DISEASE DEMENTIA WITH CLINICALLY-UNSUSPECTED LEWY BODY DISEASE. Beach TG, Malek-Ahmadi M, Zamrini E, Sabbagh MN, Shill HA, Adler CH, Jacobson SA, Belden CM, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta S, Burke AD, Shprecher D, Spann B, Tariot PN, Davis KJ, Long KE, Nicholson LR, Intorcica A, Glass M, Walker J, Callan M, Curry J, Cutler B, Oliver J, Arce R, Serrano GE, Sue LI, Reiman EM. Banner Sun Health Research Institute; Banner Alzheimer Institute; Barrow Neurological Institute; Mayo Clinic Arizona; University of Arizona; Arizona Alzheimer's Consortium.

Background: Clinical trials for Alzheimer's disease dementia (ADD) over the last two decades have so far failed to identify disease-modifying treatments. Although biomarkers are expected to improve clinical trial success rates, the ultimate proof of an effective agent remains a clinical improvement in cognition, and establishment of this be critically hampered by subject response variability. Neuropathology has demonstrated a high rate of comorbid pathology in ADD. The most common major comorbidity is Lewy body (LB) disease, either as dementia with Lewy bodies (DLB) or Alzheimer's disease with Lewy bodies (AD-LB), the latter representing subjects with LB pathology that does not meet distribution and density thresholds for DLB. Although together these represent 50% of those with AD, it is well recognized that only a fraction of those with concurrent DLB, and virtually none of those with ADLB, are clinically recognized during life and hence are likely to be included with "pure" AD subjects in clinical trials. Although it has been established that AD subjects with concurrent DLB have a more rapid cognitive decline than those with AD alone, it is still unknown whether ADLB subjects, who represent approximately one-third of all those with AD, have a different clinical course.

Methods: Subjects with pure AD (n = 137), AD-DLB (n = 64) and AD-LB (n = 114) were selected by a database search of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP) and National Alzheimer's Coordinating Center (NACC) data for the National Institute on Aging Arizona Alzheimer's Disease Core Center. Search criteria specified that subjects had two or more complete Mini Mental State Examinations (MMSE) and a full neuropathological examination after death.

Results: An unadjusted linear model of annualized MMSE change showed that both the AD-DLB and the AD-LB groups had significantly faster rates of decline relative to the pure AD group ($p = 0.04$, $p = 0.002$, respectively). This difference remained significant in a second model that included age and neuropathology interactions ($p = 0.02$, $p = 0.002$, respectively). In both models, the AD-DLB and the AD-LB groups had relatively similar rates of decline. Lewy body disease diagnosed at autopsy was often unrecognized during life. Of those with dementia and meeting neuropathological criteria for DLB, only 66% had been diagnosed with DLB during life.

Conclusions: Clinically undetected LBD significantly affects the rate of cognitive deterioration in ADD. The probable cause of clinical detection failure is the lack, for many DLB subjects and the great majority of AD-LB subjects, of a sufficient set of characteristic core clinical features. Compared with clinically-diagnosed DLB subjects, those that were clinically undetected had a significantly lower prevalence of parkinsonism, visual hallucinations and dream enactment behavior. Clinical identification of ADD with LBD would allow stratified analyses of ADD clinical trials, potentially improving the probability of trial success.

MULTISCALE ANALYSIS OF THREE INDEPENDENT SPORADIC ALZHEIMER'S COHORTS REVEALS DISRUPTION OF PATHOGENIC MOLECULAR, GENETIC, AND CLINICAL NETWORKS BY HUMAN HERPESVIRUS. Readhead B, Haure-Mirande J, Funk C, Richards M, Shannon P, Haroutunian V, Sano M, Liang W, Beckmann N, Price N, Reiman E, Schadt E, Ehrlich M, Gandy S, Dudley J. Arizona State University; University of Arizona; Banner Alzheimer's Institute; Icahn School of Medicine at Mount Sinai; Institute for Systems Biology; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Investigators have long suspected that pathogenic microbes might contribute to the onset and progression of Alzheimer's disease (AD) although definitive evidence has not been presented. Whether such findings represent a causal contribution or reflect opportunistic passengers of neurodegeneration has also been difficult to resolve. We constructed multiscale networks of the late onset sporadic AD-associated virome, integrating genomic, transcriptomic, proteomic, and histopathological data across four brain regions from human postmortem tissue. We observe increased abundance of specific human *Herpesviridae* across multiple regions from subjects with AD compared with controls. These results were readily replicated in two additional, independent and geographically dispersed cohorts.

Methods: We performed a multiscale evaluation of the human AD-associated virome, integrating matched genomic, transcriptomic, proteomic, and histopathological data across four brain regions from human post-mortem tissue from clinically and neuropathologically characterized persons with and without AD.

Results: We generated multiple perspectives for linking viral activity with diverse indicators of AD biology, including differential viral RNA/DNA abundance, correlation with AD traits, AD genetic enrichments in host DNA markers that associate with viral abundance, and viral regulation of AD risk genes. We observed the presence of many viral species in the ageing brain, and linked multiple viral species with AD biology, including regulation of AD genetic risk networks, AD gene expression changes, and association with clinical dementia rating and neuropathology burden. We found an especially prominent role for several *Herpesviridae*, which were implicated across multiple domains.

Conclusions: This study elucidates networks linking specific molecular, clinical, and neuropathological features with viral activity and is consistent with viral activity constituting a general feature of the brain affected by late onset sporadic AD.

MODELING THE ALZHEIMER'S GUT MICROBIOME-BRAIN AXIS USING NEXT GENERATION SEQUENCING – OPPORTUNITIES AND COLLABORATIONS AT THE PATHOGEN AND MICROBIOME INSTITUTE. Emily Cope, J Gregory Caporaso, Paul Keim. Northern Arizona University; Translational Genomics Institute; Arizona Alzheimer's Consortium.

The human body hosts trillions of microorganisms, collectively termed the microbiome. Recent evidence has expanded our understanding of the extent that these microbes contribute to host health, including neurological health. The Pathogen and Microbiome Institute (PMI) at Northern Arizona University is a premier institution for microbiome research. The academic Microbiome Center, led by Dr. Greg Caporaso, focuses on bioinformatics software development including the widely used QIIME platform, host-microbiome interactions at mucosal surfaces using animal model and *in vitro* systems, and microbiome data analysis. We are currently collaborating with other Arizona-based institutions to examine the gut microbiome-brain axis in aging and autism. Here, we will discuss opportunities and collaborations related to brain function and Alzheimer's disease at the PMI.

THE POTENTIAL ROLE OF MICROBES IN THE DEVELOPMENT OF ALZHEIMER'S DISEASE. Garilyn Jentarra. Midwestern University; Arizona Alzheimer's Consortium.

While the brain pathology that is characteristic of Alzheimer's disease (AD) is well-described, what triggers that pathology remains unclear. Deposition of amyloid beta into plaques and formation of hyperphosphorylated tau into neurofibrillary tangles have been widely regarded as resulting from aberrant processes, which then drive activation of microglia as well as inflammation, leading to the eventual loss of neurons. However, treatments aimed at preventing or clearing amyloid and tau pathology have failed in clinical trials, and to date there are no treatments for AD that are more than marginally effective. Perhaps the very premise that the cellular processes that induce amyloid plaque and neurofibrillary tangle production are aberrant should be re-examined. But, if they are not aberrant, then what purpose do they serve? Because of the many ways in which the pathology of AD resembles a response to infection, the idea that infection somehow be involved in the development of AD has been explored by many researchers over the years. However, findings have been controversial, particularly in light of the fact that while many microbes have been linked to AD, no single microbe has been reliably implicated in all cases. In the last few years, data demonstrating that amyloid beta can function as a very strong anti-microbial peptide has been rapidly accumulating. In addition, cell culture models have shown that infection of cells can induce hyperphosphorylation of tau. We propose, as have others, that the accumulation of plaques and tangles therefore be evidence of the brain defending itself against the entry of microbes. We have chosen to explore this idea using both human tissue and animal studies. In particular, our recent 16S rRNA gene sequencing data from human subjects indicate that many different types of bacteria are entering the brains of individuals with both AD and mild cognitive impairment (MCI), while only limited bacterial DNA is found in tissue from normal control subjects. The inclusion of MCI patients in studies such as this be crucial, as the particularly debilitated state of AD patients near the time of their death make them more susceptible to opportunistic infection, which could lead to the misinterpretation of microbial presence as causative of AD rather than as a result. As a second and more direct means of assessing the ability of microbes to induce pathology consistent with AD, our animal studies are focused on determining if microbial infection can drive AD pathology in susceptible animal models of AD. Given the wide variety of microbes that have been previously implicated in AD, as well as our own findings, we suggest that the pathology seen in AD be a non-specific response to any invading microbe and not to a specific microbe. This explain why, although the distribution of microbes throughout the world varies widely, the presentation of AD does not.

Institutional Information

Research Summaries and Key Personnel from Each Participating Institution

ARIZONA STATE UNIVERSITY

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 three years (2015-2017). 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 animal models of Alzheimer's disease to study new treatments as well as mechanisms and trajectory of pathology (Oddo laboratory), 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 (e.g., Sierks, Hecht, and Johnson laboratories), in epigenetics, transport mechanisms, and pathophysiology of Alzheimer's disease (Coleman laboratory), in the development and use of animal models to characterize the influence of reproductive senescence and hormonal influences on brain aging and cognition (Bimonte-Nelson laboratory), in the development and implementation of computational image analysis and biomathematical techniques to increase the power to detect and track Alzheimer's disease (Chen and Wang laboratories), in the development of "big data" analyses of post-mortem omics, ante-mortem electronic health record and other relevant data sets (e.g., the new Dudley/Readhead laboratory); and in the development of improved care models for patients and family caregivers, including the HOPE memory partner program to explore the role of community health workers in Alzheimer's disease research and clinical practice (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 and institutes 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 ASU-Banner Neurodegenerative Disease Research Center (NDRC)¹. The center is an extension of the partners' work with the Arizona Alzheimer's Consortium and is expected to become one of the world's largest basic science centers for the study of Alzheimer's and other neurodegenerative diseases. The Center, which will formally open in BioDesign Building C later this year is expected to include a new director, 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.

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

² <https://psychology.clas.asu.edu/content/psychology-behavioral-neuroscience-phd>

³ <https://neuroscience.asu.edu>

ARIZONA STATE UNIVERSITY

Key Personnel

Name (last, first)	Degree	Role on project
Ahmed, Kinza		Undergraduate Research Assistant
Barker, Charlotte		Undergraduate Research Assistant
Belfiore, Ramona		Visiting Researcher
Berns-Leone, Claire		Undergraduate Research Assistant
Bhandarkar, Siddhi	BS	Graduate Researcher
Bimonte-Nelson, Heather	PhD	Co-Investigator
Brafman, David	PhD	PI
Branca, Caterina	PhD	Postdoctoral Fellow
Brookhouser, Nicholas	MS	Graduate Researcher
Bulen, Haidyn		Undergraduate Research Assistant
Bustos, Lynette		Graduate Student
Caccamo, Antonella	PhD	Assistant Research
Chang, Yung	MD, PhD	Co-Investigator
Chandrashekar, Pramod	MS	Graduate Research Assistant
Coleman, Paul	PhD	Research Professor
Cutts, Joshua	MS	Graduate Researcher
Daniels, Carter	BS	PhD student responsible for implementing mouse behavioral experiments
Dave, Nik		High School Student
Delvaux, Elaine	MS	Research Technologist
Dudley, Joel	PhD	
Ferreira, Eric		Associate Research Technologist
Fu, Tong	MD	Technician
Gerkin, R	PhD	Human and mouse olfactory performance and electrophysiology
Gilchrist, Rachel	BS	Research Assistant
Gupta, Tanya	BS	PhD student responsible for implementing mouse behavioral experiments
Hadder, Bryanna		Undergraduate Research Assistant
Hiroi, Sheri	PhD	Postdoctoral Fellow
Jia Guo	PhD	Assistant Professor
Knowles, Sara		Graduate Masters Student
Koebele, Stephanie		5 th year graduate student
Ladwig, Ducileia		Undergraduate Research Assistant
Liu, Li	MD	PI
Lue, Lih-Fen	PhD	Co-Investigator

Name (last, first)	Degree	Role on project
Ma, Jason		Undergraduate responsible for implementing mouse behavioral experiments
Mann, Abigail		High School Research Assistant
Mastroeni, Diego	PhD	Assistant Research Professor
Melikian, Ryan		Undergraduate Research Assistant
Morgan, Daylin	BS	Graduate Researcher
Neeley, Rachel		Undergraduate Research Assistant
Nguyen, Cuong	BS	Graduate Researcher
Nolz, Jennifer	AAS	Assistant Research Technologist
Northup-Smith, Steven		Laboratory Manager
Oddo, Salvatore	PhD	Co-PI on genetically modified mouse line
Palmer, Justin		Undergraduate Research Assistant
Pena, Veronica		2 nd year Graduate Student
Porwal, Anika		High School Research Assistant
Prakapenka, Alesia		5 th year Graduate Student
Raman, Sreedevi	MS	Graduate Researcher
Readhead, Ben		Assistant Research Professor
Rodin, Alexis		Research Technician
Sanabria, Federico	PhD	Collaborator for behavioral studies
Sarette, Patrick		Undergraduate Student
Schatzki-Lumpkin, Alex		Undergraduate Research Assistant
Schrier, Ally		Undergraduate Research Assistant
Shukla, Prakriti		Undergraduate Student
Sierks, Michael	PhD	PI
Smith, Brian H	PhD	PI and Project Director
Srinivasan, Gayathri	MS	Research Technician
Strouse, Isabel		Undergraduate Research Assistant
Surendra, Likith		Undergraduate Student
Turk Willeman, Mari	PhD	Postdoctoral Fellow
Turner, Emily	PhD	Postdoctoral Fellow
Valenzuela Sanchez, Maria		High School Research Assistant
Van Bourg, Joshua	BS	Graduate Student
Vartak, Rasika	PhD	Postdoctoral Fellow
Velazquez, Ramon	PhD	Postdoctoral Fellow
Winslow, Wendy	BS	Laboratory Manager
Wojtulewicz, Laura		ADCC Coordinator
Woner, Victoria		1 st year Graduate Student
Wynne, Clive D. L.	PhD	Project Director

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. 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 a prospective 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 systems, a 3T MRI, cyclotron, radiochemistry laboratory, and computational image analysis laboratory. It provides imaging resources and expertise, research PET tracers, image-analysis methods, data and biological samples for researchers inside and outside of Arizona. In collaboration with Mayo Clinic, it includes a longitudinal brain imaging study of cognitively unimpaired persons with two copies, one copy, and no copies of the APOE4 allele, reflecting three levels of genetic risk for late-onset AD, and image-analysis techniques with improved power to characterize subtle brain changes over time. In collaboration with the University of Antioquia and a Harvard post-doctoral student, it also includes a study of PSEN1 E280A mutation carriers and non-carriers from the world's largest autosomal dominant AD kindred in Colombia. It is a member of the AD Neuroimaging Initiative (ADNI) PET Core, where it is responsible for the development, testing and use of voxel-based

image analysis techniques with improved power to detect and track AD. It has played pioneering roles in the study of preclinical AD.

AARC funds complement research activities supported by competitive grant awards from several NIA-sponsored research grants, private foundation grants, and clinical trials. In conjunction with our NIA-sponsored ADCC, subjects, images, other data, and image-analysis techniques from our study of cognitively normal APOE ε4 carriers and non-carriers provide a core resource for interested investigators inside and outside of Arizona.

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, and a growing number of trials now in development. The first three 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 provide 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); and empower persons at highest risk in the scientific fight against AD.

API also includes exceptionally large registries to support interest and possible enrollment in prevention studies. In partnership with the University of Antioquia, the API Colombian Registry, in collaboration now includes >5,800 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 >290,000 people and continues to grow rapidly; our GeneMatch Program (www.endALZnow.org/genematch) has enrolled >50,000 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 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 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 addresses the needs of patients and families at 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 (BAI)

Key Personnel

Name (last, first)	Degree	Role on project
Reiman, Eric	MD	Executive Director, BAI Director, Arizona Alzheimer's Consortium
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, Anna	MD	Dementia Specialist
Burke, William	MD	Director, Stead Family Memory Center
Chen, Kewei	PhD	Director, Computational Brain Imaging Program Director, ADCC Data Management & Statistics Core, Biomathematician
Copeland, Jacquelynn	PhD	Neuropsychologist
DeMarco Kathryn	BS	Manager, Clinical Research Program
Dougherty, Jan	RN, MS	FAAN FCS Special Projects Consultant
Ghisays, Valentina	PhD	Post-Doctoral Fellow
Goradia, Dhruvan	PhD	Bioinformatics Scientist
Hall, Geri	PhD, ARNT, CS, FAAN	Clinical Nurse Specialist, Family & Community Services
High, Nellie	MS	Research Project Coordinator
Jaeger, Chad	BS	Senior Director, Research Operations
Jakimovich, Laura	RN	Multi-Center Clinical Trials Manager
Jansen, Willemijn	PhD	Post-Doctoral Fellow
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
Malek-Ahmadi, Michael	PhD	Bioinformatics Scientist
Nisson, Lori	MSW/LCSW	Director, Family & Community Services
Pandya, Sachin	BS	Clinical Research Coordinator
Patel, Roma	MS	Clinical Trials Senior Manager
Perrin, Allison	MD	Physician Dementia Specialist
Protas, Hillary	PhD	Bioinformatics Scientist
Saner, Don	MS	Senior Director, Data Science Director, ADCC Data Management Program
Savage, Cary	PhD	Senior Scientist and Director of Imaging Research
Weidman, David	MD	Physician Dementia Specialist

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), Parkinson's disease (PD), other age-related brain disorders, and healthy aging. BSHRI has historically included: **a)** 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 processing, brain inflammation, epigenetics, and the roles of cholesterol and cerebrovascular disease in AD that have now completed relocation to ASU; **b)** a world-class Brain and Body Donation Program (BBDP) for the study of AD, PD, related disorders, cancer and normal aging; **c)** clinical, family and community service, wellness, clinical research, and extensive clinical trials programs for AD, PD, and related disorders; **d)** a Center for Healthy Aging, with an additional longitudinal cohort of nearly 1,000 research participants, including nearly 200 in their 90s and 100s, for the study of aging and age-related brain disorders; **e)** an extensive outreach, education, and volunteer programs, including 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; and **f)** close working relationships with researchers throughout Arizona and around the world. 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.

Directed by Dr. Thomas Beach, the BBDP includes >800 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 of whom have consented to donate their brains and/or bodies after they die. 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 approximately 1,800 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, 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 about 700 expired donors since 2005, and the opportunity to relate brain pathology to biological features of other body organs; and **d)** approximately 150 annual 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, helping contribute to FDA approval for use of some of these measurements in the clinical setting. It 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, publications, and findings each year.

Since 2016, BSHRI has been undergoing a period of significant change, setting the stage for BSHRI and its organizational partners to further develop its AD, PD related disorders, and aging programs. These changes include the following: **a)** continued harmonization of Banner Alzheimer's Institute's AD-related clinical, family and community services, clinical research and clinical trials programs on its downtown Phoenix and BSHRI campuses; **b)** further development of our Memory and Movement Disorders Center; a formal partnership with the emerging Arizona State University-Banner Neurodegenerative Disease Research Center (NDRC), including ASU's commitment to support 20 basic/translational research laboratories, construction of state-of-the-art laboratory space for NDRC researchers at ASU's BioDesign Institute (scheduled to open in the summer of 2018), and new research collaborations among all of the participating organizations in the Arizona Alzheimer's Consortium; **e)** a developing plan to enhance BSHRI's longevity cohort, harmonize some of the elements in the longevity and BBDP programs, and support the study of AD and resilience to cognitive decline in the oldest old; and **f)** ongoing development of a strategic plan for the development and further growth of clinical and clinical research programs on the BSHRI campus. In addition to BSHRI's large clinical, family and community services, PD-related "NeuroWellness", and clinical trials programs, its outreach efforts include >100 community presentations per year. **g)** We are also setting the initial stage to develop a center to advance innovations in elder, dementia and end-of-life care at Banner Health. **h)** We are working to expand the BBDP in several important ways, including expansion to 1,000 annually assessed prospective brain donors by the end of 2019; 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, starting with funding from a large NOMIS foundation grant.

BANNER SUN HEALTH RESEARCH INSTITUTE

Key Personnel

Name (last, first)	Degree	Role on project
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
Liu, Ming-Jai	MD, PharmD	Movement Disorder Neurologist
Moorley, Naudia	PsyD	Neuropsychologist
O'Connor, Kathy	MS	Outreach Program Manager/Longevity Program Coordinator
Powell, Jessica	PsyD	Neuropsychologist
Reade, Marina	NP	Nurse Practitioner
Schmitt, Andrea	BS, CRA	ADCC Administrative Director
Serrano, Geidy	PhD	Anatomist Supervisor, BBDP
Shprecher, David R	DO, MD	Movement Disorders Program Director, Movement Disorders Neurologist
Spann, Bryan	MD	Dementia Neurologist
Sue, Lucia	BS	Coordinator and Tissue Donation Manager, Neuropathology Core and BBDP
Zamrini, Edward	MD	Memory Clinic Director; ADCC Clinical Core Site PI, Interim Director, Center for Healthy Aging Dementia Neurologist

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

Institutional Abstract

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 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 are being developed at Barrow. The Alzheimer's disease and Cognitive Disorders Program has seen a 200% increase in patient clinic visits in the past year, which enhances recruitment of patients for research. We received United Council for Neurologic Subspecialties approval to start a fellowship in geriatric neurology, allowing for further training of new clinician-scientists. 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.

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

Name (last, first)	Degree	Role on project
Sabbagh, Marwan	MD	Principal Investigator
Shi, Jiong	MD, PhD	Neurologist
Chacon, Bianca	BSN	Program Manager
Thomas, George	BS	Study Coordinator
Rice, Gabe	MS	Study Coordinator
Seal, Lynda	BSN	Study Coordinator
Rowcliffe, Stacey	BS	Psychometrist
Jensen, Allyson	BS	Psychometrist
Garcia, Angelica	BS	Research Assistant
Quintanilla, Sandy	--	Research Assistant
Ghaffari, Layla	BS	Research Technician
Sattler, Rita	PhD	Investigator
Mufson, Elliott	PhD	Investigator
Perez, Sylvia	PhD	Research Associate Professor
Nadeem, Mohammad	PhD	Research Lab Manager
Kelly, Christy	PhD	Research Fellow
Miguel, Jennifer	PhD	Research Fellow
Baxter, Leslie	PhD	Neuropsychologist, Interim Principal Investigator
Valles, Claudia	MS	Clinical Coordinator
Nespodzany, Ashley	MS	Research Assistant
McGee, Sam	BS	Research Assistant
Debbins, Josef	PhD	Research Engineer
Stokes, Ashley	PhD	Imaging Scientist
Liu, Qiang	MD, PhD	Investigator
Wood, Kristofer	BS	Technician
Shi, Jiong	MD, PhD	Investigator
Yin, Junxiang	MD, PhD	Research Associate
Cao, Runjing	MD	Post-Doctoral Fellow
Braden, Brittany Blair	PhD	Post-Doctoral Fellow
Nielsen, Megan	--	Student
Carcione, Tanner	--	Student
Ming, Gao	PhD	Research Associate

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, 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.

CRITICAL PATH INSTITUTE

Key Personnel

Name (last, first)	Degree	Role on project
Arnerić, Stephen	PhD	Principal Investigator
Burton, Jackson	PhD	Mathematician
Conrado, Daniela	PhD	
Kern, Volker	PhD	Project Manager, Grants Administrator
Romero, Klaus	MS, MD	Alzheimer's Clinical Expert
Stafford, Robert	MA	Data Manager

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 initial 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.

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
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. expand our biobanking efforts to include all those 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. Develop a relationship 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	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, 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 has created a formal group (the Midwestern Alzheimer's Advisory Committee- the MAAC) dedicated to research into Alzheimer's disease and related conditions. This group now includes faculty from 16 departments and 6 colleges. The goals of Midwestern University 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 at activities at Midwestern:

- 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 be useful for modifying the cognitive outcome in patients.
- 3) Developing and validating new pharmacological treatments 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 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
Potter, Pamela	PhD	Co-Principal Investigator
Kaufman, Jason	PhD	Co-Principal Investigator
Tullop, Tony	MD	Co-Principal Investigator
Jones, T.B.	PhD	Co-Principal Investigator
Vallejo-Elias, Johana	PhD	Co-Principal Investigator
Jones, Douglas	PhD	Co-Principal Investigator
Al-Nakkash, Layla	PhD	Principal Investigator
Plochocki, Jeffrey	PhD	Principal Investigator
Broderick, Thomas	PhD	Principal Investigator
Bae, Nancy	PhD	Principal Investigator
Swanson, Mark	PhD	Principal Investigator
Eckman, Delrae	PhD	Principal Investigator
Jones, Carleton	PhD	Co-Principal Investigator
Powell, Jessica	PsyD	Co-Principal Investigator
Virden, Tom	PhD	Consultant
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

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 and every laboratory within the Division performs research related to aging or AD.

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 the 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 (5) the collaborative discovery of a novel cognitive enhancing agent based on the genetic finding in episodic memory. Recently the focus within several laboratories in the Division is in the area of biomarker development for the early assessment of AD and/or dementia risk. TGen is also helping to spearhead a recently funded collaborative effort to generate a public resource of RNA sequencing data from five different cell types and six different brain regions that differ in their vulnerability or resilience to different elements of AD pathology in 100 clinically and neuropathologically characterized brain donors with and without AD. This effort is expected to provide a foundation to help consortium researchers generate postulated disease networks and drivers of these networks to help clarify disease mechanisms and discovery new or repurposed drugs.

**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	Post-Doctoral Fellow
Huentelman, Matthew	PhD	Principal Investigator
Jepsen, Wayne	BS	Research Associate
Lechuga, Cynthia	MBA	Sr. Grants & Contract Administrator
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
Talboom, Joshua	PhD	Post-Doctoral 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) developing novel behavioral and pharmacological 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.

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

Neuroimaging development and application. Our researchers are developing and implementing new MRI techniques and statistical analysis methods that 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, such as MRI-guided transcranial magnetic stimulation, have expanded our resources for studies of aging and age-related disorders.

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 memory changes in autobiographical memory, disturbances in patterns of daily thought, as well as novel biological markers such as the gut microbiome that 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 and familial risk,

health factors such as hypertension, heart disease, head injury, and obesity, as well as sleep disturbance and shifts in circadian rhythm.

Interventions. We are actively developing and testing of several novel interventions that have the potential to decrease risk for AD, slow the progression of the disease, and ameliorate cognitive impairments associated with normal aging and AD. These interventions include lifestyle factors that decrease risk such the combination of exercise and cognitive engagement, novel pharmacological interventions such as the alpha-2 noradrenergic receptor agonist guanfacine and Mas receptor agonists, and innovative approaches to treating sleep disturbance through light therapy.

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. In addition, 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, with administrative support for a pilot grant program and the center Internal Scientific Advisory Committee, with an Annual Conference on Successful Aging to support 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
Billheimer, Dean	PhD	Investigator; Epidemiology and Biostatistics
Brinton, Robbie	PhD	Investigator, Center for Innovation in Brain Science, Pharmacology, Neurology, Psychology, Evelyn F. McKnight Brain Institute
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
Furenlid, Lars	PhD	Investigator; Optical Sciences, Medical Imaging
Glisky, Elizabeth	PhD	Investigator; Psychology, Evelyn F. McKnight Brain Institute
Gmitro, Art	PhD	Investigator, Biomedical Engineering, Medical Imaging, Optical Sciences
Grilli, Matthew	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Hay, Meredith	PhD	Investigator; Physiology, Psychology, Evelyn F. McKnight Brain Institute
Hishaw, G. Alex	MD	Investigator; Neurology, Psychiatry
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

Name (last, first)	Degree	Role on project
Mehl, Matthias	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Raichlen, David	PhD	Investigator; Anthropology
Rapcsak, Steven	MD	Investigator; Neurology, Psychology, Speech/Language and Hearing, Evelyn F. McKnight Brain Institute
Rodgers, Kathleen	PhD	Investigator, Center for Innovation in Brain Science
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 with two medical school campuses: the Tucson campus located at the Arizona Health Sciences Center and University Medical Center, and the Phoenix campus located on the Phoenix Biomedical Campus (PBC). The UA College of Medicine – Phoenix is part of the University of Arizona and is governed by the Arizona Board of Regents. UA College of Medicine – Phoenix shares the PBC site 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 laboratory, translation, and clinical research.

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 on Medical Education (LCME) in June 2017. At its current size, the program matriculates 80 new doctors each year, with a class goal 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 thrives on life-long learning and critical thinking. Medical students are required 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, which cumulates with a thesis as part of their graduation requirements.

The UA College of Medicine – Phoenix is positioned uniquely 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 and collaborations with local institutions. Some examples include the development of the Translational Neurotrauma Research Program, a collaborative program of the UA College of Medicine – Phoenix, Phoenix Children’s Hospital, Barrow Neurological Institute of St. Joseph’s Hospital and Medical Center, and the Phoenix Veterans Administration Healthcare System. The Translational Neurotrauma Research Program continues to evolve into the premiere destination for neurotrauma research, training and clinical investigation. The program has attracted visiting scientists, collaborators, scientist trainees, and physicians from multiple world-renowned institutes and will continue to grow and prosper under these strong collaborations. More recently this program is engaging in collaboration with the Maricopa County Attorney Office, Mesa Police Department, and HonorHealth Patient Advocacy Center to execute a program in traumatic brain injury and domestic violence lead by The CACTIS Foundation.

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

Name (last, first)	Degree	Role on project
Lifshitz, Jonathan	PhD	PI, Associate Research Professor
Rowe, Rachel K.	PhD	Assistant Research Professor
Law, L. Matthew	PhD	Post-Doctoral Fellow
Ortiz, J. Bryce	PhD	Post-Doctoral Fellow
Saber, Maha	PhD	Post-Doctoral Fellow, Project Lead
Tallent, Bret R.	LATG	Laboratory Manager
Griffiths, Daniel R.	BS	Senior Laboratory Technician
Giordano, Kathrine R.	BS	Technician
Hur, Yerina		Technician
Christie, Immaculate		Undergraduate Research Assistant

Project Progress Report

Project Progress Report
Arizona State University

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Surgical menopause in a mouse model of Alzheimer's disease: effects of duration of ovarian hormone loss. Heather Bimonte-Nelson, PhD, Salvatore Oddo, PhD. Arizona State University; ASU-Banner NDRC; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: To determine the cognitive and neuropathological effects of short-term and long-term surgical ovarian hormone loss in transgenic mice expressing both APP and PS1 mutations.

Background and Significance: Approximately two-thirds of individuals with AD are women. The decline of 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. In the last several years there has been an increase in investigation of menopause in women and its link to dementias including AD. In women, a younger age at surgical menopause was related to faster memory decline and increased AD pathology and use of estrogen-containing hormone therapy was related to a lesser decline in global cognition (Bove et al., 2014). Moreover, women with increased AD risk who took 17 β -estradiol (E2, the most potent naturally occurring estrogen in women and rodents) continuously exhibited better memory compared to those that did not; at a two-year follow up evaluation, women who had taken E2 exhibited better memory, an effect not shown when women had taken another type of estrogen therapy, conjugated equine estrogens, indicating that type of estrogen in hormone therapy impacts outcomes (Wroolie et al., 2015). Recent numbers linking menopause and AD risk are striking; one publication reports that menopause increased dementia risk in women, with numbers reporting as high as a statistically significant 70% increased risk with surgical menopause before 49 years old, with some offset of risk with estrogen therapy (Rocca et al., 2012). However, there is controversy regarding whether there is a meaningful impact of menopause and hormone therapy on cognitive and brain outcomes, and if there is, what the underpinnings are for the effects.

Thus far, the few studies testing menopause and hormone therapy using a mouse model of AD have shown that surgical menopause (surgical removal of the ovaries) increased AD-like pathology, and that E2 therapy given immediately attenuated these effects. There has been no corresponding work evaluating timing of such effects. This is critically important, as there is evidence that there is likely a critical window for ovarian hormone loss and replacement effects on the brain and its function (Koebele and Bimonte-Nelson, 2015; Koebele and Bimonte-Nelson, 2016). Indeed, there has also been no AD rodent model work evaluating whether timing and type of hormone therapy impacts AD pathology and cognition, even though these factors linking to trajectory of change are becoming apparent in the human literature. The AD mouse model could afford critical information, garnered in a controlled and systematic way, regarding whether menopause and hormone variants alter trajectory of pathologies, as well as cognition.

Experimental Designs and Methods: For this study, we used female APP/PS1 mice (Jankowsky et al., 2004). Both female transgenic (Tg) and wildtype (Wt) control animals were used for this study. To evaluate the effects of short-term (ST) versus long-term (LT) ovarian hormone deprivation, we randomly assigned mice to one of eight treatment groups: Wt Sham ST (n=15),

Wt Sham LT (n=15), Wt Ovx ST (n=15), Wt Ovx LT (n=15), Tg Sham ST (n=15), Tg Sham LT (n=15), Tg Ovx ST (n=15) and Tg Ovx LT (n=15). We tested animals on a battery of cognitive and control behavioral tasks and sacrificed them to evaluate brain tissues to determine effects of surgical menopause on plaque load and A β levels. A β pathology will be assessed via immunohistochemistry and ELISA. We will then correlate brain measurements with behavioral outcomes.

Progress:

The current work done to date includes breeding, surgeries, and behavioral testing. Results showed an interaction between genotype and surgical menopause status, with surgical menopause exacerbating a genotype effect. Additional behavioral analyses are being performed. Neuropathology evaluations have yet to be performed and will allow us to determine relationships between surgical menopause status, cognition, and AD-like neuropathology.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Using a three-dimensional (3-D) human induced pluripotent stem (hiPSC)-based model of Alzheimer's disease (AD) to dissect disease mechanisms and test potential therapeutics. David Brafman, PhD, Sarah Stabenfedlt, Xiao Wang, Christopher Plaiser, Karl Willert, Richard Caselli, MD, Winnie S. Liang, PhD, Matt Huentelman, PhD, Thomas Beach, MD, PhD. Arizona State University; University of California San Diego; Mayo Clinic Arizona; Translational Genomics Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Generate a comprehensive library of hiPSC from familial and sporadic AD patients (FAD and SAD, respectively) to examine specific phenotype-genotype relationships in hiPSC-derived neural cells.

Aim 2: Establish a reference genetic signature that defines allows for the phenotype assessment of hiPSC-derived cortical neurons.

Aim 3: Evaluate the potential of A β and tau modifying therapeutics using hiPSC-derived 3-D cortical cultures.

Background and Significance: Alzheimer's disease (AD) affects over 120,000 individuals in Arizona and has a direct cost to Arizona that is estimated in excess of \$5 billion/year. Although the pathological hallmarks of AD, such as axonal transport defects, synaptic loss, and selective neuronal death, are well-characterized, the underlying mechanisms that cause AD onset and age-related progression are largely unknown, thereby making it difficult to design effective therapies. Rodent models have provided valuable information in understanding AD but these models do not recapitulate all aspects of the human disease. To date, studies of AD with human neuronal cells have been restricted to experiments with cadaveric tissue samples which are limited in supply and only provide an end-stage view of the disease. With hiPSC technology it is possible to obtain a fully differentiated cell type (such as a skin cell) from an AD patient and reprogram it back into a cell type that is capable of differentiating into all of the cell types of the mature, adult body (such as cortical neurons). Therefore, with hiPSC-based technologies we have the potential to probe AD disease mechanisms and design molecularly targeted therapies.

Preliminary Data and Plan:

Aim 1: We have previously developed a robust non-integrating protocol for the generation of hiPSCs from patient samples. We are currently using this method to generate hiPSCs from FAD generated a unique panel of hiPSC lines from FAD patients with mutations in APP and PS1 as well as SAD patients, with an emphasis on individuals with genetic risk factors associated with increased SAD risk. In addition, we are using targeted gene modification strategies to generate isogenic hiPSC lines with defined FAD mutations or SAD-associated risk factors.

Aim 2: Previous studies have demonstrated that the CNS undergoes extensive transcriptional and epigenetic changes during development and subsequent aging. Although previous studies have profiled transcriptional and epigenetic changes in human brain tissue of various ages, these studies are limited by: (i) analysis of heterogeneous brain tissue samples or regions of non-cortical identity and (ii) examination of too few samples to make rigorous correlations between transcriptional or

epigenetic changes and age. The goal of this aim is to define that the transcriptional and biochemical signatures associated with specific neural populations most affected by AD to provide meaningful read-outs to rapidly assess the effectiveness our hiPSC-based models.

Aim 3: Current pharmacological interventions for AD only provide modest, short-term symptomatic relief and do not treat the underlying disease etiology. While the causes of AD have been highly debated and difficult to precisely ascertain, aggregation of amyloid beta (A β) and tau have been associated with the vast majority of AD cases, including almost all sporadic cases. Because of the prevalence of A β and tau pathology in AD and its progressive spread throughout the brain, targeting A β - and tau-induced neuronal toxicity is a very promising therapeutic approach. Yet, because A β and tau are carefully regulated proteins critical for normal cell health and function, effective therapies should selectively target toxic variants and not variants necessary for normal brain function. Dr. Sierks has previously generated a panel of antibody reagents that selectively bind A β and tau present in human AD tissue but not control samples. However, to date, most AD therapeutics have been evaluated in (1) rodent models, while providing valuable information in understanding AD, do not recapitulate all aspects of the human disease, (2) immortalized cell culture models which are aneuploid with unknown dosage at key genes and do not display disease-related phenotypes, or (3) neuronal cells from cadaveric tissue samples which are limited in supply and rapidly lose disease-related phenotypes upon extensive *in vitro* culture. As such, we will utilize these nanobodies against disease specific A β and tau variants in conjunction with our hiPSC-based models of AD to determine which nanobodies represent the most promising therapeutic targets for treating AD.

Proposed One-Year and Long-Term Outcomes:

Aim 1: Continue to develop a comprehensive library of hiPSC lines with defined FAD mutations and SAD-associated risk factors. In the future, we will be able to use these lines to address important research questions such as: (1) What is the genetic contribution to disease onset and progression? (2) What are the phenotypic effects of genetic risk variants? (3) Are there new risk variants associated with observed *in vitro* phenotypes? (4) Do FAD mutations or SAD-related risk factors converge on common biochemical, molecular, and transcriptional pathways?

Aim 2: Continue to develop methods for biochemical and transcriptional characterization of single-cell suspensions from rapidly-autopsied human brains. Moving forward, analysis of these cells will provide a reference map that will allow us to systematically and rapidly refine and validate our *in vitro* disease modeling methods.

Aim 3: Our collaborator, Dr. Michael Sierks, has generated a panel of antibody reagents that selectively bind A β and tau present in human AD tissue but not control samples. Moving forward, we investigate the extent to which the nanobodies ameliorate or reverse AD-related biochemical phenotypes in a hiPSC-based model.

Funds have been used to complement but do not overlap with funding provided by the National Institute on Aging (NIA), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of General Medical Sciences, and the Arizona Biomedical Research Commission (ABRC).

Year End Progress Summary:

Aim 1: Over the past year, in collaboration with Dr. Richard Caselli, we have generated hiPSC lines from non-demented control (NDC) and AD patients with various ApoE genotypes. These patients have been selected from two research cohorts (Arizona ApoE Cohort and Arizona

Alzheimer's Disease Center Clinical Core), which has been developed by Dr. Caselli over the past 20 years. It is important to note that among the disease and control patient are a large number of ApoE4 homozygotes, a relatively rare resource. To that end, the hiPSC lines that we have generated from these patients represent a unique and valuable resource that to date does not exist anywhere in the US. In addition, because each patient has detailed longitudinal neuropsychological profile and full post-mortem pathological examinations, we are uniquely positioned to determine if phenotypes identified from the collection of patient hiPSC lines correlates with the clinical phenotypes observed in individual patients.

Aim 2: During the past year, in collaboration with Dr. Thomas Beach, we have developed, optimize and standardize a method for producing single-cell suspensions from rapidly-autopsied human brains and their subsequent analysis by flow cytometry and qPCR.

Aim 3: Over the past year, Dr. Brafman and Dr. Sierks have worked together to identify a pool of candidate nanobodies that selectively bind A β and tau species present in hiPSC-derived AD neural cultures.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Novel mechanisms of neuronal death in Alzheimer's disease. Caterina Branca, PhD, Paul Coleman, PhD. ASU-Banner NDRC; Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Collaborators: Banner Sun Health Research Institute; Translational Genomics Research Institute.

Project Description: Alzheimer's disease (AD) is characterized by severe neuronal loss. However, the mechanisms by which neurons die remain elusive. Additionally, it is also unclear why some neurons within the same brain region are more resistant to neurodegeneration than others. We focused on necroptosis, a programmed form of necrosis, triggered by receptor-interactive protein kinases (RIPK) 1 and 3 and executed by the mixed lineage kinase domain-like (MLKL) protein. During necroptosis activation, RIPK1 binds to and activates RIPK3. In turn, activated RIPK3 binds to and activates MLKL. To achieve our goal, we proposed to use laser capture microdissection (LCM) to capture neurons from human AD brains and perform RNAseq. Tissue will be immunolabeled with RIPK1 and pMLKL antibodies. This will allow us to divide the stained cells in two groups: one where necroptosis has been activated (positive for RIPK1 and pMLKL) and one in which necroptosis has not been activated despite the high levels of RIPK1 (positive for RIPK1 but negative for pMLKL).

Progress to date: For the proposed experiments, we started with the validation of the staining protocol for the LCM procedure. Frozen samples of human brain from the middle temporal gyrus of AD and control patients were obtained from the tissue bank at the Banner Sun Health Research Institute. These samples were processed with the cryostat to obtain 10 μm thick slices. To validate RIPK1 and pMLKL antibodies, we followed different staining protocols at different conditions: with primary and secondary antibodies, without primary antibody, without secondary antibody, and with no antibodies. No specific staining was detectable for any of the used conditions. To evaluate the possible degradation of the tissue (due to incorrect conservation or processing), H&E staining was performed. This revealed that the tissue was in good condition and suitable for staining. Therefore, the antibodies suggested to perform the experiments proposed in the grant are not suitable for LCM procedure. Considering the outcome of our experiments, we are pursuing a different approach to study RIPK1 function. We have generated RIPK1 floxed mice which will allow us to study the role of RIPK1 in AD and why some neurons within the same brain regions are more resistant to neurodegeneration than others.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Early nuclear loss of H3k4me3 affects synaptic and mitochondrial pathways in Alzheimer's brain. Paul Coleman, PhD, Diego Mastroeni, PhD. ASU-Banner NDRC; Arizona State University; Banner Sun Health Research Institute; Maastricht University; Arizona Alzheimer's Consortium.

Hypothesis: Reduced nuclear H3K4me3 plays a significant role in altered expression of synaptic and mitochondrial genes in Alzheimer's disease, and novel multiplexed single-cell in situ analysis will allow us to determine which genes, and to what extent they are affected.

Specific Aims:

Aim 1: Develop cleavable fluorescent antibodies for highly multiplexed single cell in situ protein epigenetic factors analysis. We have demonstrated that by tethering antibodies to fluorophores through a azide-based cleavable linker developed recently in our group, more than 12 different proteins can be quantified in single cells in situ. To further develop this technology, we will optimize our cleavable linker and conjugate varied spectrally separable fluorophores to primary antibodies through the cleavable linker. In this way, our approach will enable the quantification of the identities, positions and abundances of over 100 different protein and synaptic and mitochondrial at the sub-diffraction-limit resolution in cells that have been defined as nuclear or non-nuclear H3k4me3 reactive.

Aim 2: Quantify various epigenetic factors and investigate their effects in Alzheimer's and normal neurons. Using the cleavable fluorescent probes developed in Aim 1, we will explore the positions and abundances of H3k4me3, study the 3-D genome architectures and investigate the chromatin accessibility in Alzheimer and well-matched control subjects. Power analysis indicates a minimum of 10 AD and 10 control subjects.

Rationale and brief experimental design:

At a basic science level, the emphasis on epigenetic and gene expression methods at the level of identified neurons offers the opportunity for more precise (cell-type specific) elucidation of molecular events in early AD. We believe that we are uniquely positioned to carry out these studies, which will advance our ability to further the basic understanding of molecular events early in the course of disease that are needed to develop early diagnosis and optimal treatment before Alzheimer's disease can devastate the brain. Synaptic deficits occur early in the course of Alzheimer's disease. We have published data that reduced presence of H3K4me3 in the cell nucleus is also an early event in the cellular cascade of Alzheimer's disease in the human brain. Starting in 1986 (Wolozin et al., 1986), Peter Davies and coworkers published a series of papers describing antigenic sites and a series of antibodies to selected modifications of tau in Alzheimer's disease. Recently this team has identified a conformational change in tau revealed by their antibody, MC-1, as the earliest change in tau in the progression of Alzheimer's disease. We have recently (Mastroeni et al., 2015a) shown that reduced H3K4me3 in neuronal nuclei, can be detected well before the earliest tau modification described by Davies (e.g., Weaver et al., 2000). Tri-methylated H3K4 is a mark of genes being actively transcribed or poised for transcription and is notably related to transcription of genes related to synaptic structure and function. The ability to

quantify a large number of different proteins, transcripts and genomic loci early in single cells in situ is crucial for our understanding of the effects of epigenetic manipulation and the impacts of different epigenetic factors on gene expression regulation. Due to the inherent complexity of epigenetic regulatory networks, comprehensive molecular profiling is required to systematically infer the functions of different epigenetic factors in a pathway. The differences between individual cells in complex biological systems have significant consequences in the function and health of the entire systems. Thus, single cell analysis is required to explore such cell heterogeneity. The precise location of cells in a tissue and epigenetic factors in a cell is critical for effective cell-cell and biomolecule-biomolecule interactions, which can determine cell fates and functions. Therefore, to fully understand the effects of epigenetic manipulation and the impacts of different epigenetic factors on gene expression regulation, comprehensive molecular profiling in single cells in situ is required. However, existing single cell technologies do not allow integrated in situ analysis of large numbers of molecules. Additionally, as carried out on isolated and amplified biomolecules, these approaches mask the spatial complexity of epigenetic factors.

Expected deliverables at the end of the one-year project period:

These experiments will provide the preliminary data we need for a competitive R01 submission. As I have done with previous AARC awards, at least one manuscript will be submitted.

Expected deliverables in a more long-term context; for example, within two years (including manuscript and grant submission/s): Long term would be to extend our findings in a larger sample cohort including MCI subjects.

If you received monies from the Arizona Alzheimer's Consortium in the last two years, list the paper/s and/or grant/s submitted from these funds, or those that plan to be submitted (including a timeframe):

Results to date:

The proposed technology has now been successfully applied to sections of human brain. The expression of sixteen proteins has been quantified in the normal aged hippocampus. The resulting data has shown the ability to distinguish sub-regions of the hippocampus on the basis of patterns of immunoreactivity of these sixteen proteins. In addition, the multiple expression profiling has revealed subregions in the dentate gyrus. A paper describing these novel findings is being prepared for publication. In addition, the success of this work is leading to preparation of an R01 that will be submitted for an April 17, 2018 deadline.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Determine the role of necroptosis in Down Syndrome. Antonella Caccamo, PhD, Elliot Mufson, PhD. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aim: Determine the effects of reducing necroptosis on neuronal loss in Ts65Dn mice.

Background and Significance: Down syndrome (DS) is caused by triplication of chromosome 21 and affects one of every 700 births in the United States. DS patients have a high risk of developing Alzheimer's disease (AD). Indeed, virtually 100% of DS patients have sufficient A β deposits and tangles by the age of 40 years for a neuropathological diagnosis of AD. Additionally, 60% of individuals with DS will develop dementia by the age of 60. Despite the progress made in understanding the pathogenesis of DS, the mechanisms by which neurons die remain elusive. Here we provide compelling evidence that necroptosis, a programmed form of necrosis, is activated in a mouse model of DS known as Ts65Dn. We will test the overarching hypothesis that necroptosis contributes to neuronal death in DS. To address this question, we propose the following Specific

Progress to date: Our preliminary data indicate that necroptosis is activated in Ts65Dn mice. In our grant application we proposed to treat 14-month-old Ts65Dn mice and 2N (controls) mice with necrostatin (0.2 mg/g in drinking water), a RIPK1 inhibitor for one month. We used 14 month-old age mice, because at this age the Ts65Dn mice have severe neuronal loss especially in the cerebellum. We successfully completed the treatment, sacrificed the mice and assessed the effects of reducing necroptosis on neuronal loss by unbiased stereology. We found a significant decrease in cell loss in the cerebellum for both the granule and Purkinje cells. These exciting data provide compelling evidence that necroptosis contribute to neurodegeneration in Ts65Dn mice. We are now in the process of assessing the biochemical changes associated with this improvement. In the meantime, we have leveraged these novel and exciting data to submit an R01 application, which goes to study section on February 21st, 2018.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Refining an intervention protocol for caregivers of people with DS/ID + ADRD. David W. Coon, PhD. College of Nursing & Health Innovation, Arizona State University; the Desert Southwest Chapter of the Alzheimer's Association; the Arizona Developmental Disabilities Planning Council. Arizona Alzheimer's Consortium.

Collaborators:

Arizona State University: Phil Carll, Jami Goldman, Berta Carbajal, Abi Gomez Morales, Lourdes Cordova, Allison Glinka, Kassey Stotler, Leah Carbajal, Richard Montague, Marilysse Cortes

Specific Aims: (1) To utilize recent data gathered by the team to refine and finalize a protocol for a psychoeducational skills-training intervention for formal and informal caregivers of people with Down Syndrome (DS) or other Intellectual Disability (ID) who developed ADRD as they aged. (2) To gather feasibility and acceptability data on the intervention's protocol from a group of caregivers and other key informants.

Background and Significance: An underserved and understudied group of family caregivers impacted by Alzheimer's Disease and related dementias (ADRD) are those who assist adults with Down syndrome (DS) or another Intellectual Disability (ID) who develop ADRD as they age (DS/ID + ADRD). Recent research estimates that at least 25% of these adults will be affected after age 40, and between 50% and 70% will be affected after age 60. Lifelong caregiving, amplified by the onset of ADRD, create "double jeopardy" for informal caregivers helping people with Down syndrome or another ID. Moreover, no evidence-based interventions have been identified to help these family members and friends manage changes in care, caregiving associated stressors, and caregiver-related distress.

Preliminary Data: This project will build on initial research activities by our interdisciplinary/interprofessional (behavioral science, social work, education, and nursing) team. (1) Data collected at a recent small conference about DS/ID +ADRD found that the vast majority of conference participants believed major components and key strategies from proven psychoeducational skill-training programs like CarePRO and EPIC would be useful in alleviating caregiver stress and distress. (2) Meetings with key informants identified several other critical issues. For example, interventions should serve both family caregivers in the community and professional caregivers in group homes; they should be built on shorter targeted sessions in group homes to address staffing and cost challenges; and, they ought to consider a combination of in-person and online or telephone group-based modes of delivery. While these results and preliminary activities by our team are promising, the proposed project will build on this work using both qualitative and quantitative methods.

Experimental Designs and Methods: This project proposes to: (1) collect additional data to further refine and finalize the intervention, its components and strategies, and its related recruitment, screening, and interview protocols through key informant feedback; and (2) use a

single-arm quasi-experimental design to gather feasibility and acceptability data on the intervention and its protocol from a group of DS/ID +ADRD caregivers.

Proposed One-Year and Long-Term Outcomes: The proposed short-term outcomes would be additional data collection to help in the refinement of an intervention for family caregivers of people with DS/ID +ADRD, then refine and investigate the feasibility/acceptability and preliminary efficacy of the intervention of caregiver outcomes. In addition, these findings would be used to develop professional presentations at meetings such as the Gerontological Society of America, the American Society on Aging, or American Psychological Association and the submission of the pilot results to venues such as *The Gerontologist (Practice Concepts Section)*, *the Clinical Gerontologist*, or *Dementia*. Based on the findings, the PI and his community partners would hope to submit an R21 or perhaps a smaller R01 submission, depending on the pilot project's findings.

Year-End Progress Summary: The project is on track for completion 6/30/18. Additional data were collected to gather a fuller picture from an ethnically and racially diverse group of family caregivers and professionals (N=95) regarding their perceptions of key components of the proposed intervention. Participants described themselves as non-Hispanic White (68.4%), Hispanic/Latino (15.8%), African American/Black (6.3%), Native American (5.3%), Asian American (3.2%), no primary group or another ethnic/racial minority (10.5%). Respondents varied in their roles with regard to caregiving: (a) family or friend caregivers (40%); (b) professionals helping develop or manage programs to serve these individuals (14.7%); (c) professionals working directly with people with DS/ID and/or their families (9.5%); or (d) people with multiple roles (35.8%). Over 96% of the participants who responded to the survey rated each of the components as useful. Focus groups with family caregivers and professionals with experiences relevant to caring for people with DS/ID + ADRD are underway; however, recruitment has been somewhat challenging. Therefore, we secured IRB approval to conduct individual focused interviews as an alternative for those that cannot attend a focus group due to travel constraints or difficulties finding someone to stay with their care recipient. These focus groups are integral to the project assisting additional intervention refinement. To date, informants raised several other issues for consideration: the potential for a combination of in-person and telephone or online modes of delivery; the need for interventions for individuals in group home/group living situations; and the need for interventions for staff that recognize challenges in time for continuing education and intervention delivery costs. A small pilot of the intervention is planned for May.

We hope to coordinate our efforts with Dr. Marwan Sabbagh's (Barrow Neurological Institute) in Down Syndrome and ADRD.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Synbodies as novel TNF α pathway inhibitors. Boris DeCourt, PhD, Chris Diehnelt, PhD. ASU-Banner NDRC at the Biodesign Institute; Biodesign Center for Innovations in Medicine; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: Develop synbodies which can inhibit TNF α , TNF receptors I and II *in vitro*.

Background and Significance: The three major neuropathological features of Alzheimer's disease (AD) are chronic inflammation, mainly driven by tumor necrosis factor α (TNF α), and the aggregation of amyloid beta (A β) into extracellular plaques, and the intracellular accumulation of hyperphosphorylated tau into tangles. Inflammation has been shown both *in vitro* and *in vivo* to exacerbate A β and tau pathologies, thus represents a therapeutic target to lower the severity of AD if given at an early stage of the disease [1-4]. Recently, our group (Dr. Diehnelt) has developed antibody alternatives, called synbodies, that bind with high affinity and selectivity to protein targets [5-9]. Synbodies are bivalent peptides that are quickly identified in an *in vitro* screening system, are prepared by standard peptide synthetic approaches, and a large array of synbodies can be developed for multiple targets in parallel. They offer a lower cost alternative to antibodies and are ideally suited to inhibiting protein-protein interactions. Synbodies are easily modified to incorporate additional functional groups, such as cell penetrating peptides, without altering synbody binding [5].

Preliminary Data: We have previously developed synbodies to TNF α [9], however these synbodies were composed of L-amino acids and subject to protease degradation. We have improved the synbody discovery system so that peptides with protease stable, D-amino acids are discovered, providing synbody candidates with improved performance [5-6]. We will use this improved discovery system for the proposed project.

Experimental Designs and Methods: In this project, we will develop a series of TNF α - and TNF α receptors-inhibiting peptides, then use the selected peptides to create anti-TNF α synbodies (month 1-5). Specificity and selectivity will be assessed by *in vitro* screening with recombinant human and mouse proteins, similarly to a method previously published by Dr. Decourt (month 6-7). Synbodies capable of capturing TNF α selectively will be tested in *in vitro* assays for their capability to inhibit the binding of TNF α to its receptors, and further confirmed functionally in cultured cells (human and mouse neuroblastomas) with comparison to function blocking anti-TNFR1 and anti-TNFR2 antibodies (R&D Systems; month 7-9). Furthermore, the binding of synbodies will be validated using human and mouse samples (plasma, CSF, brain, and other tissues; month 9-12).

Proposed One-Year and Long-Term Outcomes: At the end of year one, we will have demonstrated *in vitro* functionality of TNF α synbodies. We will evaluate the commercial potential of these molecules and file a disclosure with AZTe for synbody compositions that are TNF α /TNFR1 or TNFR2 inhibitors if warranted. These molecules will be the basis for additional

grant applications to explore their use as TNF α inhibitors and their development as therapeutic agents. Given the rapidity of testing for synbodies in *in vitro* experiments, we anticipate applying for an NIH Director's Transformative Research Awards in September 2017. If successful, the data from this project will be compiled into at least one scientific publications and used for RO1 grant applications (June or October 2018) aiming to test the synbodies on transgenic mouse models of Alzheimer's disease.

Year End Progress Summary: In September 2017, we initiated the TNF synbody discovery portion of the project. Peptide array screening for TNF was performed using matching funds from CIM prior to release of project funds in October 2017. After the account was established, we ordered peptides identified from the peptide array screen and used these peptides to produce a library of 41 synbodies for TNF α screening prior to testing TNF/TNFR1 inhibition. This was fewer than the 55 synbodies that should have been produced in the library creation. This was driven by

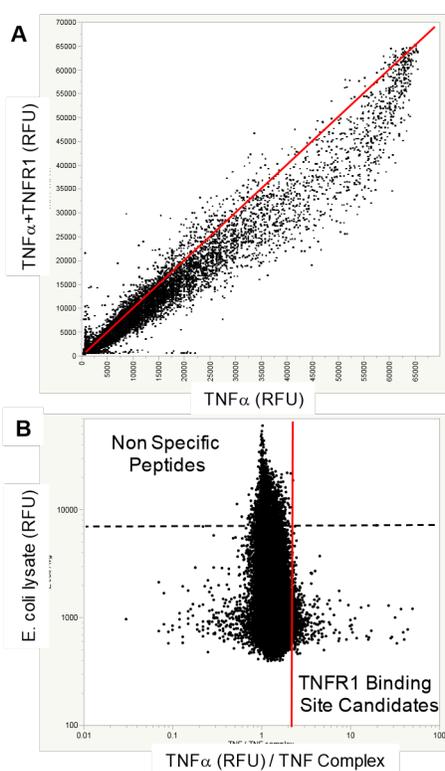


Figure 1. A) TNF α (x-axis) and TNF α +TNFR1 complex (y-axis) binding to 125k peptide microarray. Each spot represents the signal from a single peptide. **B)** TNF α binding peptides blocked by TNFR1 (green) versus labeled *E. coli* lysate.

poor solubility of 1 peptide used for library construction that led to the failure in synthesis of all synbodies that contained that peptide. We will repeat the conjugation reactions again under different conditions to produce synbodies that contain that peptide. Project funds were used for an undergraduate research student, Joshua Reus, who performed the TNF synbody development work prior to his graduation in December 2017. The preliminary data from the peptide array screen were used in an RO1 application submitted in October 2017. Synbody library screening is planned for March 2018.

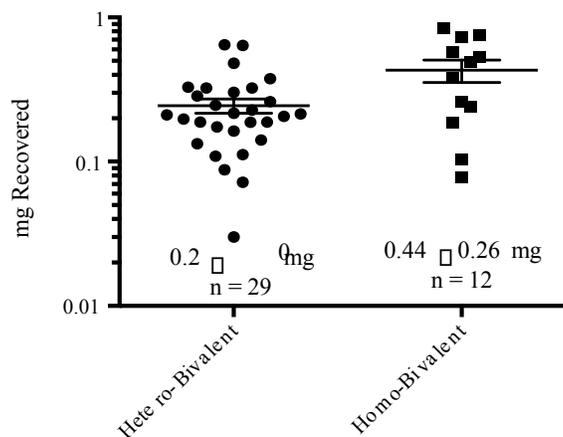


Figure 2. Amounts of each TNF α synbody produced. This library will be used for screening for TNF α /TNFR1 inhibitors.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Can we use peripheral monocytes to predict brain inflammation in Alzheimer's disease?

Diego Mastroeni, PhD, Winnie Liang, PhD. ASU-Banner NDRC; Arizona State University; Banner Sun Health Research Institute; Maastricht University; Translational Genomics Institute; Arizona Alzheimer's Consortium.

Hypothesis: Brain microglia and peripheral monocytes in Alzheimer's disease brain will share common inflammatory, and phagocytic expression profiles, such that we can predict brain inflammatory state using peripheral monocytes.

Specific Aims:

Aim 1: It is critically important to this work that peripheral monocytes and microglia are extracted from the same individuals. To this end, we have already isolated peripheral monocytes from clinically and now pathologically confirmed AD, and normal control (NC) subjects. Power analysis (Cohen's $d = .95$) indicates that 10 cases per condition (e.g., 10AD/10ND – microglia and monocytes) are required (40 samples total) for the probability of superiority. The inclusion/exclusion criteria we have used in previous studies (e.g. gender, age, ApoE status, history of inflammatory diseases (metabolic syndrome) and extended use (>6 months) of anti-inflammatory medications) will also be considered in this study. The focus of Aim 1 is designed to address monocytic expression profiles with a focus on innate/adaptive inflammatory and phagocytic expression profiles. RNA isolated in Aim1 will be subjected to whole transcriptome sequencing (RNA sequencing) to be completed at TGEN, under the guidance of Winnie Liang. QPCR validation, and data analysis will be done using the same successful methods used in our published (Mastroeni et al. 2017, 2018) and preliminary studies.

Aim 2: In specific Aim 2, we will identify the innate/adaptive inflammatory and phagocytic expression profiles in Laser captured microglia from the Mid Temporal Gyrus in the same AD, and NC patients we secured monocytes from in Aim 1. We experimentally determined that 600 microglia are necessary to represent the population using an estimate of 1×10^6 microglia/10um tissue section (confidence level-99%). We will isolate 600 microglia near, but not within, the neurovascular unit (approx. 1 mm from vessel wall) in AD and NC subjects. Clinically diagnosed patients in specific Aim 1 will be pathologically validated. AD cases will be devoid of pathology other than that for their respective diseases, and NC cases will be clean of AD pathology besides what is normally observed in aging. If we find overlapping or multiple pathologies exist at autopsy, we can use these subjects to test the validity of AD-specific inflammation vs. other types of neurodegenerative diseases. QPCR validation will be performed to ensure no other cell contamination within cut samples. To demonstrate a relationship between monocytes in Aim 1 and microglia in Aim 2, we will perform a differential analysis as implemented in the DESeq2 R-package, with a 2-factor design including cell type and disease status as previously published (Mastroeni et al. 2017, 2018).

Rationale and brief experimental design: It is now well in press that neuroinflammation constitutes an important feature in Alzheimer's disease (AD), wherein the exact role of innate immunity remains unclear. The notion that microglia are the resident monocyte of the CNS is well

in press. What is not understood is the parallel or discordance between brain microglia and peripheral monocytes, albeit both are innate mediators of the inflammatory cascade. Peripheral monocytes and microglia are both acute regulators of brain and peripheral inflammation, acting as the first line of defense to any foreign body, including pathogenic lesions. Although known associations exist between brain and blood, it is not clear why one should expect that expression profiles of peripheral monocytes would reflect what is going on in CNS microglia. Intuitively, one would expect that these distinct classes of cells would share common expression profiles because both originate from the same myeloid precursor cells in utero, but more than development, both cell classes share the same cellular morphology, phagocytic activities, expression of cell surface markers, cytokine production, and similar gene expression profiles. Throughout the brain, monocytes travel through blood vessels comprised of neurovascular units containing microglia. This exchange of information between CNS microglia and peripheral monocytes begs the question, do peripheral monocytes and microglia share an overarching inflammatory expression profile? Research from our laboratory, and preliminary data suggest we can use peripheral monocytes to predict brain inflammation. We have shown that microglia have a strong affinity for amyloid beta (A β) plaques, and preliminary data from our laboratory also show that peripheral monocytes share this same affinity for A β . In fact, in the early 90's Wisniewski and colleagues proposed that monocytes, not microglia, were the primary cells responsible for A β phagocytosis. Because microglia and peripheral monocytes are in many ways indistinguishable, the idea that both innately favor the clearance of A β supports an argument in favor of an overarching expression profile among monocytes and microglia in AD. Using peripheral monocytes to predict brain inflammation be a minimally invasive diagnostic tool with a substantial impact. Perhaps equally important, successful diagnostics often illuminate underlying mechanisms of disease. Thus, a prognostic for brain inflammation could have value well beyond its clinical utility. Our previous research and that of others has strongly suggested that Alzheimer's disease pathology is accompanied by an innate inflammatory response, but do brain microglia and peripheral monocytes in AD share common expression profiles, such that we can predict brain inflammation state?

Proposed One-Year and Long-Term Outcomes: The findings and funds from this research will be used in a way that complements but does not overlap with other funding; like the funds provided by the Alzheimer's Association, where I will be looking at astrocytes in the same individuals and regions. In addition, these findings will compliment my funded ABRC grant where I will be looking at neurons in the same brain regions and individuals. The Goal is to be able to determine the ability of one class of cells to influence the expression of another cell class. The crosstalk or the potential miscommunication between cell classes is an important step in the disease process that has yet to be fully explained. The data obtained will serve as preliminary data for applications to NIH in response to an announcement of support for studies of single cells. We also expect that the data will serve as preliminary data for a collaborative proposal with Lih-Fen Lue and other collaborators at Banner Sun Health Research Institute.

Year End Progress Summary:

Aim 1: All samples have been selected and secured. We thank Dr. Thomas Beach, Lucia Sue, Dr. Geidy Serrano and their staff for provision of tissue samples and postmortem evaluations. All matching peripheral leukocyte samples have been secured and RNA extracted. Laser capture experiments of LN3 positive microglia are under way. We have cut and extracted RNA from

twelve cases thus far. All samples (blood and brain) will be ready for sequencing by the end of March 2018.

Aim 2: Samples will be sent to TGEN in April, where Dr. Liang will perform the RNA sequencing and the bioinformatics.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Discovering the roles of genetic diversity and cellular adaptability in Alzheimer's disease. Li Liu, Yung Chang, Pramod Chandrashekar, Fu Tong, Richard Caselli. ASU-Banner NDRC; Arizona State University; Mayo Clinic Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background and Significance: Alzheimer Disease (AD) is a disease of high heritability (>60%) and high heterogeneity. For better risk assessment and disease management, a precision medicine approach needs to take into account variability in genes, environment, and lifestyle for each person. Unfortunately, in spite of ongoing research, our knowledge on the genetic basis of AD is far from being complete. On one hand, except APOE variants, all common genetic variants associated with AD discovered to date have small effect sizes (odds ratio ranges between 0.8 and 1.2) and account for only 8% of the genetic variance. On the other hand, the hunt for rare variants with large effect sizes is largely fruitless. One possible explanation of this dilemma is that a large number of genetic variants with nearly neutral functional impact influences an individual's disease susceptibility. In this application, we propose to study the roles of genetic diversity, a result of the accumulation of many nearly neutral variants, in the pathogenesis of AD. We hypothesize that increased genetic diversity leads to higher cellular adaptability that reduces the disease risk.

Specific Aims: In Aim 1, we will examine the association using computational approaches. We will analyze genotype and clinical data for >1,500 patient samples collected from three large-scale studies. We will compute several indices to measure the genetic diversity at the genome-wide level and at the pathway level. Using robust statistical tests, we will examine the association of genetic diversity with clinical diagnosis, and with the age of onset of AD. We will identify critical biological pathways that have significantly varied genetic diversity among phenotypic groups. We will also evaluate the predictive power of genetic diversity indices in assessing an individual's risk of developing AD.

In Aim 2, we will conduct in vitro validation of the adaptability of biological pathways associated with AD. Via a collaboration with Mayo Clinic, we will collect peripheral blood mononuclear cells from 20 individuals, including roughly equal numbers of early-onset AD patients, LOAD patients and age-matched healthy controls. We will perform whole-exome sequencing on these samples and estimate the genetic diversity. We will also conduct in vitro experiments on these samples to assess the adaptability of critical pathways. Specifically, we will examine a wide range of stress response pathways, including but not limited to DNA-damage response, oxidative stress response, and inflammatory response.

Proposed One-Year and Long-Term Outcomes:

1. Establish the roles of biological adaptability in AD development at genetic and cellular levels.
2. Discover specific pathways with reduced adaptability as potential biomarkers.
3. Build accurate predictive models for AD risk assessment.

Progress Summary:

Aim 1: We have successfully completed all the computational analysis, detected significant association between genetic diversity and AD development, and discovered pathways with reduced genetic diversity in AD patients.

1A. We found that young AD group has the lowest genetic diversity, the octogenarian healthy controls has the highest genetic diversity, and late-onset AD group has the intermediate genetic diversity (Fig. 1A).

1B. We developed a standardized homozygosity score to estimate the genetic diversity for an individual. We found a significant association between the genetic diversity of a personal exome and the age of AD onset (Fig. 1B).

1C. We identified two pathways, the genetic diversity of which are significantly associated with the age of AD onset. They are the heterotrimeric G-protein signaling pathway and the Notch signaling pathway. Both pathways have been linked to A β production.

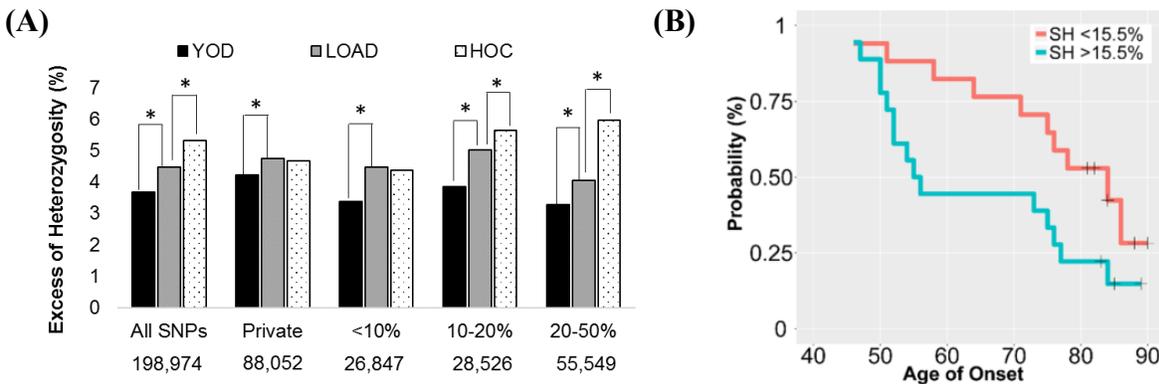


Figure 1. Genetic diversity is associated with AD. **(A)** Excess of heterozygosity is higher in the healthy octogenarian control (HOC) group than that in the late-onset AD (LOAD) group, which in turn is higher than that in the young AD (YAD) group. Asterisks indicate comparisons with significant p-values < 0.05. Excess of heterozygosity is computed as the percent of increase of the observed heterozygosity over the expected heterozygosity. **(B)** Kaplan-Meier plot shows higher homozygosity is associated with the age of onset of AD (p-value=0.02). Homozygosity is computed as an allele-frequency-weighted homozygosity rate (i.e., standardized homozygosity, SH, range [13.7%, 16.8%]). The median SH score was used as the cutoff.

Aim 2: We are in the process of conducting in vitro assays to examine cellular responses to DNA-damages, reactive oxidation stresses and A β . We have obtained IRB approvals from Mayo Clinic and from ASU. Patients are being contacted to collect blood samples. We expect to finish all in vitro assays and related data analysis by July 2018.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Staging the progression of AD-like pathology in 3xTg-AD mice. Salvatore Oddo, PhD, Heather Bimonte-Nelson, PhD. ASU-Banner NDRC; Arizona State University; University of Arizona College of Medicine Phoenix; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Collaborators:

Arizona State University: Ramona Belfiorel, Caterina Branca, Lynette Bustos, Antonella Caccamo, Nik Dave, Eric Ferreira, Sara Knowles, Alexis Rodin, Patrick Sarette, Prakriti Shukla, Likith Surendra, Emily Turner, Rasika Vartak, Ramon Velazquez, Wendy Winslow.

Specific Aim:

The lack of effective treatments for Alzheimer's disease (AD) is alarming since more than 5 million Americans are currently affected by this disorder, and that the number of people with AD in the United States is projected to grow to over 15 million by 2050. Animal models of AD represent an invaluable tool to evaluate potential therapeutic compounds and study mechanism underlying the pathogenesis of the disease. The 3xTg-AD mice are one of the most widely used models. Indeed, these mice, which we generated almost 15 years ago, are being used by more than 100 investigators throughout the world. Such widespread use of these mice, has led to the generation of multiple independent colonies diffuse throughout the world. Converging evidence indicates that the phenotype of 3xTg-AD mice has shifted over the years and contradicting reports about the onset of pathology and cognitive deficits are apparent in the literature. The goal of this grant application is to stage the current progression of AD-like pathology in 3xTg-AD mice. *The data obtained will serve as a benchmark for investigators in the field using these mice. In addition, our results will facilitate the design of preclinical studies in which these mice are used to test new therapeutic approaches.*

Progress to date: We have successfully completed all of the experiments proposed in this grant application and are currently writing a manuscript, which we anticipate submitting early in March 2018. Briefly, we used a cross-sectional approach and used 3-, 6-, 12-, 16-, and 20-month-old 3xTg-AD and wildtype mice (n = 15/age group/genotype). We found that cognitive deficits are first apparent at 6 months of age and become progressively worse as the mice age. The earliest detectable neuropathological change is an increase in soluble A β and tau levels, which precedes the onset of cognitive deficits. Extracellular A β plaques are first apparent in 6-month-old mice and are present in 100% of 12-month-old mice. Neuroinflammation also follows an age-dependent pattern. These data will serve as a benchmark for investigators in the field using these mice. In addition, our results will facilitate the design of preclinical studies in which these mice are used to test new therapeutic approaches.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Validating reagents for use in diagnosing AD. Michael Sierks, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Collaborators: Mayo Clinic Arizona

Specific Aims: The specific aims of this project are:

1) Validate the target specificity of antibodies generated against brain derived variants of tau.

Background and Significance: Biomarkers that can facilitate presymptomatic diagnosis of Alzheimer's disease (AD) and distinguish it from other dementias would be extremely valuable clinical tools. The primary constituents of the two major pathological features of AD, amyloid plaques and neurofibrillary tangles, are respectively, the amyloid beta (A β) and tau proteins. Substantial efforts have been expended to identify biomarkers for AD and other neurodegenerative diseases, where the most promising biomarkers for AD to date are variants of A β and tau, in particular the 42 amino acid variant of A β (A β 42) and phosphorylated variants of tau [1-4]. While A β and tau biomarkers suffer from a relatively low sensitivity and specificity for diagnosing AD, they still hold great promise for early detection of AD as changes in CSF levels of A β 42 and tau have been shown to occur well before symptoms develop, up to 25 years earlier for A β 42 [5]. While CSF Protein Variants as Blood Based Biomarkers for Neurodegenerative Disease and Brain Injury and tau levels correlate with AD, the vast majority of studies have focused on detection of non-toxic monomeric forms of A β 42 and phosphorylated tau rather than on detection of the actual toxic protein species responsible for neurodegeneration. Both A β and tau can exist in a variety of different forms and aggregate morphologies and numerous studies indicate that specific oligomeric forms of both A β [6-9] and tau [10-12] are involved in neuron degeneration and spread of toxicity, and can interfere with important functions such as long term potentiation. Therefore, a more powerful and sensitive diagnosis for AD and other dementias would be to specifically detect the individual protein species that are involved in disease onset and progression. Because misfolded and aggregated variants of A β and tau are intimately involved in the progression of AD, detection of specific variants of these proteins in CSF and/or serum has great promise for an early definitive diagnosis of AD and for following progression of the disease or effectiveness of different therapeutic regimens. In a parallel manner, misfolded toxic oligomeric variants of the protein alpha-synuclein (a-syn) have been correlated with the onset and progression of Parkinson's disease (PD) and related synucleinopathies [13-15] so detection of the relevant toxic oligomeric a-syn species should facilitate early diagnosis of synucleinopathies such as PD and Dementia with Lewy Bodies (DLB) and help distinguish these diseases from AD. Recent evidence has suggested that cytoplasmic misfolding and aggregation of TAR DNA binding protein 43 (TDP-43) associates with the pathology observed in a high percentage of FTD and ALS cases [16] and more recently in other neurodegenerative diseases including AD and traumatic brain injury. TDP-43 is also prone to misfolding and forms aggregate species, where disease associated TDP-43 mutations similar to A β and a-syn aggregate more readily [17]. Therefore, selected toxic aggregated variants of A β , tau, a-syn and TDP-43 all have potential value as early and sensitive diagnostic biomarkers to distinguish different neurodegenerative diseases, and also as promising therapeutic targets. In

addition, we have shown that levels of these protein variants are present in sera of patients that have suffered traumatic brain injury. The presence of the different protein variants account for the increased incidence of neurodegenerative disease in patients that suffer brain trauma.

We have developed novel protocols in our lab that enable us to generate reagents that very selectively recognize individual protein morphologies and we also developed a simple novel sandwich ELISA that enables femtomolar or better detection of target antigens in biological samples[18]. We have generated a panel of such antibody based (nanobody) reagents generated in our lab that selectively recognize different toxic aggregated species of A β , tau, a-syn and TDP-43. We have shown that we can detect the presence of the biomarkers in human AD and PD brain, CSF and blood samples, and that they have great promise to detect blood based biomarkers that can presymptomatically detect AD{Williams, 2017 #1196;Williams, 2015 #1163}. The purpose of this proposal is to demonstrate that the reagents isolated against tau variants bind a conformationally distinct form of tau that is present in human AD samples, but not normal samples. In our novel technology to isolate the reagents, we ensure that we remove all reagents that bind to any protein forms that are present in normal human samples and are selectively for a disease state.

Progress to Date:

Aim 1). We have assayed several different nanobodies against tau variants and showed that while they do bind human AD brain tissue, csf and sera samples, they do not bind normal human samples. We used ELISA and dot blot analyses to confirm this result. We have also analyzed several of the reagents by western blot to determine what size tau variant they bound to. We expect that our nanobody reagents all bind disease related protein conformations, but that they do not bind linear epitopes on the proteins. We confirmed this by western blot analyses where our nanobodies did not show reactivity to the denatured samples, while control antibodies did show binding. This confirms that our reagents do not bind a linear epitope on tau but do bind a conformational epitope such as would be found in an oligomeric protein aggregate or other complex that is denatured on a western gel.

Proposals:

ABRC grant awarded with Dr. Ted Trouard (UA). Additional proposals to DOD to study protein variants as biomarkers for traumatic brain injury and for Parkinson's disease are pending.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Odor detection and classification in a mouse model of Alzheimer's disease Brian H Smith, Federico Sanabria, Richard C Gerkin, Salvatore Oddo. Arizona State University; ASU-Banner NDRC; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aim: The sense of smell is an early harbinger of neurodegenerative disorders such as Parkinson's disease, and it is also affected in Alzheimer's disease possibly through a different mechanism or time course. Some diagnostic pathologies target early processing in the olfactory system. The objective of the research under this award is to test a series of hypotheses about how pathologies target neural networks in the mammalian olfactory system. The ultimate impact will be to contribute to an understanding of how the sense of smell can be used as an early diagnostic test.

Background and Significance: The PI's (Smith) funded research program with insects such as the honey bee and fruit fly has focused on how early processing of sensory information about odors sets up representations for odors in early olfactory processing. In particular, this work has shown that non-associative and associative plasticity, which are driven by aminergic modulation related to food reinforcement, is important for helping animals detect and discriminate important odors in their environments. In the past few years his lab has extended this work to the mouse model with the aim of testing how neurodegenerative pathologies affect neural networks in the mammalian brain. This past year we have developed three new training protocols for the mouse. Two (Smith & Gerkin) involve habituation to novel odors and extinction of learned responses to odors. The third (Smith & Sanabria) involves detection of odors against constant versus novel backgrounds, which tests a prediction from Smith's work with insects. In the latter protocol, our data analyses to date point to rejection of "component learning" about odor mixtures in favor of "configural learning". We now propose to extend both protocols to use of APP/PS1 mice, a widely used animal model of Alzheimer's disease, maintained at ASU (Oddo; Jankowski et al., 2004). These mice express Alzheimer's pathologies in defined brain regions at well-established post-natal time courses. In brief, the habituation/extinction protocol involves exposure of subjects to fruit (strawberry) odors that have innate attractions, and then allowing subjects to feed or not feed on the strawberry. Without feeding, unreinforced exposure produces habituation. Unreinforced exposure after feeding trials produces extinction. The odor-detection protocol involves training two groups of subjects; one group is exposed to a target odor (X) in a constant background (A) that only *varies across subjects*, and the second group is exposed to X in backgrounds that *vary across trials*. Each group is then tested for detection of X against a new background odor (Y) not previously experienced by either group. Preliminary data show that subjects trained on the variable background perform better on the transfer test than subjects trained against a constant background. We predict that this variable-background-training advantage will be reduced in subjects from the genetic line that expresses Alzheimer-like pathologies in the hippocampus, relative to controls. This would be consistent with a hippocampal-based configural-learning deficit in the AD model. If confirmed, this model system will represent a powerful assay for the early onset of AD, which can be used to test interventions in future studies.

Jankowsky JL, Fadale DJ, Anderson J, Xu GM, Gonzales V, Jenkins NA et al. Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for augmentation of a 42-specific gamma secretase. *Hum Mol Genet* 2004; 13: 159–170.

Proposed One-Year and Long-Term Outcomes:

- We will soon begin preparation of a manuscript on the habituation/extinction protocol once the final data are collected in Summer 2017; we expect submission in Fall 2017 or Spring 2018
- We are currently preparing a manuscript on the odor background protocol; we expect submission in Summer or Fall 2017 or
- This coming year we will submit a grant application to NIH and/or NSF for extending the odor background problem using the genetic line described above (Smith, Sanabria, Gerkin, and Oddo will be co-PIs)
- We will collect data on performance of mice with hippocampal damage on non-spatial configural learning
- We plan and possibly begin to gather preliminary data using healthy human subjects on how they perform on the odor background problem. This will begin extending the hypotheses developed from the animal work, as described above, to humans.
- We will extend our work performing chronic electrophysiological recordings from the olfactory bulb in awake behaving mice while they perform the odor tasks we have developed.

Year End Progress Summary:

Single vs Multiple Training, Target/Background Discrimination

This study carried over from previous year funding and was completed within this fiscal year. It was designed to test the hypothesis that training mice to detect a target odor from multiple background odors (M trained mice) would facilitate transfer to novel background odors better than training mice to detect a target odor from a single background odor (S trained mice). The obtained data support this hypothesis, M trained mice transferred better than S trained mice when tested with three novel background odors. Interestingly, S trained mice tested with multiple novel background odors first transferred better to a single novel background odor than S trained mice tested with a single novel background odor first. Given the seven-day transfer test, this suggests that the benefit of training with multiple background odors does not require 14 sessions of training. Despite these effects, the mineral oil test suggested that mice might have relied on auditory as well as odor cues to discriminate between the trial types. Thus, in a second experiment we replicated Experiment 1 while controlling for the auditory cues. Data of Experiment 2 also supported the hypothesis, utilizing only a three day transfer test.

Status: Currently being written into manuscript for submission by May or June 2018.

APP/PS1 Olfactory Patterning Experiment, Cohort 1

For a new series of experiments with a genetic line of mice expressing age related pathologies in hippocampus, we designed as *Instrumental Patterning* task for testing elemental and configural stimulus representations within subject. This task is based off the positive and negative patterning tasks in classical conditioning. In positive patterning subjects learn A-, B- and AB + and in negative patterning subjects learn A+, B+, and AB-. The negative but not the positive patterning task requires an appeal to configural representations. In contrast, positive patterning can be

explained by assuming elements A and B are conditioned with some subthreshold positive value that sums when presented in compound. The present task is an instrumental variant that avoids the problem with positive patterning; i.e., can be explained without an appeal to configural learning. Below is a Table indicating the 6 potential trial types and a diagram of the task.

Table 1: Trial Types

Elemental Trials	Odorant 1	Odorant 2	Odorant 3	Odorant 4	Reinforcement
A	1-Nonanol	Myrcene	MO	MO	Left
B	2-Heptanol	Methyl Butyrate	MO	MO	Left
C	1-Hexanol	Methyl Benzoate	MO	MO	Right
D	1-Decanol	2-Octanone	MO	MO	Right
Configural Trials					
AB	1-Nonanol	Myrcene	2-Heptanol	Methyl Butyrate	Right
CD	1-Hexanol	Methyl Benzoate	1-Decanol	2-Octanone	Left

Mice will be trained with 6 potential trials, four of which involve presentation of a single binary mixture (Odorant 1 + Odorant 2) and two of which involve presentation of a double binary mixture (Odorant 1 + Odorant 2, Odorant 3 + Odorant 4). Mice will first be trained with only single binary mixture trials to confirm that elemental learning is intact in all mice, after which double binary mixture trials will be introduced to test configural learning. In single binary mixture trials mice might receive mixture A, B, C or D. If they receive A or B, they must go to the left reinforcement port for reward. If they receive C or D, they must go to the right reinforcement port for reward. In double binary mixture trials mice might receive A and B or C and D. If they receive A and B they must go to the right reinforcement port for reward. If they receive C and D they must go to the left reinforcement port for reward. Note that in single binary mixture trials two jars are activated, one containing the binary mixture odor and another containing just mineral oil. This controls for the number of solenoids turning on and off.

Importantly, this design ensures that (a) mice have equal experience with both reinforcement ports and (b) that subthreshold conditioning cannot sum in the configurations to drive choice, and (c) biases the configural trials to requiring configural representations because previous research indicates that mixtures with three or more components is usually perceived as a configuration and the mixtures presented on configural trials will be composed of 4 odorants. Note that (b) has to be the case because it is unclear how the elements can be conditioned to their respective choice responses and subthreshold conditioned to the opposite response. Nevertheless, simulations were conducted testing and confirming this intuition. Although these simulations were conducted with all trials intermixed from the outset of training, the results generalize to the described training regimen.

Progress as of February 2018: 24 APP/PS1 mice (12 mutant, 12 control) are being trained on an olfactory instrumental patterning task, studying elemental and configural learning. In this task mice will be trained with 6 trial types, four of which involve presentation of a single binary mixture, and two of which involve presentation of a double binary mixture. In single binary mixture trials mice might receive mixture A, B, C, or D. If they receive A or B, they receive reinforcement at the left reinforcement port. If they receive C or D, they receive reinforcement at the right odor port. In compound trials, if they receive A and B, they must go to the right reinforcement port for reinforcement. If they receive C and D they must go to the left reinforcement

port for reinforcement. In other words, the response required for the compound trials are the opposite of those required for their constituent elements. This design ensures that the mice cannot use their knowledge of the elements to learn the responses associated with the compounds.

Currently, in the initial phase, mice are being trained with only single binary mixture trials (elemental trials; A or B or C or D). In the olfactory patterning pilot, mice with six months prior experience in a different olfactory discrimination study were able to learn this task in about 8 sessions. As of the 29th session, 17 of the 24 APP/PS1 mice in the current study are performing above chance (Mean P (Correct) = 0.74). The remainder of these mice are performing at chance (Mean P (Correct) = 0.50). Overall mean P (Correct) = 0.70. One mouse is excluded from the current data due to failure to acquire the task. Currently, these learning rates do not seem to be affected by genotype, and both control mice and mutant mice constitute both of these groups. It is possible that the mice in the patterning pilot were informed by their experience in the previous odor discrimination experiment, and that this facilitated more rapid acquisition of the elements. Alternatively, this is a strain difference. Upon reaching overall mean p (correct) = 0.75 for a minimum of five days, configural trials will be introduced.

Phase 2, Configural Trials

Configural trials (consisting of two binary mixtures) were introduced on Day 43 of the experiment, after 6 weeks of elemental training. Unlike in the patterning pilot, animals in this experiment were only given one compound trial type, either AB or CD. As previously discussed, these compounds require the animals to produce the response opposite to that required for its constituent elements. After 8 days of training on the compounds, the majority of animals are still performing at chance (mean p (Correct|Compound) = 0.52). Compound training will continue for 42 days.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Canine Science Collaboratory. Clive D. L. Wynne, PhD, Heather Bimonte-Nelson PhD, Salvatore Oddo, PhD, Joshua Van Bourg, Rachel Gilchrist. Arizona State University; ASU-Banner NDRC; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Collaborators:

Arizona State University: Josh vanBourg, Lisa Gunter, PhD, Rachel Gilchrist

Texas Tech University: Nathan Hall, PhD

Oregon State University: Monique Udell, PhD

Princeton University: Bridgett vonHoldt, PhD

Virginia Tech: Erica Feuerbacher, PhD

Specific Aim: To refine and deploy a memory test in aging pet dogs

Background and Significance: Dogs are the only non-primates to spontaneously develop Alzheimer's disease-like symptoms (AD), they age seven times faster than people, and around 80 million dogs live as pets in homes in the United States. These three facts indicate that the pet dog could be an excellent animal model for AD.

Preliminary Data and Plan: We have developed a simple memory task for deployment with pet dogs. In order to maximize cooperation from the owners of these dogs, we have been constraining the task to be achievable in a single one-hour visit to the dog lab. The task uses two boxes behind which a piece of food can be hidden. The two boxes are 2 m from the starting position of the dog and separated by 2 m, equidistant from the dog, thereby forming an equilateral triangle with the dog's starting position at one vertex, and the two food boxes at the other two vertices. On each trial one box (pseudo-randomly selected) is baited. The dog clearly sees the baiting of the box but is prevented from making an immediate response by being restrained behind a small gate. We use a simple staircase procedure of progressively increasing delays to ascertain the longest delay at which each dog can reliably find the food.

We have tested 40 dogs on this procedure, from a wide range of breeds and up to ten years of age. We have obtained excellent buy-in from the community and can readily obtain participants. Preliminary results indicate that although the task can be completed by most dogs, only older dogs, with their relatively shorter maximum delay at which they can still find the hidden food, can complete the task within the one-hour session. Younger dogs, who typically showed signs of strong memory performance even with a three-minute delay between baiting and their opportunity to retrieve the hidden food item, reached the end of 60 minutes without our having established a reliable upper estimate of their memory.

Proposed One-Year and Long-Term Outcomes:

By the end of the first 12 months we expect to have a reliable validated test of dog memory that can be easily deployed to assess memory changes in pet dogs. We anticipate a manuscript reporting this new paradigm.

Year End Progress Summary:

Aim 1: We are continuing to refine our memory test for pet dogs. We will be inviting dogs and their owners back for a second session. We are confident, from our interactions with the dogs' owners, that attrition due to requesting a second session will be small, and the benefit will be that we gain better estimates of the memory of the younger dogs in our sample.

Project Progress Report
Banner Alzheimer's Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Native American Outreach Program. Dawn Batchuluun, CCRP, Sachin Pandaya, CRC, Anna Burke, MD, David Weidman, MD, Lori Nisson MSW, LCSW, Edward Zamrini, MD, Jan Dougherty, RN, MS, Nicole Lomay; Richard J. Caselli, MD, Eric M. Reiman, MD, Pierre N. Tariot, MD. Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To forge a close working relationship with members of our Native American Community in the awareness, care, and scientific understanding of Alzheimer's disease (AD) through educational and service-related outreach activities.

Aim 2: To support the participation of interested Native Americans in the Arizona Alzheimer's Disease Core Center (ADCC) Clinical Core and research studies of interest to them without detracting from our other outreach and partnership-development goals.

Aim 3: To work with our Native American partners to identify and begin to prepare for one or more research studies that advance the understanding of Alzheimer's disease and/or service to patients and families from this understudied, underserved population.

Background and Significance: Native Americans facing the problem of Alzheimer's disease constitutes 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 ADCC Clinical Core.

Preliminary Data and Plan: To date, 77 Native Americans have been followed through the ADCC and whose clinical findings are reported in a national database. As of January 2018, there are 54 active participants, 23 have withdrawn, and 1 died. Over the past year, over 3,500 Native Americans have participated in education and outreach efforts. We continue working relationships with 20/22 Arizona tribes and have had participation in outreach efforts from tribes outside of Arizona including New Mexico, Colorado, California, Utah, Oklahoma, Nevada and Minnesota. We have hosted the 13th Annual Conference on AD in Native Americans in October in Tucson, AZ with over 75 professional participants in our preconference intensive and 180 community participants in our full day training. We introduced our newly designed Native American and Dementia Tool Kit to include a comprehensive collection of training materials to better equip tribal team members to assist families in effectively caring for a person with dementia. In addition, we introduced a Native American Caregiver: Hearing our Voices video featuring 4 Arizona tribal family caregivers who shared their personal thoughts and perspectives on caring for a loved one with dementia. We are currently formulating a committee to plan the 14th Annual Conference on AD in Native Americans in October in the Northeastern region of the state and anticipate drawing more than 250 community participants. We are using the 60 Minutes video, "The Alzheimer's

Laboratory” to educate the community about the benefits of research and the impact it has on a family from Colombia. Along with the video we are able to share dementia and brain health materials, this method enables them to ask questions and provides a picture about the impact dementia has on families. We have established a consistent and solid working relationship with many urban and tribal communities to continue on 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 our other colleagues will continue to establish close working relationships with stakeholders from different 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. Retain the 54 Native American cohorts in the ADCC trial in the next 12-months with a goal of recruiting 6 new participants.
3. Refine methods to reach more Native Americans from youth to elders to educate using the Native American Brain Health program.

Funds have been used in a way that complements but does 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 Tohono O’odham Nation and Salt River Pima-Maricopa Indian Community to support development of culturally sensitive memory screening/brain health programs.

Annual Progress Summary:

Aim 1: During the past year, our education and outreach programs included 1,785 community participants and 806 professionals from the Native American community across Arizona. We hosted the 13th Annual Conference on AD in Native Americans in October in Tucson, AZ with over 75 professional participants in our preconference intensive and 180 community participants in our full day training. We introduced our newly designed Native American and Dementia Tool Kit to include a comprehensive collection of training materials to better equip tribal team members to assist families in effectively caring for a person with dementia. We introduced a Native American Caregiver: Hearing our Voices video featuring 4 Arizona tribal family caregivers who shared their personal thoughts and perspectives on caring for a loved one with dementia.

Aim 2: Also, during the past year, we enrolled 5 new participants, are preparing to enroll 6 additional participants, and completed 23 assessments. 26 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.

Aim 3: BAI Native American Program received funding from the Salt River Pima-Maricopa Indian Community and Tohono O’odham Nation to support development of culturally sensitive outreach efforts, teaching tools, and educational materials, with a focus on raising awareness of improved brain health and recognition of warning signs of AD/dementia. These funds helped make it possible to develop our Native American and Dementia Tool Kit and to be able to provide them for caregivers and professional alike.

In July of 2016, the University of Arizona and Banner secured one of the national Precision Medicine Initiative’s (PMI’s) first Health Provider-led grants. Under this grant, we are preparing

to enroll 100,000 members of Banner Health, who agree to a brief evaluate, provide their anonymized medical records, DNA, blood samples, and be reassessed 3 years later. Our organization will aim to include 7,500 Native Americans and 90,000 Latinos. We have engaged Dedra Buchwald from the University of Washington ADCC Native American Satellite Program at Washington State University to forge collaborations in our PMI Cohort (“All of Us”) program, as well as an ongoing genetic, MRI and cognitive study of >1,000 Native Americans from the Strong Heart Stroke Study.

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2017-2018 Scientific Progress Report

Advanced image analysis techniques for the detection, tracking and prevention of Alzheimer's disease. Kewei Chen, PhD, Hillary Protas, PhD, Dhruvan Goradia, PhD, Wendy Lee, MS, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To further develop, test and apply several voxel- and region-of-interest based image analysis techniques for the early detection, tracking, differential diagnosis, and study of Alzheimer's disease (AD) and the evaluation of AD-modifying and prevention therapies.

Aim 2: To share our data analysis algorithms with the field in highly productive and usable ways.

Aim 3: To further develop our data management program for the Arizona APOE4 Gene Dose Study, such that it is harmonized with the developing program for the Arizona ADCC, sets the foundation to incorporate information about related images and biospecimens, and permits us to share de-identified data from our longitudinal cohort I the most productive, available, user-friendly and HIPAA compliant way.

Background and Significance: The Computational Image Analysis Laboratory at the Banner Alzheimer's Institute (BAI) has continued to develop, refine, test and apply image processing and analysis techniques to detect, track, and diagnosis AD, clarify genetic and non-genetic risk factors, and evaluate AD-modifying and prevention therapies with improved power. In the past, our image analysis techniques have permitted us to advance the study of preclinical AD, help clarify the impact of genetic and non-genetic risk factors, clarify the neuropathological diagnostic and prognostic value of several imaging measures, and informed the design size and future analysis of our prevention trials. During this funding period, we have been using non-overlapping funds from NIA grants and the Arizona Alzheimer's Consortium to further refine, test and use several of our image analysis algorithms, permit them to be shared in the most widespread and productive way. We have also begun to revamp the data management program for our highly valued longitudinal data sets, including that from persons with two, one and no copies of the APOE4 allele (the major genetic risk factor for late-onset AD), such that we will be able to provide an even more widely used and productive public resource of de-identified data and biological samples for the field. Our computational image-analysis resources have already had a profound impact on the field, and we intend to leverage this resource to the fullest extent possible as we go forward.

Preliminary Data and Plan: This project has capitalized on amyloid (PiB and/or florbetapir), FDG, and flortaucipir PET images, as well as structural and resting state functional connectivity (fc) MRI images from the AD Neuroimaging Initiative (ADNI), our Arizona APOE4 Gene Dose Cohort Study of persons at three levels of genetic risk for AD, the Alzheimer's Prevention Initiative Biomarker Study (API-BIO) of PSEN1 E280A mutation carriers and non-carriers from the world's largest autosomal dominant AD (ADAD) kindred in Colombia, and from collaborators in China. In this project, we will do the following: **1a)** We will further refine our hypometabolic convergence index (HCI) to characterize the magnitude and spatial extent of AD-related cerebral hypometabolism in a single measurement; and we will compare it to our other methods in terms

of its power to detect and track AD and evaluate disease-modifying and prevention therapies. **1b)** We will extend our multi-modal partial least squares algorithm to characterize the relationship between covarying patterns of not only regional gray matter and regional cerebral metabolic rate for glucose measurements, but also to regional amyloid PET and fMRI data. **1c)** We will refine and further assess the use of our cerebral white matter reference ROI approach to the tracking of cerebral-to-reference region standard uptake value ratios (SUVRs) using different amyloid radioligands. **2)** We will continue to revise our image analysis platform, such that our algorithms can be shared and used in the most widespread, productive and reproducible way by researchers from other laboratories. **3)** Under Don Saner's leadership, we will continue to develop our data management program, such that we can share data from the Arizona APOE Gene Dose Cohort and ADCC in the most rigorous, user-friendly, widespread, productive and appropriate way. (As noted in the Data Management Development Project, we continue to develop a friendly graphical user interface for sharing data from these longitudinal cohorts.

Proposed One-Year and Long-Term Outcomes: During the one-year funding period, we will complete the new HCI, MMPLS and the white matter reference refinements noted above. Using independent NIA funds, we will then compare these and other methods to the preclinical detection and tracking of AD and the evaluation of AD prevention therapies. Our long term goal is to provide tools and data needed for the field to advance the study of preclinical AD, contribute to the differential diagnosis of AD and related disorders, and accelerate the evaluation of early clinical and preclinical AD treatments. Our methods developed have been used as our strengths in a number of grant applications submitted or awarded. Along the way, we will continue to leverage these tools by supporting existing collaborations and forging new collaborations with our colleagues inside and outside of Arizona, and by helping our colleagues to generate impactful findings, publications and grants to advance the scientific fight against AD.

2017-2018 Progress Summary:

Aim 1: We investigated the use of white matter versus other reference regions of interest in the analysis of cross-sectional and longitudinal florbetapir and PiB PET measurements from ADNI and API-BIO. Longitudinally, cerebral-to-white matter standard uptake value ratios (SUVRs) were stable in cognitively unimpaired subjects from ADNI and mutation non-carriers from API-BIO and, compared to cerebral-to-cerebellar SUVRs, more closely related to declines in cerebral glucose metabolism. Cross-sectionally, cerebral-to-white matter SUVRs were comparable to cerebral-to-cerebellar SUVRs in their ability to distinguish AD dementia, MCI and cognitively unimpaired groups and more significantly correlated with cognitive decline. Our findings support the value of using a white matter reference region for the analysis of cross-sectional and longitudinal amyloid PET data, particularly in the preclinical stages of late-onset and autosomal dominant AD (AAIC Abstr 2018 in press). Our manuscript describing sample size estimates for 24-month prevention trials in cognitively unimpaired amyloid positive older adults using different brain imaging endpoints is in final preparation, and these analyses were used to support a prevention trial grant application that received a favorable impact score. We have demonstrated the ability of a cerebral tau index (CTI) derived from the Braak-related ROIs introduced in the Jagust lab to distinguish flortaucipir PET measurements in AD dementia, MCI and cognitively unimpaired control groups, and we have begun to compare it to other SUVR measurements in its ability to distinguish these three subject groups. We have further refined methods for the respective pre-processing and network analysis of diffusion tensor imaging (DTI), such that the methods are

now fully automated. We have assisted our ASU colleague Yalin Wang to model the surface of brain structures, including the hippocampus, identify those features that optimize the classification of persons with AD, and used them to classify AD dementia, MCI and unimpaired controls than existing FreeSurfer methods. In terms of statistical developments, we demonstrated limitations in using data from two time points to estimate sample sizes and for clinical trials in which there is a difference between the observed and planned duration between measurements; we introduced a Monte-Carlo simulation procedure to differences in the onset of progressive biomarker onset; we have begun to use Deep Learning techniques to improve the detection of AD using MRI and amyloid PET measurements; and we have reported our findings in AAIC abstracts (in press) and submitted manuscripts.

Aim 2: We have continued to share our expertise, analysis teams, and platforms with researchers inside and outside of the Arizona Alzheimer's consortium. Examples include researchers from each of the Consortium's participating institutions, Natalie Rasgon and her colleagues at Stanford, Robert Green and his CTE research colleagues at Boston University, and researchers from several institutions in Shanghai, Taiwan and Beijing. This year, we have revamped our Summer Scholars Program, such that our image analysis program, the BSHRI Brain and Body Donation Program, and the basic and translational research programs in the new Neurodegenerative Disease Research Center at ASU will be able to mentor a large number of undergraduate and graduate students. We continue to provide mentorship, support and collaborations for a growing number of young researchers in Arizona. We have also hosted and supported several international researchers and two new post-doctoral fellows who plan to forge their careers in AD research. We have also been working with several colleagues to optimize and select the image analysis techniques that will be used in our API trials.

Aim 3: We have made great progress in revamping our data management platform using REDCap to promote automatic and portable data entry and the central data lake together with application programming interface (API) to perform the mining, sharing and use of data from our longitudinal cohorts. We have also been reviewing our data sharing processes with Banner's legal team such that we will be able to share relevant data and samples in a more simplified and rapid way. We have helped Willemijn Jansen prepare an ADCC pilot grant proposal to provide a shared resource of blood samples from many thousands of blood samples from persons with PET or CSF biomarkers to help the field develop an amyloid blood test as soon as possible. We have also recommended ways in which to galvanize data and sample sharing in a session of the 2018 NIH AD Summit that was co-chaired by Dr. Reiman. With that emphasis in mind, we are working as hard as we can to provide the appropriate vehicles in which to share de-identified data and samples from observational studies and our prevention trials in the most productive, secure, anonymized and accessible way.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

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:

Aim 1: To increase enrollment into the Alzheimer's Prevention Registry through community outreach and other related efforts.

Aim 2: To compare the effectiveness of various approaches to promote study opportunities to Alzheimer's Prevention Registry members, tracking members' interest in each study opportunity.

Aim 3: To disseminate information about the Alzheimer's Prevention Registry to the scientific community.

Background and Significance:

The suffering caused by Alzheimer's disease (AD) remains one of the greatest unmet medical needs of our times. In the United States, an estimated 7.1 million people 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 have been focused on accelerating efforts to prevent and effectively treat the disease by 2025. With a heightened sense of urgency, numerous AD prevention trials are being launched over the next several years, requiring an unprecedented number of healthy older adults to step forward and participate. The challenge is finding enough participants to fill these trials. In 2017, an estimated 55,000 participants were needed to fill 150 AD trials, requiring screening of over 550,000 individuals, based the recommended 10:1 recruitment-to-enrollment ratio. These numbers will undoubtedly skyrocket with the upturn in AD trials, particularly prevention trials. At the same time, 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. Moreover, even when trials do meet their enrollment goals, individuals from diverse populations, particularly African Americans and Hispanics/Latinos, are often underrepresented due to a multitude of reasons including mistrust and insufficient information dissemination in these communities. Only 5% of African Americans and 1% of Hispanics comprise clinical trial participants despite their 12% and 16% representation in the US population, respectively. The Alzheimer's Prevention Initiative (API), initially growing out of efforts at the Banner Alzheimer's Institute (BAI), is a multi-institutional, multi-partner collaborative mechanism to evaluate promising preclinical AD treatments. The API includes preclinical treatment trials in individuals at high risk for developing dementia as well as registries to help support the enrollment into these and other trials. 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, this

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, and IRB research program open to adults age 55-75 in the United States who do not have a diagnosis of cognitive impairment to submit a sample of DNA for APOE genotyping, the results from which are used in part to help match to studies.

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 the end of January 2018, the Registry had over 290,000 enrollees and GeneMatch enrolled over 53,000.

Aim 1: During the funding period, considerable effort was undertaken to increase enrollment into the Alzheimer's Prevention Registry through community outreach and other related efforts. We have activated over 20 GeneMatch partner sites across the United States, allowing sites to enroll individuals into the Registry and GeneMatch and distribute recruitment materials. As a result of these efforts we have seen an increase in enrollment into the Registry and GeneMatch, as well as an increase in referrals to studies at those sites. In addition, we ran a successful online advertising campaign throughout 2017 to increase enrollment into the Registry and GeneMatch.

Aim 2: The Registry has helped recruit for more than 50 AD-related studies. As part of our engagement strategy, Registry members have the opportunity 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 nine months, the average newsletter email open rate is 43% (compared to nonprofit healthcare industry average of 16%); average email click rate is 7% (compared to the industry average of 1.6%). We are currently analyzing the relationship between newsletter readership and willingness to consider participating in a research study. In addition, we are preparing to launch geographically targeted social media advertising to assess its impact in helping to recruit for AD-related studies. The overall goal of understanding the "science of recruitment" was the focus of a recent R01 grant application to the NIA, leveraging the Registry and GeneMatch. Although this R01 was not funded based on the initial application, we are working on a revision to be submitted in 2018.

Aim 3: Our team has been actively disseminating information about the Registry & its GeneMatch program to the scientific community. As described above in Aim 1, we activated over 20 GeneMatch partner sites, helping us to achieve the goal of continuing to develop collaborations with academic and non-academic partners to increase enrollment into the Registry. In addition, our team serves on a number of national and international workgroups and advisory committees aimed at developing strategies to help accelerate recruitment and enrollment into programs such as the Registry and GeneMatch. In addition, we have presented the Registry and GeneMatch at several state-wide, national, and international conferences. Lastly, our team hosted a booth at the 2017 Alzheimer's Association International Conference (AAIC) to raise awareness about the Registry and GeneMatch.

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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:

Aim 1: To conduct a preclinical trial/surrogate marker development program in ADAD mutation carriers within 15 years of their estimated age at clinical onset.

Aim 2: To conduct a preclinical trial/surrogate marker development program in APOE ε4 homozygotes ages 60-75.

Aim 3: To conduct a preclinical trial/surrogate marker development program in APOE carriers (homozygotes and heterozygotes with elevated brain amyloid) ages 60-75.

Aim 4: To further refine trial designs for other preclinical treatment trial programs/surrogate marker development programs in cognitively normal individuals who are for ADAD or LOAD.

Aim 5: To continue to support registries designed to assist with participant recruitment.

Background and Significance: Alzheimer's disease (AD) is the most common form of dementia. This devastating illness takes a significant toll on clinically affected persons and family caregivers and will take an overwhelming financial toll on society. Results from observational studies suggest that the pathophysiological process of AD begins many years before the onset of cognitive impairment. It is possible that at least some therapeutic interventions, including those that target amyloid pathology, need to be started before the clinical onset of AD, when there is already extensive neuropathology, to exert their most beneficial effects.

API was established to accelerate the evaluation of promising AD prevention therapies and to find and support the approval and availability of those that work as soon as possible. API currently includes three prevention/surrogate marker development trials in cognitively unimpaired persons who based on their genetic background or biomarker findings are at increased risk for the clinical onset of AD: (1) The API ADAD Colombia Study, the first funded trial of an investigational AD prevention therapy, which is evaluating the amyloid antibody therapy crenezumab in more than 250 unimpaired 30-60 year-old PSEN1 E280A mutation carriers and placebo-treated non-carriers from the world's largest autosomal dominant AD (ADAD) kindred in partnership with Drs. Francisco Lopera and his colleagues from the Neurosciences Group at the University of Antioquia, Yakeel Quiroz and her colleagues at Harvard, Genentech/Roche and NIH; (2) the international API Generation Study 1, which has begun to evaluate the BACE1 inhibitor CNP520 and active immunotherapy CAD106 in more than 1,300 unimpaired 60-75 year-old apolipoprotein E4 (APOE4) homozygotes in collaboration with Novartis, Amgen and NIH; and (3) the international API Generation Study 2, which has begun to evaluate CNP520 in about 2,000 additional APOE4 homozygotes and amyloid-positive APOE4 heterozygotes in collaboration with Novartis, Amgen and NIH. The trials are intended to be license-enabling; provide better tests of the amyloid hypothesis than failed trials in later preclinical and clinical stages of AD; clarify the predictive and theragnostic value of brain imaging and CSF biomarkers and provide evidence needed to qualify those biomarker endpoints that are associated with a therapeutic response as surrogates in future trials; to help establish ways in which to share a person's APOE genotype and biomarker risk in

the era of prevention trials; to provide precedent-setting public resources of baseline data and trial data and biological samples; to complement and support other prevention trial programs (e.g., DIAN and A4), new trials and other efforts to support the accelerated evaluation and approval, availability and affordability of AD prevention therapies; and to empower at risk persons in the fight against AD.

API also includes Colombian and North American Alzheimer's Prevention Registries to support enrollment into these and other studies. To date, the Colombian Registry includes medical and family histories, cognitive and clinical assessments, genotypes, and DNA in more than 5,800 PSEN1 E280A kindred members, including nearly 1,200 living E280A mutation carriers and 6 homozygotes as young as 8 years of age. As noted in another progress report, the Alzheimer's Prevention Registry (www.endALZnow.org) includes nearly 300,000 registrants, who have expressed an interest in prevention research, receive regular updates about relevant prevention studies; API's GeneMatch Program, which has shared DNA sampling kits and been performing APOE genotypes in more than 50,000 interested late-middle-aged and older adults for their potential participation in prevention trials; and API's StudyMatch program which supports enrollment of interested "opt-in" participants in numerous trials, and other studies and Registries.

Finally, API includes independently funded efforts to detect and track the brain imaging, fluid biomarker and cognitive changes that precede the clinical onset of AD in the Arizona APOE4 Gene Dose Cohort, the PSEN1 E280A kindred, ADNI and other relevant cohorts; help inform selection criteria, study design, endpoints, sample sizes and power in prevention trials; provide a foundation for other prevention trials; and provide resources of data and samples to advance the scientific study of AD.

Progress Summary: **1)** The API ADAD Colombia Study continued to meet its stated goals (Clinicaltrials.gov Identifier: NCT01998841). 365 participants were screened, 252 were randomized (66% PSEN1 E280A mutation carriers), with the last participant randomized on February 27, 2017. While fewer than the proposed 300 participants, including 200 mutation carriers and 100 kindred non-carriers, were randomized, we expect similar or even improved power to detect a treatment effect due to a higher than predicted retention rate and incorporation of a common close design, such that all participants continue blinded treatment until the last participant enrolled completes 60-months of treatment. Our analyses, presented at CTAD 2017, indicate that the common close design will increase power by approximately 22%. The last participant/last visit will be in February 2022, at the latest. To accommodate the addition of tau PET at approximately month 30 and 60 study visits, we have prepared a separate protocol and informed consent and anticipate enrollment will begin in mid-2018. Post-study data and sample sharing were key components of our original collaboration agreement with Genentech/Roche, and the current grant provides support for the post-study data and sample sharing program infrastructure. In June 2016, after submission of the current grant, we reached conceptual agreement with Genentech/Roche to share study baseline data in accordance with Collaboration for Alzheimer's (CAP) principles. **2)** In September 2013, we were awarded a \$33.2 million grant from the NIH for our second prevention trial in cognitively unimpaired 60-75 year-olds with two copies of the APOE4 allele, the major genetic risk factor for developing AD at older ages. In July 2014, we announced that Novartis was selected as the industry partner for this trial, and instead of studying 1 drug in 650 individuals, we would be studying 2 drugs – an active immunotherapy (CAD106) and an oral BACE inhibitor (CNP520) in approximately 1,300 individuals. In 2015, Novartis announced that Amgen would be co-developing CNP520. As with our first trial, we are

contributing \$15 million in philanthropic funding. The trial, now known as the API Generation Study 1, is taking place in North America, Europe, and Australia (NCT0256551). 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. The first participant was enrolled into the trial in November 2015. **3)** In 2017, we expanded our collaboration with Novartis and Amgen to conduct the API Generation Study 2, a trial of CNP520 in approximately 2,000 cognitively healthy adults ages 60-75 who either have one or two copies of the APOE ε4 allele (those with one copy must also have elevated brain amyloid) (NCT03131453). This trial expands upon the genetic testing and disclosure program in Generation Study 1 to also include amyloid disclosure. The first participant was enrolled into the trial in August 2017. **4)** We continue to further refine trial designs for other preclinical treatment trial programs/surrogate marker development programs in cognitively normal individuals who are at elevated risk for ADAD or LOAD. Our team submitted a large (approximately \$30 million) grant to the NIH for a fourth prevention trial in people with elevated brain amyloid, with a goal of beginning enrollment in 2019. **5)** We continue to expand the Alzheimer's Prevention Registry, a web-based registry focused on encouraging enrollment into prevention studies. It is intended to be an online community of individuals who want to stay informed and engaged about Alzheimer's prevention research, including receiving email notifications about study opportunities, providing a shared resource to accelerate enrollment in other prevention trials. The Registry has over 290,000 enrollees. 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. GeneMatch is serving as one of the primary recruitment sources in the United States for the API Generation Study. To date, over 50,000 people have joined. We exceeded our ambitious goals for the Colombian API Registry, to date having enrolled over 5,800, including nearly 1,200 mutation carriers and several new families.

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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 and Kewei Chen, PhD (Co-PIs), Laura Wojtulewicz, Davy Weissenbacher, 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:

Aim 1: Increase the number of real time metric reports available through our online reporting site to better monitor progress towards program goals.

Aim2: Extend the work accomplished in the past year to include additional data sources including a) APOE4 Gene Dose Cohort; b) Neuropathology; c) Meta-data on imaging; d) Genomic information; e) Biospecimen data; and f) Biomarker data.

Aim 3: Establish a data sharing platform which researchers can use to search the database to find cohorts of interest and then request the associated phenotypic, genomic, biomarker and imaging data.

Aim 4: Extend the code that generates files for upload to NACC to include consistency checks to reduce the number of errors received when uploading data to NACC and reduce the average time to packet finalization.

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. a) 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. b) 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 longitudinally assessments from older adults who consent to brain donation after they die, neuropathological data and exceptionally high quality brain and

body tissues from >1,500 expired BBDP participants; it has been the world's leading resource of neuropathology data and brain and other body tissue samples for AD, PD and other neurodegenerative disease researchers around the world, has contributed to hundreds of research publications and grants, and continues to make major contributions to the study of AD, PD, related disorders, and brain aging. c) 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, might benefit from either a shared data management program and/or mechanisms to find other relevant data in the future. In this project, we propose to enhance the work done in the previous year on a centralized robust data management platform to include more real time reporting, include more data sources, optimize the code that extracts data for NACC submissions to include data consistence checks and create a data sharing platform.

Preliminary Data and Plan:

Over the past year, with the support of AARC funding, significant progress has been made in development of a scalable, robust centralized database to support Alzheimer's disease projects. We have implemented data collection instruments in REDCap for all versions of the UDS (1.4, 2 and 3) and have imported historical data from NACC into the respective REDCap projects. By leveraging REDCap, we are able to be more agile in the creation and maintenance of electronic capture forms by eliminating the need for time consuming custom coding.

A general purpose custom software application, REDCap2Relational (R2R), has been created which leverages the REDCap Application Programming Interface (API) to query the meta-data for a REDCap project and dynamically generates a relational database schema. The software can then export the data from a REDCap project into the newly created relational schema through the API. Having the data in a relational database schema helps facilitate integration, reporting and sharing of data. This software will be able to be re-used for other projects, such as the APOE4 Gene Dose Program, to rapidly integrate data collected from other projects that are using REDCap.

In order to facilitate the transfer of data to NACC, a central web based portal has been created where data management core staff can download a single file in the format needed for upload to NACC. Additionally, we have deployed a web based reporting tool that will serve as a centralized location for consortium members to access real time reports for monitoring the progress of various studies.

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 the specific aims proposed in this report. We are happy to report that the backlog of Uniform Data Set (UDS) paper packets have been entered into our system and transmitted to NACC. This was in a large part due to the 2016 AARC funding which enabled the construction of the core infrastructure which continues to expand.

In this funding period, we have implemented seven online reports to help the Clinical Core Director, Dr. Rick Caselli, better monitor the progress of our ADC program. Each report sources data from our centralized database which includes data from REDCap as well as finalized data downloaded from NACC. A significant effort was put in to align the numbers across the individual reports and ensure consistency with standard NACC reports. These efforts also informed us how to better structure our centralized database.

We have leveraged previously written code to automatically import data from the APOE REDCap project to our centralized database. Migrating historical data from disparate sources into REDCap required significant effort, but we now have UDS, Biospecimen availability (including blood and CSF), Imaging meta-data and genomic information imported into REDCap and then exported into our centralized database. Going forward, REDCap will be used to capture newly acquired data for the APOE project.

With the APOE data being cleaned and in a relational database, we have also begun construction of a data sharing site that will permit researchers to explore the APOE data utilizing a web based tool in an aggregate manner to find cohorts of interest. We anticipate releasing the first production version of this tool by the end of the funding period.

With the construction of a pipeline to capture data and submit to NACC, it was recognized that the process of resolving errors and validation with our constituent sites was very onerous and error prone due to its reliance on emails between the Data Core and Clinical Sites. In order to resolve this we created a custom web base tool, Issue Tracker, where all errors from NACC are entered into the tool and stored alongside our data in our centralized database. This permits us to run metrics over the data to find variances in the time to correct data across our ADC sites. The tool was rapidly adopted and has received positive feedback from Clinical Coordinators and Data Managers at each site. Having all the errors in a database will also permit us to query and determine the most common types of errors that are occurring and implement checks prior to uploading data to NACC.

Project Progress Report
Banner Sun Health Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Towards single-cell analysis in human brain neurodegenerative disease: a pilot study.

Thomas G. Beach, MD, PhD, (PI), Geidy Serrano, PhD, David Brafman, PhD, Lih-Fen Lue, PhD, Matthew Huentelman, PhD (Co-I's) and colleagues from each of the participating Alzheimer's Consortium sites. 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 Aim 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.

Specific Aim 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).

Specific Aim 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, especially from Alzheimer's disease (AD) and Parkinson's disease (PD) patients, has produced much of what is known about these conditions, and has led to the major FDA-approved therapies. The typical approach has been to homogenize whole pieces of brain tissue and separately characterize the proteins, RNA, DNA and other macromolecules within. While this has been sufficient to identify large changes, there is very little ability to identify small changes, or changes in small subsets of cells. Furthermore, neurodegenerative disease often leads to massive losses of the targeted and disease-relevant cells, for example the entorhinal cortex layer II stellate neurons or substantia nigra pigmented neurons. Whole-homogenate analysis of such brain regions can give completely misleading results, as any biochemical constituent that is selectively localized to the depleted cells will appear to be "down-regulated", while 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. Laser-capture microscopy (LCM) is an early method that could pick individual cells off a cryostat section but is severely limited by the large time and personnel investment as well as the limited ability to phenotypically mark target cells. In recent years, methods have been developed that allow an initial creation of single-cell suspensions from solid tissue followed by analysis of phenotypically-defined cells sorted on the basis of cell-type identifying proteins or RNA expression. These methods are much more time and labor-efficient than LCM and allow sorting by a much more diverse panel of markers. Some groups have already published intriguing results from AD brain cells, but as yet there has not been a comprehensive exploitation of these novel technologies. This set of experienced neuroscience investigators, together with a unique rapid-

autopsy brain tissue resource, are well-suited to apply these methods on a large scale to AD and other neurodegenerative brain diseases.

Preliminary Data: The PI is Director of the Banner Sun Health Research Institute's Brain and Body Donation Program (BBDP), a clinicopathological study of aging and neurodegenerative disease based in Sun City, AZ since 1987. The BBDP has made rapid autopsy a priority, with a 3.0-hour median postmortem interval for the entire collection. Tissue quality is correspondingly high, with a median RNA Integrity Number (RIN) for frozen brain tissue of 8.9. Between 80 and 110 autopsies are done each year, allowing the rapid acquisition of relatively large numbers of new subjects. The PI and Co-Pis have prior experience with LCM single-cell harvesting and population analysis of phenotypically-defined human control and AD neurons and glia derived from the BBDP. Dr. Lue has focused her entire career on separation and culture of a variety of cell types from BBDP postmortem human brains. Dr. Brafman is experienced in the usage of fluorescence-activated cell sorting (FACS) for antibody-based separation and analysis of defined cell types, including neural progenitor cells. Dr. Huentelman has developed novel methods of genomic and cellular analysis and applied these to several disease conditions, especially Alzheimer's disease.

Progress Summary from July 1, 2017 to February 28, 2018:

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 single cells and phenotypically-specified cell populations.

To date, 112 autopsies have been performed by the BBDP since the funding start date for this continuing project (July 1, 2016). Of these, tissue from 53 has been used to process cells using the hypothermic dissociation protocol. In this current funding year (beginning July 1, 2017), we have obtained cell suspensions using the hypothermic protocol from 28 autopsies. Multiple combinations of mechanical and enzymatic digestion have been trialed to optimize both quantitative cell recovery and biochemical integrity.

Specific Aim 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).

Characterization of RNA obtained from dissociated cell preparations using hypothermic cell-dissociation method. The objective is to create dissociated-cell suspensions with intact protein and RNA, allowing for comprehensive biochemical characterization. Two criteria were used to assess RNA quality, yield and integrity. RNA isolation was performed in unfixed or fixed samples. By the end of 2017 we experimented with different fixation methods, derived from literature reports and in consultation with industry FACS experts, and compared how these fixations affected protein and RNA. It is possible that a mild fixation will both help preserve RNA and structural integrity, allowing cells to remain intact after passage through FACS and the 10x platform. We fixed single cell suspensions for 10 minutes in 10% formalin, 4% paraformaldehyde and 100% methanol. Formalin and paraformaldehyde severely degraded the RNA. However, our data showed that relatively intact RNA can be isolated from unfixed and methanol fixed suspensions, as demonstrated by relatively good RIN values (Table 2). RNA integrity number (RIN) in unfixed cell suspensions is currently ranging from 2 to 8, with an average RIN of 6. The yield of RNA is

ranging from 4-350 ng/million cells, with an average yield of 55 ng/million cells. Similarly, from methanol-fixed samples RIN ranged from 2-10, with an average RIN of 5 and an average e yield of 60 ng/million cells (Table 1).

In Year One of this project (2016-2017), the physiological protocol had superior cell and RNA yield and superior RNA quality. However, continual adjustments to the hypothermic protocol resulted in considerable improvement so that throughout this current funding year (2017-2018) the protocols are roughly equivalent. There is variability between cases, for reasons that need to be resolved. Yet, it is known, from more than two decades of work from the Lue lab, that much of the case-to-case variability is due to initial brain tissue status, which has many contributing source of heterogeneity, including differing agonal *in vivo* status of the human subject, postmortem cadaver temperatures and postmortem interval prior to commencement of autopsy.

Table 1. Results of RNA analyses from brain cells isolated with the hypothermic method. N=number of subjects; SD= standard deviation

Preparation method (n)	RIN (SD)	cells/ml (SD)	ng/million cells (SD)	cells/g(SD)
Frozen (22)	6.2 (2.1)	24 million (18 million)	55.1 (101.2)	2.4 million (1.8 million)
Methanol Fixed (12)	5.1 (3.6)	26 million (19 million)	60.3 (142.9)	2.6 million (1.9 million)

Phenotypic characterization of cells from dissociated cell preparations – IHC. Another objective is to ensure that single-cell suspensions contain representative populations of neurons and glia. To initially establish whether major cell types are present, the paraffin-embedded cell pellets were immunohistochemically stained with antibodies specific for neurons (neurofilament), 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 (not shown due to space constraints).

Phenotypic characterization of cells from dissociated cell preparations – RNA by qPCR.

Other cell pellets were used for RNA extraction, which was then probed using qPCR for cell-type-specific RNA for neurons (MAP2), astrocytes (GFAP) and microglia (Iba1). qPCR was performed using standard procedures. The results (not shown due to space constraints) showed that all three cell types were abundant in the suspensions. The neuronal MAP2 signal was somewhat less abundant in cells prepared with the physiological method (Lue) than the hypothermic method (Lue).

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, depending on the antibodies used. Dr. David Brafman has done preliminary FACS analysis of cell suspensions derived from the hypothermic approach.

Cells were washed twice with stain buffer (BD Biosciences) and resuspended at a maximum concentration of 5×10^6 cells per 100 μ l. For staining of intracellular proteins, cells were fixed for 10 min on ice with BD Cytifix Fixation Buffer (BD Biosciences). The cells were then washed twice with stain buffer and permeabilized with BD Phosflow Perm Buffer II (BD Biosciences) for 30 min on ice. Cells were then washed twice with stain buffer and one test volume of antibody was added for each 100 μ l of cell suspension. Primary antibodies were incubated overnight at 4°C and then washed twice with stain buffer at RT. Secondary antibodies were incubated at RT for 1 hr. Cells were analyzed on an ACCURI C6 (BD Biosciences). Gates were set using secondary only controls. Analysis of four primary cortical samples (16-50, 16-52, 16-53, and 16-57) revealed that GFAP percentages ranged from 8.0-20.5%, Neuronal Nuclear protein (NEUN) percentages ranged from 85.3-95.0%, and IBA1 percentages ranged from 84.8-96.7%.

Discussion and Future Plans:

1. Further characterization of the cell suspensions by FACS is needed to determine whether cell subsets sorted into separate aliquots with the cell-type-specific antibodies are mutually exclusive as would be expected, and to determine whether adequate numbers of neuronal and glial cells are being obtained to allow further experimental usage. Exclusivity of sorting will be ascertained with qPCR for cell-type-specific signal of the FACS-sorted cells. Once these data have been acquired, a detailed comparison will be made of the hypothermic and physiological cell dissociation methods. It is likely that the methods will be complementary, with some projects more suited to one and some projects better served by the other.
2. RNA quality analysis needs to be repeated on cell subpopulations after undergoing FACS, to ensure that RNA quality is maintained and that sorted cells will be useful for further study, e.g. transcriptome analysis.
3. 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. As scRNAseq is potentially the method that will give the greatest advances in the understanding of cell-type-specific gene expression changes in neurodegenerative disease, high priority is being given to ensure that our cell suspensions will be suitable for this.
4. A methods paper will be written and published before the end of this funding period so that user-researchers will have confidence in the methods used to prepare the cell suspensions.
5. Results from specific autopsies should be compared with those obtained using laser-capture, as this has previously been the gold standard for cell-type specific gene expression analysis.
6. 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.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 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, and 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, serum, and PBMC samples from well characterized, longitudinally assessed, and consenting participants in Arizona's Brain and Body Donation Program.
2. To develop a repository of CSF, plasma, serum and PBMC samples 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 serum samples and 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 with support from the National Institute of Neurological Disorders (NINDS)-supported National Brain and Tissue Resource for PD and Related Disorders (NBTR-PD). 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.

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.

Research Plan:

During the one-year funding period, we propose to further develop the infrastructure to conduct lumbar punctures (LPs), acquire up to 30 ml of CSF and 40 ml of blood and process CSF, plasma, and PBMCs from BBDP participants at BSHRI and APOE4 Gene Dose Program participants at BAI, to acquire, process, aliquot and store samples using standardized procedures, and to establish a repository of these samples at BSHRI. This year, we propose to acquire CSF samples in 50 returning BBDP participants at BSHRI and in 50 returning state-supported APOE4 Gene Dose Program participants at BAI who consent to LPs; and we propose to acquire blood samples in 400 returning BBDP participants and in the 50 APOE4 Gene Dose Program participants.

CSF Samples. LPs will be acquired by trained and experienced personnel standardized procedures established for other longitudinal cohorts. We will acquire up to 20 ml CSF, as the volume of CSF has not been associated with differences in the risk of post-LP headaches. CSF will 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 a randomly selected set of at least 5% of cases to conduct standard analyses on cell count, protein and glucose levels, and hemoglobin levels.

Blood Samples. We propose to acquire up to 40 ml of venous blood in EDTA tubes. Blood will be centrifuged at 1,500 rpm for 15 min at 24°C to separate plasma, buffy coat 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. The plasma supernatant will be collected and stored at -80°C. From blood samples collected at BSHRI, the buffy coat at the red blood cell/plasma interface will be diluted in Hank's Balanced Salt Solution (HBSS) to a total volume of 50 ml. A total of 25 ml of HBSS-diluted blood will be gently layered on top of 10 ml of Histopaque 1077 and then centrifuged at 400 x rcf for 30 min at 24°C. The opaque interface containing peripheral blood mononuclear cells (PBMC) will be collected and then brought up to 50 ml with HBSS. After centrifugation at 3000 x rcf for 15 min at 24°C, the supernatant will be discarded and each pellet resuspended in 3 ml of HBSS and then transferred to 1.7 ml microcentrifuge tubes. The resuspended cells will then be centrifuged at 14,000 rpm for 5 min at 4°C to pellet the PBMC. The PBMC pelleted cells will be stored at -80°C.

Fluid Repository. All samples from Specific Aims 1 and 2 will be stored at BSHRI in ultra-low temperature freezers protected with redundant temperature-activated alerts, banks of emergency CO2 tanks, redundant air conditioning units and backup diesel alternate power supply. BBDP

staff are on constant call to respond to freezer alerts. A biological sample distribution committee involving the BBPD and APOE4 Gene Dose Program PIs will evaluate all research proposals involving the use of shared biological samples.

Proposed One-Year and Long-Term Outcomes:

Our one-year goal is to collect, process and store the samples as described. Our long-term goals are to extend this effort to all consenting participants in the 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 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.

Progress Summary to February 28, 2018:

Specific Aim 1. To develop a repository of cerebrospinal fluid (CSF), plasma, serum, and PBMC samples from well characterized, longitudinally assessed, and consenting participants in Arizona's Brain and Body Donation Program.

Blood Samples. These efforts started in the 2015-2016 funding year. At present we have a total of 684 blood sample sets from 479 different subjects (some subjects have had repeated blood sampling). In the current funding year, we have collected 176 sample sets and are thus running behind schedule for our target of 400 samples by June 30th. This is due to loss of a scheduler in the BBPD in the summer of 2017 and an unexpectedly long intervening period during which we had limited scheduling capacity due to time spent recruiting and training a replacement. To avoid such delays in the future, we hired a second scheduler on a temporary basis in the fall of 2017 and are going to make this second scheduler position permanent. Despite this setback we expect to meet our target of 400 blood samples drawn this year by the funding end date of June 30, 2018 but scheduling 3-4 blood draws each working day for the remaining period.

By clinical diagnosis (non-exclusive), the collected blood samples are from 312 cognitively normal subjects (151 of whom have donated more than one sample set), 84 subjects with mild cognitive impairment (30 with repeat donations), 56 subjects with a clinical diagnosis of dementia (20 with repeat donations) and 114 subjects with Parkinson's disease (13 with repeat donations).

CSF Samples. At present, since this initiative began July 1, 2015, we have been successful in obtaining CSF on only 24 subjects. Of 187 participants that had initially agreed, on their BBPD consent, to contribute CSF samples, 82 were ruled medically ineligible for lumbar puncture, due to history of either spinal surgery or anti-coagulant therapy, and thus were not contacted as this is a medical contraindication. More than 173 others have been contacted by phone and of these, 58 have changed their minds and now decline to donate CSF; or have not returned multiple messages. Forty-seven were scheduled for lumbar puncture. Eighteen of these cancelled their clinic appointments in the few days prior to the appointment; of these, eight have stated that they are willing to be re-scheduled. Two subjects were found to have scars in the lumbar area consistent with prior surgery (despite having no database history of spinal surgery) and were thus sent home. Thirty-five subjects had a lumbar puncture of which 24 were successful but 11 did not obtain CSF. The project is thus behind schedule for the above reasons. Additionally, we have had unanticipated difficulty in hiring a suitable nurse practitioner (NP) that could learn to perform LPs. An NP was hired (Alisson Gilbert) in January 2017 and went through training with Dr. Elaine Peskind in May 2017 but then quit soon afterwards. A second NP at BSHRI, Marina Reade, also went through LP

training with Dr. Peskind and is willing and able to keep doing them, but still requires direct supervision by someone already qualified. A replacement NP, Teresa Burks, was hired but has not received training as with so few subjects undergoing LPs, it is considered the highest priority that these are devoted to consolidating the training received by Marina Reade. As mentioned above, loss of our only BBDP scheduler in the summer of 2017 crippled our ability to bring in new subjects as well. We are concentrating on devoting special attention to conveying the importance of CSF donation during consenting of newly-enrolled subjects over the coming months and are optimistic that our rate of successful LPs will increase with these new recruits but we do not anticipate meeting our goal of collecting CSF from 50 BBDP subjects this year.

Specific Aim 2. To develop a repository of CSF, plasma, serum and PBMC samples from well characterized, longitudinally assessed, and consenting participants in Arizona's APOE4 Gene Dose Program.

Longitudinal biofluid samples from 462 subjects enrolled in the APOE imaging cohort (CSF, plasma, and serum) have successfully been transferred from BAI to BSHRI. This effort has achieved the longtime need for unification of APOE imaging cohort samples in one laboratory with the required expertise. These are currently 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-powered alternate power supply.

Due to unexpected delays, subjects from the non-imaging APOE cohort have yet to undergo biofluid collection BAI for this project. The APOE study teams of Mayo Clinic and BAI are together continuing the recruitment process of non-imaging APOE study subjects currently undergoing participation exclusively at Mayo Clinic. In order to inform APOE study subjects of this new research opportunity, all study subjects were sent a recruitment mailing on behalf of Banner and Mayo Clinic. BAI has recently recruited and trained new study staff on this project and it is anticipated that blood and CSF will be obtained by the end of June 2018.

Specific Aim 3. To provide a shared resource of CSF, plasma, and serum samples and data to researchers inside Arizona and around the world.

Ultimately, because the collected samples will be tied to a postmortem neuropathological diagnosis, this will constitute a unique and invaluable "reference resource" for rigorously evaluating potential biofluid biomarkers of AD, PD and other neurodegenerative diseases. Therefore, it will be important not to disburse all of the samples prior to obtaining autopsy diagnoses. Since the project was first funded by the AAC in 2015, thirty-two blood donors have died and been autopsied in the BBDP. Of those with the neuropathological examination results available, there are a wide range of conditions represented. Two are considered cognitively normal controls, 3 had mild cognitive impairment, 5 meet NIA-AA criteria for AD, 3 meet clinicopathological criteria for PD, 3 meet neuropathological criteria for vascular dementia, 1 meets clinicopathological criteria for DLB, 2 have diagnostic pathology of progressive supranuclear palsy, two have hippocampal sclerosis, two have diagnostic pathology of corticobasal degeneration and two have FTLT-DTP.

As these deceased subjects do not yet constitute a sufficient sample size for investigations, we have not as yet undertaken any promotion of the availability of the new antemortem biofluids resource. At present we are fulfilling our sharing mandate by disbursing from our large collection of postmortem blood serum and CSF. Since July 1, 2015, we have transferred 917 serum and/or CSF samples to in 14 different researchers located in 8 different states.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 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, PhD, 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; University of Arizona; Arizona State University; Translational Genomics Research Institute; Mayo Clinic Rochester; McGill University; Arizona Alzheimer's Consortium.

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.

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.

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 [1]. 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 [2-7]. The mean time interval between RBD onset and cognitive impairment or parkinsonism is 6-7 years [8-13]. 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 [10] 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 [13]. 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 [14] 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 [15-17], however, there has never been a true population survey for the prevalence of RBD in the United States. Existing data come 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) will be available by the end of summer 2017 and are expected to provide a reliable estimate for the prevalence of pRBD in Sun City. A subset of the pRBD subjects identified by this study will be 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. This will complete the population survey by giving an estimate of the local prevalence of PSF-confirmed RBD. Additional recruiting efforts are planned, including community outreach and advertising, to attain a target BBDP enrollment of 50 pRBD subjects in this funding year. These studies are designed to establish the feasibility of conducting future RBD-based prevention trials centered in Sun City.

Preliminary Data: The principal investigators are recognized experts in the clinical and neuropathological evaluation of synucleinopathies [18-25] and have published multiple studies of preclinical markers [19;26-35] including RBD [11;12]. Dr. Shprecher has previously undertaken broad-based surveys of neurological illness [36-37], 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 [39]. 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:

The one-year outcome is expected to result in a published scientific report that would be the first truly population-based study of RBD prevalence in a US community. 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.

Year End Progress Summary:

Aim 1: As of February 2018, we have scheduled our first subject with polysomnogram-confirmed RBD for enrollment in our BBDP. We have completed three outreach lectures aimed at recruiting additional participants with possible REM sleep behavior disorder for screening and completed 3 in-person screenings. To improve recruitment, we will continue our outreach lectures (2 more scheduled this year). We will now review sleep questionnaire data collected with our established control cohort, and those with suspected RBD will be invited to undergo research polysomnograms to confirm RBD diagnosis. We will also begin newspaper advertising of the research.

Aim 2: From our phone and mail survey of Sun City residents, we have identified 21 participants with probable RBD who are willing/eligible to get screening polysomnograms. Among these, 9 were reached by phone or email and 6 declined, 1 is ill and unable to come in now; 2 were contacted and seen in person. Among these, one is an established control participant in our BBDP and is scheduled for research polysomnogram to confirm a diagnosis of RBD. Six did not return phone calls or emails and 5 provided a contact address but not a working telephone number and 1 provided no contact information at all. We will now arrange to send letters to these remaining probable RBD respondents inviting them to come in for screening interviews (and invite those who screen positive for probable RBD to complete diagnostic research polysomnograms).

Project Progress Report

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

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Cognitive and neural correlates of aging in autism spectrum disorder. Leslie C. Baxter, PhD, Blair Braden, PhD, Christopher Smith, PhD, Jiong Shi, PhD, Curtis McKnight, MD, Jieping Ye, PhD. Barrow Neurological Institute' St. Joseph's Hospital and Medical Center; Arizona State University; Southwest Autism Resource and Research Center; University of Michigan; Arizona Alzheimer's Consortium.

Specific Aims:

There are very few studies of the effects of aging in Autism Spectrum Disorder (ASD). Young adults with ASD struggle with executive functions, such as working memory, inhibition, and set shifting. Conversely, ASD individuals often have preserved or enhanced visuospatial skills, such as embedded figure recognition and detail processing. Atrophic changes associated with brain aging is more pronounced in the frontal lobe, and the cognitive profile of normal aging reflects these structural brain changes with impairment in some frontal lobe mediated functions, such working memory and set shifting. ***Given that ASD individuals struggle with many cognitive functions that are related to frontal lobe integrity in young adulthood, and that the frontal lobe is susceptible to normal age-related changes, there might be an exacerbation of deficits beyond normal aging in ASD.*** The present study expands the limited prior research in aging and autism by assessing cognitive functioning in middle-aged ASD individuals using tasks that represent both intact and impaired domains in younger patients. Further, we will correlate cognitive results with measures of functional and structural brain integrity.

Specific Aim 1: Do middle-aged (40-60 yr) ASD individuals show cognitive deficits as compared to age-matched controls?

Hypothesis: Middle-aged ASD individuals show selective cognitive deficits, performing worse on executive tasks than age-matched Controls, with preservation of semantic memory and visuospatial tasks of detailed local processing.

Specific Aim 2: Do middle-aged ASD individuals recruit brain networks differently during task-based fMRI than age-matched Controls? Do the differences correlate with cognitive profile?

- Hypothesis 1: On fluency, working memory and inhibition fMRI tasks, middle-aged ASD individuals will exhibit a more diffuse pattern of frontal lobe activation and will recruit additional posterior brain regions to perform these tasks, as compared to age-matched controls.
- Hypothesis 2: Connectivity differences will be observed comparing middle-aged ASD individuals to age matched controls, indicating reduced functional connectivity between areas of the frontal cortex and association cortices (parietal, temporal, and occipital).
- Hypothesis 3: Using multi-task learning techniques, combining cognitive and imaging (connectivity and gray matter/white matter integrity) will show different profiles based on group status, and that weaker connectivity of the frontal lobe with more posterior regions will correlate with greater impairment on executive functioning cognitive tasks.

Research Plan:

This project is capitalizing on a multi-institutional group of Arizona researchers who have expertise and interest in aging and ASD. We are partners with Dr. Christopher Smith, research director of the Southwest Autism Research and Resource Center (SARRC), who collaborates with study development and participant recruitment. Blair Braden is co-investigator with all main work, is a tenure-track Assistant Professor on the Department of Speech and Hearing Sciences at Arizona State University. We are also partnering with Dr. Jieping Ye, at the University of Michigan. Dr. Ye develops statistical packages for combining different sources of data (e.g., imaging, behavioral, cognitive, genetic) for patterns and differences. We also have scientific input from Dr. Rogalsky, with whom Dr. Baxter partners in imaging studies, and share a graduate student through the ASU-BNI Neurosciences program, Megan Fitzhugh, who has submitted a manuscript based on previously collected data on fMRI language networks in aging. Our study benefits from the combined clinical and imaging expertise of this group. We also partner with Dr. Woodruff at Mayo Clinic Arizona (MCA), who has also worked with Dr. Smith in a study of cognitive abilities in a group of 50 ASD adults ranging in age from 20 to 58 years and participates in design conceptualization. Dr. Caselli, also at MCA, has incorporated measures of ASD in his longitudinal APOE cohort.

In our third year, we continue to recruit typically developing (TD) Control males, ages 40-70, who are right-handed, and a group of ASD and TD age-matched young adults (age 18-25) to perform a battery of cognitive testing with a focus on frontal lobe/executive abilities and also undergo structural, functional (resting state and task-based) imaging. We are in the second year of funding from the Department of Defense, which enables us to expand the cohort to a total of 70 ASDs/age-matched controls and obtain two data points, two years apart.

2017-2018 Progress:

Results: We continue to recruit individuals for both older and younger cohorts, and now have over 90 individuals in this study, some of which have returned for a second time point after two years. We have successfully published our first paper on some of the older adults' first time point data (Braden et al, 2017). Briefly, we analyzed 16 ASD and 17 typically developing (TD) controls. All participants underwent cognitive testing and MRI scanning including evaluation of white matter (DTI) and gray matter integrity. Participants also performed functional MRI (fMRI) tasks during the scanning session. The cognitive tasks used the data obtained from the first cohort's baseline time point. Middle-age adults with ASD made more errors on an executive function task (Wisconsin Card Sorting Test; WCST) but performed similarly to NT adults on tests of verbal memory (Rey Auditory Verbal Learning Test) and local visual search (Embedded Figures Task). Independent component analysis of a functional MRI working memory task (n-back) showed decreased engagement of a cortico-striatal-thalamic-cortical neural network in older adults with ASD. Structurally, older adults with ASD group had decreased white matter integrity (fractional anisotropy) bilaterally in the fimbria/fornix of the hippocampus and corpus callosum genu, and reduced bilateral hippocampal volumes, as measured by FreeSurfer. Furthermore, decreased corpus callosum genu integrity predicted worse performance in the executive function task (WCST) in the ASD group, implicating white matter differences as the underlying brain mechanism of this cognitive struggle. Findings expand our understanding of ASD as a lifelong condition with persistent cognitive and functional and structural brain differences evident at middle-age. We submitted two additional manuscripts for review in December 2017, for a special

edition focusing on older adults with Research in Autism Spectrum Disorders. One manuscript examined differential engagement of neural networks in aging and autism for an fMRI fluency task. We submitted another paper showing a relationship between resting state networks and behavior in older ASD.

We have 3 abstracts in press for the International Society for Autism Research (INSAR), Rotterdam, Netherlands in May 2018 directly from this research. Dr. Braden has submitted and received a favorable score for her K-01 application entitled “Sex-Specific Brain and Behavioral Predictors of Cognitive Aging in Middle-Aged Adults with Autism Spectrum Disorder”. Her mentors are Drs. Chris Smith from SARRC and Eric Reiman from the Alzheimer’s Consortium. Finally, our study was highlighted on the Department of Defense Congressionally Directed Medical Research Website because of the success we have had with our recruitment, retention and findings.

Year End Progress Summary:

- Published first manuscript of baseline data comparing older ASD to typically developing (TD) controls showing working memory network dysfunction and decreased performance on a behavioral working memory task. Submitted two additional manuscripts for review.
- Collection of second time point for older adults underway with 90% retention. Continue recruiting new participants.
- Manuscript published that includes our data contributed to the Autism Brain Initiative Data Exchange-II (ABIDE).
- Submitted for additional Barrow Foundation funding to develop pilot data to study Transcranial Direct Current Stimulation and MRI in Autism (pending funding).

Proposed One-Year and Long-Term Outcomes:

- Continue acquiring longitudinal data from a cohort of 70 each ASD elderly and age-match controls, along with a smaller subset of younger adults, and their age-matched controls.
- Based on our promising preliminary findings, we will plan to submit for additional funding (both NIH and Department of Defense) later this year.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Role of natural killer cells in amyloid plaque clearance. Qiang Liu, MD, PhD. Barrow Neurological Institute; University of Arizona College of Medicine - Phoenix; Arizona Alzheimer's Consortium.

Collaborators:

University of Arizona College of Medicine - Phoenix: Shenfeng Qiu, PhD, Rayna Gonzales PhD

Specific Aims: 1) Test the hypothesis that brain-infiltrating NK cells promote phagocytic activity to clear A β by co-culture of NK cells with neurons, astrocytes or microglia. 2) Test the hypothesis that NK cell expansion will reduce A β levels and plaque formation in APP transgenic mice.

Background and Significance: AD is the most common type of dementia that affects ~5.5 million Americans without a cure. A β accumulation activates the immune system. Experimental, genetic and epidemiological data have indicated the disruption of BBB and brain infiltration of peripheral immune cells as a disease-promoting factor for AD pathology. However, the role for specific immune cell subsets in the progression of AD is not defined. NK cells are large granular lymphocytes of the innate immune system and are among the earliest responders to danger signals. The capacity of NK cells to rapidly release of cytokine and directly act on target cells without prior sensitization enables them to orchestrate the nature and intensity of both innate and adaptive immunity. NK cells can readily home to the brain during numerous neuropathological situations where they regulate the inflammatory milieu which might be critical for tissue injury or repair, depending on the timing and locations. However, these hypothesized roles for NK cells haven't been studied in A β pathology and AD progression.

This project aims to unveil NK cells as an immune cell type that controls A β pathology in the brain. Brain cells, mainly microglia, respond to the presence of A β plaques by helping clear them from the brain via phagocytosis of A β . Activation without prior priming and prompt release of immunomodulatory factors enable NK cells to act as critical players in the regulation of brain phagocytes, but the exact role of NK cells has not been critically evaluated. Immune therapies targeting NK cells to confer beneficial activity might reduce AD progression. The lessons learned from NK cells might also be applicable to other lymphocytes. Therefore, this proposal will have significant impact on AD by providing fundamental insight into the role of NK cells in disease progression and provide potential new therapeutic targets.

Preliminary Data and Plan:

Aim 1) Test the hypothesis that brain-infiltrating NK cells promote phagocytic activity of brain-resident cells to clear A β by co-culture of NK cells with neurons, astrocytes or microglia. As brain-infiltrating NK cells highly express MIP-1 α that can promote phagocytic activity and NK cell depletion increased A β plaques, we will determine whether NK cells impact the phagocytosis of A β by microglia, astrocytes, or neurons. We will isolate brain-infiltrating NK cells from the brains of 5xFAD mice (4 months old) using flow cytometry. NK cells from spleens of wild-type mice will be used as a control. Then, NK cells or medium will be added into primary cultures of

microglia, astrocytes, or neurons (1:1 ratio). These cells will be incubated in the presence or absence of fluorescence labeled A β ₁₋₄₂(fA β). NK cells alone will be incubated with fA β as an additional control. The fA β uptake and phagocytic efficiency will be measured based on a weighted average of ingested fluorescent microspheres per cell by combining confocal with phase-contrast images to provide views of the fA β and the entire cell to distinguish between phagocytosed fA β and fA β adhered to cell surface.

Aim 2) Test the hypothesis that NK cell expansion will reduce A β levels and plaque formation in APP transgenic mice. As NK cell depletion strongly increased A β plaques in APP transgenic mice, we will determine whether the expansion of NK cells using anti-IL-2R α -chain mAb (daclizumab, an FDA approved drug that can selectively expand NK cells) can affect A β levels and plaque formation in 5xFAD mice. Groups of APP transgenic mice (12 mice/group) will receive daclizumab or vehicle control from 1 to 4 months of age (3 month-treatment). A β levels from brain and blood will be monitored by ELISA assay. A β plaque load will be determined by thioflavin T staining of frontal cortex, entorhinal cortex and hippocampus.

Proposed One-Year and Long-Term Outcomes:

Because of increased A β plaques after NK cell depletion and NK cell production of factors to modulate phagocytosis, we expect that NK cells should promote A β phagocytosis and that the expansion of NK cells should lead to reduced A β levels and plaque formation. The ultimate goal of this application is to understand the precise role of immunity and inflammation in A β pathology. This award will enable us to obtain critical data and submit our proposals to NIH or Alzheimer's Disease Association.

Year End Progress Summary:

We found the infiltration of NK cells in the brain of patients with mild cognitive deficit (MCI) and Alzheimer's disease (AD). In APP transgenic mice, we found the infiltrating of NK cells into the brain can start from 3 months prior to cognitive decline and significant amyloid plaque formation. The number of brain-infiltrating NK cells increase afterward at least until 12 months in APP transgenic mice. In addition, depletion of NK cells strongly increased the number of A β plaques in APP transgenic mice. The results from Aim 1 suggest that NK cells promote phagocytic activity of microglia to clear A β . We are performing experiments in Aim 2 to verify the potential benefit of expanding NK cells in APP transgenic mice.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Chitinase 3-like protein 1 (CH13L1) and complement component C1q protein levels during the progression of Alzheimer's disease. Elliott J. Mufson, Sylvia E. Perez, Muhammad Nadeem. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Collaborators:

Barrow Neurological Institute: Sylvia Perez, Muhammad Nadeem, Bin He, Christy Kelley, Jennifer Miguel, Erum Mian,

Barrow Neurological Institute and ASU: Laura Mahady, David Moreno

Background and Significance: Chitinase 3-like protein 1 (CH13L1 or YKL-40; 39kDA) and C1q are involved in immune regulation in several inflammatory conditions and neurodegenerative diseases, including Alzheimer's disease (AD) (Yasojima et al., 1999). In brain, CH13L1 and C1q are secreted mainly by innate immune cellular elements, astrocytes and microglia, which are involved in anti-inflammatory responses (Fraser et al., 2010). Astrocytes and microglia are increased in areas of the brain displaying amyloid beta (A β) and tau pathology in AD, suggesting the involvement of CH13L1 and C1q in the pathogenesis of AD. While a few studies have shown an upregulation of CH13L1 and C1q in cerebral spinal fluid and temporal cortex in AD (Choi et al., 2011, Melah et al., 2016), virtually nothing is known about the evolution of these inflammatory markers within the subfields of the dorsal mode network (DMN; frontal, precuneus and posterior cingulate cortex) and the medial temporal lobe (MTL) memory circuits, which display extensive amyloid and tau pathology, respectively, early in the progression of AD (Gordon et al., 2018; Mufson et al., 2015, Ikonovic et al., 2011). The data derived from these studies will provide novel information about the interaction of CH13L1 and C1q protein levels indicative of an active gliosis process associated with an anti-inflammatory response early in AD and differentiate the involvement of these proteins in the pathogenesis of the DMN.

Specific Aims:

1. We will test the hypothesis that there is a rostral to caudal upregulation of chitinase 3-like protein 1 (CH13L1) and C1q protein levels within the subcomponents of the default memory circuit (frontal, precuneus and posterior cingulate cortex) during the progression of AD and that these changes correlate with cognitive performance and AD neuropathological criteria.
2. We will test the hypothesis that CH13L1 and C1q protein level dysregulation occurs in a spatial temporal progression within the medial temporal lobe memory circuit (transentorhinal to entorhinal to hippocampus) during the progression of AD and that these changes correlate with cognitive performance and AD neuropathological criteria.
- 3.

Methods Overview:

Subjects: Study included cases that died with an antemortem clinical diagnosis of NCI (n=14), MCI (n=13) and mild/moderate AD (n=12) from RROS. Additional cases with a diagnosis of severe AD (n=11) were obtained from the RADC. All RROS participants the received neuropsychological testing within 12 months of death, which included Mini Mental State

Examination (MMSE) and a battery of nineteen cognitive tests (Global cognitive score). All groups were matched by age and postmortem interval and underwent detailed postmortem neuropathological analyses. Neuropathological diagnosis included Braak staging of NFTs, NIA-Reagan criteria, and recommendations of CERAD.

Quantitative Western blotting will be applied to frontal cortex tissue obtained from the RROS using antibodies against CH13L1 and C1q using previously published procedures (Perez et al., 2015).

Statistical Analysis: Data were compared across clinical groups using non-parametric tests: Kruskal-Wallis and Mann-Whitney. Spearman rank correlation assessed associations between the individual proteins and the cognitive composite scores, MMSE, and Braak stage. Statistical significance was set at 0.05 (two-sided).

Results: Initial investigation of chitinase 3-like protein 1 (CH13L1) and C1q alterations during the progression of AD:

1. Frontal cortex CHI3L1 levels were unchanged during the progression of AD:

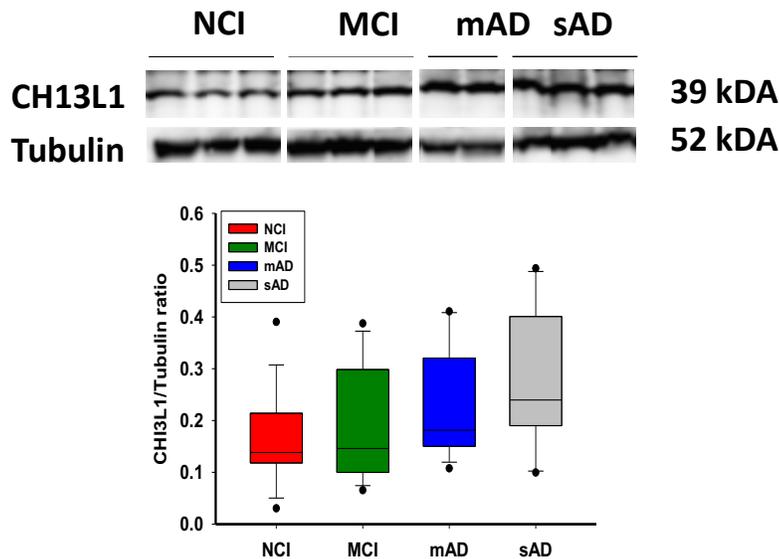
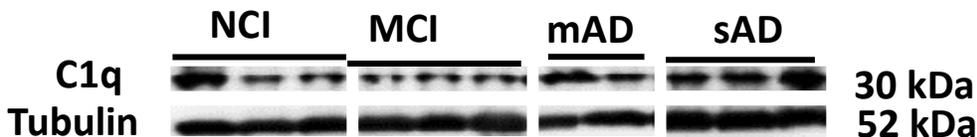


Fig. 1. Representative immunoblot and box plot of frontal levels of CHI3L1 from cases clinically diagnosed as NCI, MCI, mAD and sAD. (A). Frontal cortex CHI3L1 protein levels were unchanged across clinical groups ($p=0.086$). Note that there was a trend for CHI3L1 levels to increase during the progression of AD. NCI, non-cognitive impairment, MCI, mild cognitive impairment, mAD, mild to moderate AD, sAD, severe AD. Circles in the box plots indicate outliers.

2. Frontal cortex C1q levels were stable during AD progression



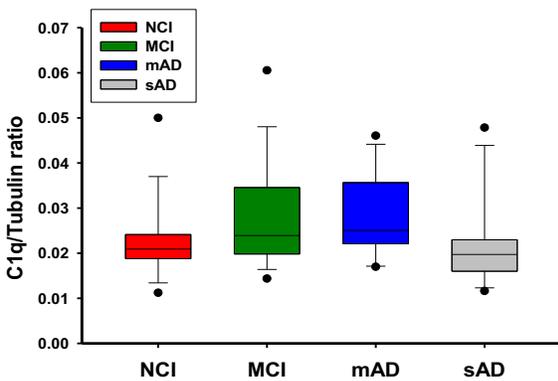


Figure 2. Representative immunoblot and box plot of the frontal levels of C1q) from cases clinically diagnosed as NCI, MCI, mAD and sAD. (A). There were not significant differences of C1q levels in the frontal cortex across clinical groups ($p=0.072$). Note there was a trend towards an increase in C1q levels in MCI and mAD. NCI, non-cognitive impairment, MCI, mild cognitive impairment, mAD, mild to moderate AD, sAD, severe AD. Circles in the box plots indicate outliers.

3. CHI3L1 protein levels strongly correlated with the microglial inflammatory markers C1q and TREM2 in early stages of disease progression

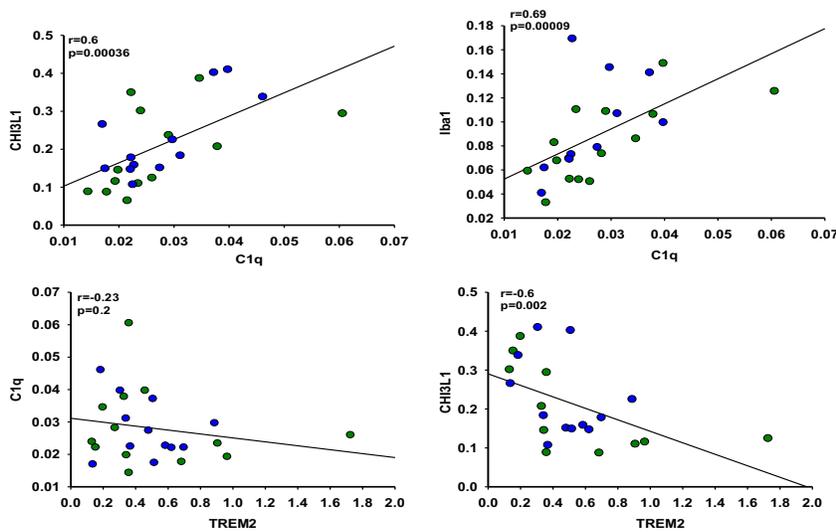


Figure 3. Scatter blots showing that CHI3L1 levels correlated with C1q and TREM2 levels and C1q protein levels correlated with Iba1 in MCI and mAD.

Summary: These data suggest that increases in CHI3L1 and C1q protein levels in the frontal cortex are indicative of an active gliosis process associated with an anti-inflammatory response early in the disease process.

Future studies: We are investigating other variants of CHI3L1 in the DMN hubs using antibody cytochemistry and western blotting. Specific Aims 2 will be initiated after we complete the investigation of the DMN.

Publication:

Nadeem, M., Perez, S. E. and E.J. Mufson: Frontal cortex chitinase 3-like protein 1 (CHI3L1) and complement component C1q protein levels during the progression of Alzheimer’s disease, Soc. Neurosci. Abstract. 2017.

Time Line: We anticipate the first publication resulting from the ADRC support will be in 2019. Following publication of our work, we will leverage the published data as part of a grant.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Characterization of neurons differentiated from patients with Down's syndrome. Elliott Mufson and Rita Sattler. Barrow Neurological Institute; Dignity Health at St. Joseph's Hospital and Medical Center; Arizona Alzheimer's Consortium.

Collaborators:

Barrow Neurological Institute: Sylvia Perez, Muhammad Nadeem, Bin He, Christy Kelley, Jennifer Miguel, Erum Mian,

Barrow Neurological Institute and ASU: Laura Mahady, David Moreno

Aim 1: Generation and characterization of iNeurons from patients with DS and age-matched controls. Our laboratory has access to fibroblasts from healthy controls and subjects with DS. We will differentiate fibroblasts into iNeurons and characterize the cultures by immunostaining for neuronal morphology (dendritic tree, spine density, synapse density), neuronal marker protein expression (MAP2, Brn2, GluRs) and neuronal activity (action potential firing rates).

Aim 2: Genetic profiling of DS iNeurons. RNA will be isolated from differentiated induced neurons (iNeurons) to obtain genome-wide transcriptomes via RNA seq. Differential expression and gene expression network analyses will be performed to identify genes and networks that are perturbed in DS compared to healthy controls subjects such as synaptic and cell survival genes that can be used for future mechanistic studies and drug discovery efforts.

Rationale and Significance

Trisomy 21, Down Syndrome (DS) is a common genetic disorder, which results in the onset of dementia and intellectual disability. Individuals with DS have an increased likelihood of developing Alzheimer's disease (AD) pathology at a young age (before age 40), although not all DS cases develop dementia. Therefore, the clinical heterogeneity of subjects with DS despite a similar neuropathologic phenotype provides a unique opportunity to study molecular and cellular mechanisms of accelerated ageing and neurodegeneration leading to dementia. Although animal models of DS have provided some insights into the neurobiology of DS³, they do not fully replicate the disorder. Tissue based neuropathology studies have provided a window into the pathobiology of DS but tissue for these studies is not readily available to the DS field. Moreover, most human tissue studies lack clinical data from the cases examined.

The groundbreaking technology of generating neurons from fibroblast-derived induced pluripotent stem cells (iPSCs) for the study of neurodegeneration is a major break-through in the neurodegenerative field. However, it has since been demonstrated that iPSC reprogramming reliably erases the cells' memory of their donors' age, leaving researchers with epigenetically rejuvenated cells, therefore limiting their use as a predictive model for late onset disease induced dysfunction as seen in DS. Recently, a technology termed induced neurons (iNeurons) allows for the generation of functional brain neurons without going through the reprogramming step, providing a unique state of the art disease model to investigate cellular and molecular events

associated with the onset of clinical dementia-causing neuronal dysfunction and cell death associated with DS.

Cortical neurons are selectively vulnerable in DS similar to AD. The proposed pilot project will provide preliminary data supporting the use of the iNeuron disease model to study DS pathogenesis and to validate disease phenotypes and aberrant genetic profiles of DS neurons compared to healthy control neurons. As part of a long-term investigation, we will collect transcriptome profiles from iNeurons from young, middle and older patients with DS. We will subdivide the older cases into those with and without dementia to test the hypothesis that phenotypic changes at the transcriptome level are relevant to the disease pathogenesis related to dementia. Transcriptional DS signatures will be compared to an independent set of cortical neurons generated from AD and mild cognitive impairment (MCI) subjects.

Preliminary results

Our preliminary data supported the differentiation of patient fibroblasts into neurons. Figure 1 A shows a phase contrast image of differentiated neurons displaying the typical neuronal morphology. We then stained these neurons with MAP2, which confirmed their neuronal phenotype. Finally, we double labeled neurons for pre and postsynaptic marker proteins to confirm the generation of synapses on these human differentiated iNeurons (Fig. 1C).

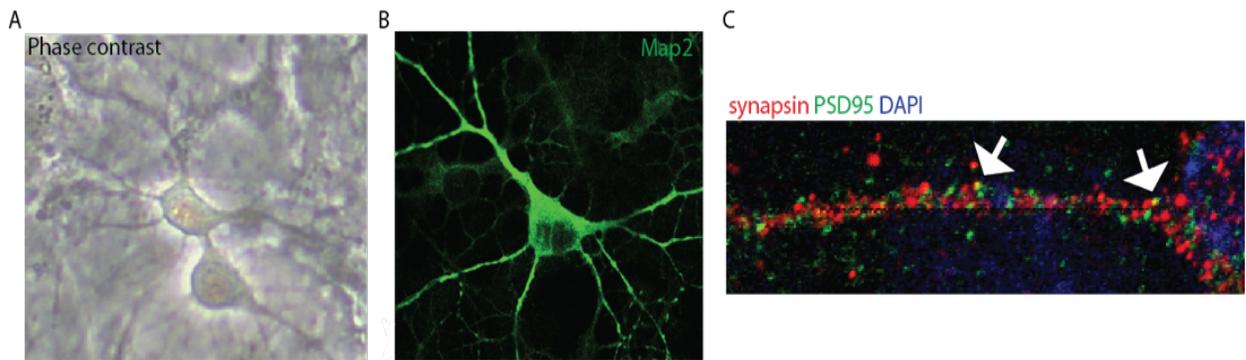


Figure 1. Characterization of iNeurons. Patient fibroblasts were induced and differentiated to iNeurons using published protocols. Typical neuronal morphology is obtained (A+B) and synapses (arrow) are formed as shown by co-localization of pre- and postsynaptic marker proteins synapsin (red) and PSD95 (green)(C).

Progress Report:

Specific Aim 1: While waiting to collect DS patient fibroblast with the help of Drs. Kruer (PCH) and Sabbagh (BAI), we purchased DS fibroblasts from the NIH coriel cell repository. DS cells and healthy control subject fibroblasts, were propagated and underwent direct neuronal differentiation.

To determine alterations in synapse formation, we DS and control neurons were immunostained for the presynaptic marker VGlut (vesicular glutamate transporter) or VGAT (vesicular GABA transporter) and the postsynaptic marker PSD-95. Quantitation of triple fluorescent immunostaining for pre- and postsynaptic markers revealed that DS iNeurons display significantly less synapses compared to healthy control iNeurons (Fig. 2 A-D).

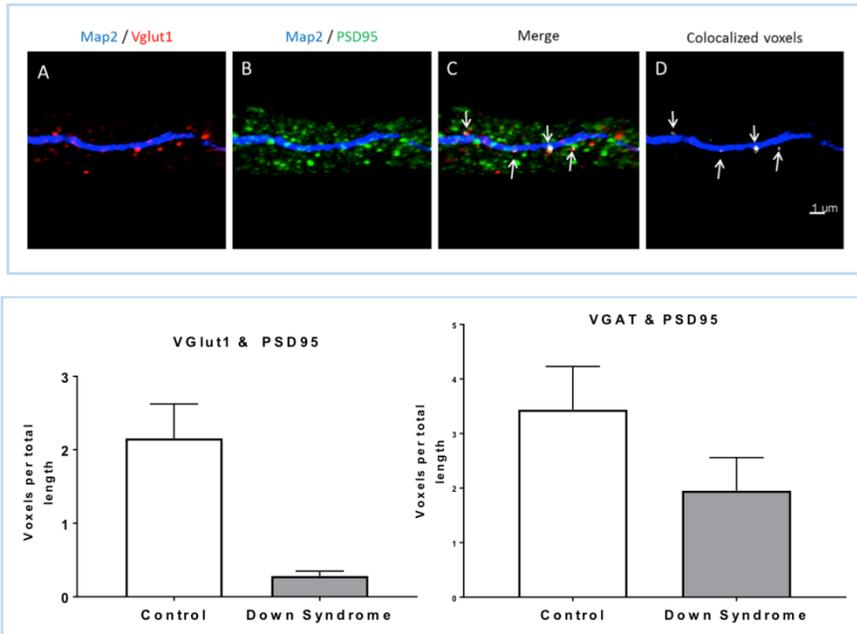


Figure 2. Decreased synapse numbers in DS iNeurons. A-D. Representative immunostaining of iNeurons with neuronal marker protein MAP2 (blue), presynaptic marker VGlut1 (red) and postsynaptic marker PSD-95 (green). Below are quantifications of the overlapping voxels between pre and postsynaptic marker proteins, indicating the DS iNeurons have a reduced number of synapses.

We also examined neuron dendritic arborization and branching using Sholl analysis. Preliminary studies found reduced dendritic branching at distal dendrites in DS iNeurons (Fig. 3).

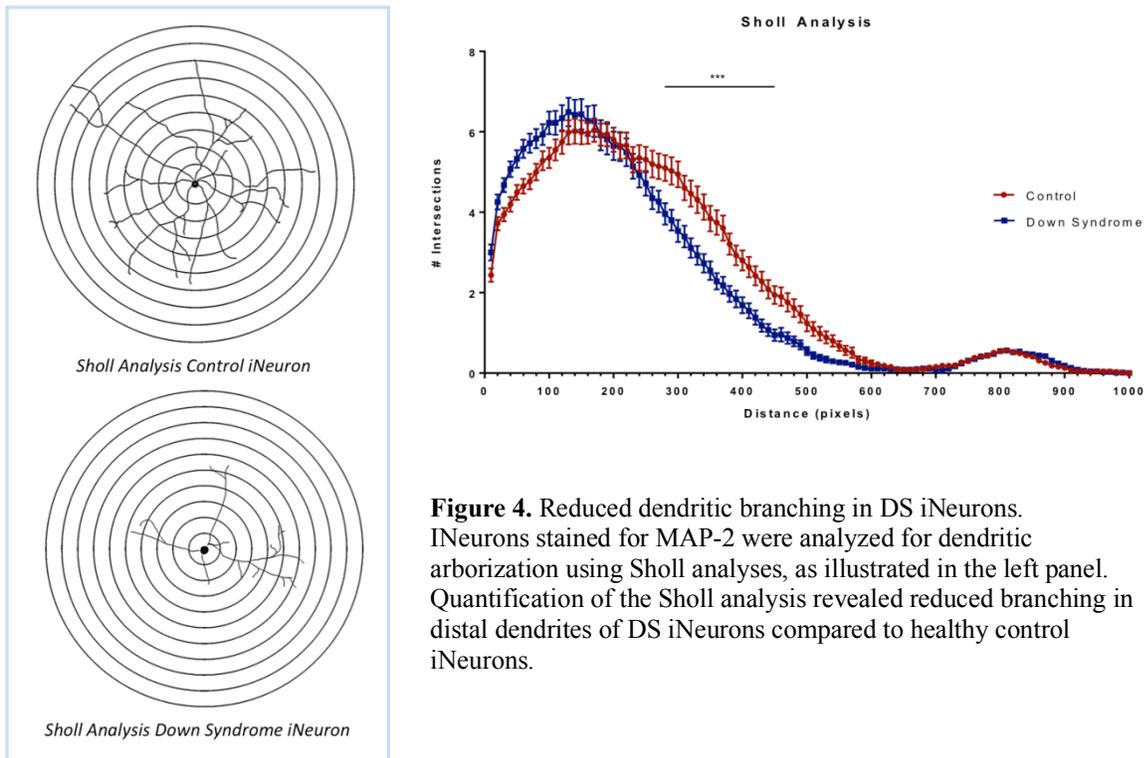


Figure 4. Reduced dendritic branching in DS iNeurons. iNeurons stained for MAP-2 were analyzed for dendritic arborization using Sholl analyses, as illustrated in the left panel. Quantification of the Sholl analysis revealed reduced branching in distal dendrites of DS iNeurons compared to healthy control iNeurons.

Specific Aim 2: While working on iNeuron generation, it became apparent that the yield of iNeurons is very low and inconsistent and might prevent the generation of sufficient numbers and reliable cells for RNA seq. To overcome this caveat, we changed our paradigm to iPSC-differentiated cortical neurons. We are currently collecting blood from patients with DS at Dr. Kruer's clinic at PCH to isolate peripheral blood mononuclear cells (PBMCs). We will reprogram PBMCs to iPSCs and differentiate them into cortical neurons for RNA seq analyses, as well as to repeat and validate our morphological analyses proposed in Aim1.

Future steps: We will repeat all of our morphological analyses using iPSC-derived cortical neurons. In addition, we will use those neurons to measure neuronal function via MEA analysis.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Evaluation of A β 42 in saliva as a low cost and non-invasive biomarker for early onset Alzheimer's disease. Marwan N. Sabbagh, MD, Jiong Shi, MD, PhD, Moonhee Lee, PhD, Lisa Arnold, BS, Yazan Al-Hasan, MD, PhD, Patrick McGeer, MD, PhD. Barrow Neurological Institute; Aurin Biotech; Arizona Alzheimer's Consortium.

Specific Aims: 1) To test-retest reliability – (Group 1- 5 NC, 5 AD) For 10 subjects, we want to take two samples to ensure the values are stable from sample to sample with low variance to test assay reliability. The hypothesis is that assay is stable, and the sample values will be within 10% of each other in duplicate. 2) Test two center assay validation – (Group 1 – 5 NC, 5 AD) We will aliquot one of the saliva samples collected into two aliquots and send one sample to the lab at BNI and the other to the lab at UBC. The hypothesis is that with the standardization of the assay, this will yield <10% variance in values between sites. 3) Measurement of values in MCI, PD, PDD, DLB, PPA, NPH (Group 2) to determine specificity. The hypothesis is that values differ by group and could establish specificity. 4) Correlation with amyloid positivity on PET – (Group 3) BNI has amyloid status on >90 patients with MCI and dementia. We will compare the salivary A β 42 values who are amyloid positive on PET to subjects who are negative. The hypothesis is that amyloid PET positive subjects will have higher values of salivary amyloid than amyloid negative subjects. 5) Assessment of age effects – (Group 4) In the NC cohort, we wish to determine the stability of salivary A β 42 levels in ages ranging from 40-90. The hypothesis is that salivary A β 42 does not increase with age in normal aging.

Background and Significance: Successful treatment of AD will ultimately depend upon early intervention. Biomarkers that can detect the disease before clinical signs appear are urgently required. To date, biomarkers that might detect AD in its early stages involve expensive and invasive procedures. These include CSF analyses of A-beta 42 (A β 42) and tau, and positron emission scanning for A β deposits using Pittsburgh compound B. A cheap, non-invasive indicator would be an extremely valuable asset for physicians, patients and their families. A β 42 levels in saliva show promise of being such a biomarker. Saliva can readily be obtained through a simple and non-invasive procedure. Bernajo-Pareja et al. (BMC Neurology, 2010 10108; <http://www.biomedcentral.com/1471-2377/10108>) have reported, after analyzing 126 saliva samples from AD cases and controls, as well as 51 Parkinson disease (PD) saliva samples, that A β 42 levels were significantly elevated in mild to moderate AD cases but not in severe AD cases. They found no difference between PD cases and controls. Average levels were in the range of 2.89-11.70 pg/ml of saliva. Proteins averaged 6.6 micrograms per ml of saliva. They also measured A β 40 levels in the saliva. These were in the range of 21-26 pg/ml of saliva but no differences were found between AD patients and controls.

Preliminary Data and Plan: Fifteen patients with mild to moderate AD were enrolled. All 15 met the AD criteria established by the National Institute on Aging and the Alzheimer's Association (NIA-AA). Inclusion criteria were Mini-Mental State Examination (MMSE) scores of 10-26 and age \geq 50 years. For comparison, 7 healthy patients with normal cognitive functioning were included as controls. The controls had no dementia or cognitive impairment

and no neurodegenerative disease; they were intact functionally, physically, and socially; were age ≥ 50 years; and had MMSE scores ≥ 28 . We excluded subjects with a medical history of major systemic diseases that could possibly affect cognitive function, such as cardiopulmonary failure, hepatic or renal failure, diabetes mellitus, head injury, stroke, or other neurodegenerative disease.

The mean age of the 15 AD patients (7 men and 8 women) was 77.8 ± 1.8 years, and the mean age of the 7 controls (2 men, 5 women) was 60.4 ± 4.7 years. The mean MMSE scores for the patients and controls were 19.0 ± 1.3 and 29.0 ± 0.4 , respectively. The AD patients were significantly older ($p < 0.01$) and more impaired per their MMSE scores ($p < 0.01$) than controls.

After saliva levels were stabilized and mixed with an anti-bacterial agent, we quantitated the $A\beta_{42}$ in a series of samples using ELISA-type assays (Aurin Biotech, Inc.). The $A\beta_{42}$ levels in saliva were found to be significantly higher in AD patients than in controls (51.7 ± 1.6 pg/mL for AD patients and 21.1 ± 0.3 pg/mL for controls, $p < 0.001$).

In our preliminary data, we report results of a simple, non-invasive test to potentially be used as an adjunct to diagnose Alzheimer's disease (AD). In that pilot study, we found the Salivary $A\beta_{42}$ levels were significantly different between AD and NC. A protocol amendment is currently pending IRB approval where we propose to develop the salivary test further with multiple validation studies including: test-retest reliability, two center assay validation, assessment of longitudinal variance, measurement of values in MCI, PD, DLB, PPA, NPH to determine specificity, correlation with amyloid positivity \pm on PET, assessment of age effects.

Proposed One-Year and Long-Term Outcomes:

4. Complete the specific aims.
5. Reproduce the pilot data and perform test validity.
6. Apply for an NIH Exploratory/Development Grant, R21.

Year End Progress Summary:

Aim 1: Manuscript of preliminary data results, as described above, has been submitted.

Aim 2: IRB application for additional samples to fill the groups in specific aims has been submitted, pending approval.

Aim 3: Supplies for assays for additional saliva sample collection and processing have been ordered.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Effects of aging on brain pituitary adenylate cyclase activating polypeptide, pathology and cognition. Jiong Shi, MD. Barrow Neurological Institute at St. Joseph's Hospital and Medical Center; Arizona Alzheimer's Consortium.

Collaborators: Mayo Clinic Arizona

Specific Aims:

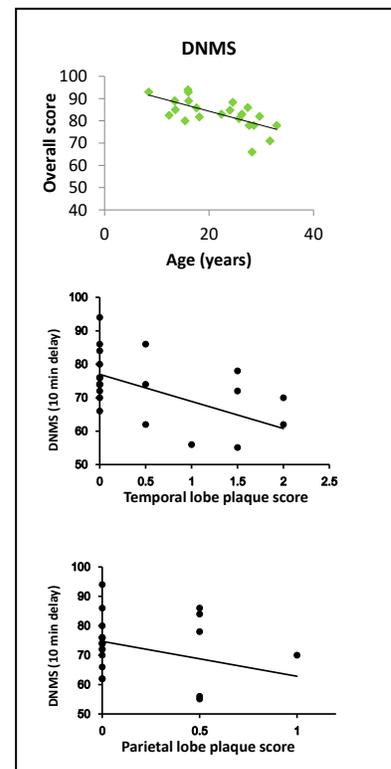
- 1) To characterize cognitive performance and PACAP protein in nonhuman primates ranging in age equivalent to human ages from 24 to 96 years.
- 2) To investigate cognitive performance, amyloid plaques, and PACAP protein in hAPP transgenic mice and compared to their wild type (WT) littermates that were in an age range equivalent to 40 to 80 human years, within the age range of onset of both familial and sporadic AD.
- 3) To compare these key AD features in the animal models during aging, and to compare them with that in human AD.

Background and Significance:

Alzheimer's disease (AD) is diagnosed by the presence of amyloid plaques, neurofibrillary tangles (NFT), and functional impairment in multiple cognitive domains. Our recent studies report a deficit in the levels of pituitary adenylate cyclase activating polypeptide (PACAP) in human AD brains, suggesting that intrinsic protective factors are involved in AD pathogenesis. The role of PACAP in cellular metabolic function is supported by observations that PACAP protects mitochondrial function in the presence of β -amyloid toxicity. Consistently, the reduction of PACAP in human AD correlates with both cognitive decline and severity of pathologic markers. However, the effects of aging alone on PACAP remain unclear.

Nonhuman primates are evolutionarily close to humans, and like other mammals, do not spontaneously show the full spectrum of neuropathological features characteristic of human Alzheimer's disease. On the other hand, macaques do show age-related memory deficits that are reminiscent of those observed in humans and rodents. Additionally, it has been reported that older monkeys can show diffuse amyloid plaques, but rarely show mature neurofibrillary tangles. Little is known about what impact these neuropathological markers might have on cognition in these animals.

A majority of transgenic animal models that are used to study AD involve the human amyloid precursor protein (hAPP) gene, which harbors one or more mutations found in familial AD. In the J20 mouse model, containing hAPP harboring multiple mutations, amyloid plaques typically appear



around 8-10 months of age. Pathologic and cognitive features are less explored in these mice during advanced age even though aging is the most paramount risk factor associated with AD. An understanding of what makes an aging brain more susceptible to such pathological conditions is critical for the design of preclinical studies that aim to prevent or delay disease progression.

Preliminary Data and Plan:

We tested DNMS performance at a long delay (10 min), and it progressively decreased with increasing age ($r = -0.670$, $P = 0.0003$, Figure 1A).

Plaques were evident in the temporal and inferior parietal lobes in most of the old rhesus monkeys. Of the areas analyzed, the temporal lobe had the highest plaque density. Furthermore, DNMS performance inversely correlated with both temporal and parietal lobe plaque density (Figure 1B: $r = -0.609$, $p = 0.002$; Figure 1C: $r = -0.547$, $p = 0.007$). Of note, only two (both aged 28 year old) showed amyloid plaques in the hippocampus. There was no evidence of neurofibrillary tangles in the brain.

Year End Progress Summary:

Aim 1: Cognitive performance in nonhuman primates decreases with age and shows an inverse correlation with plaque scores in the temporal and parietal lobes. This is consistent with the findings in human brain. Interestingly, PACAP levels increase from age 10-20 and then decrease from age 20-30, suggesting PACAP is critical in brain development and decompensates along with aging.

Aim 2: Wild type mice have an age dependent impairment in Morris water maze. APP mice have cognitive impairment at early age but they don't have age dependent decline. Similarly, PACAP is reduced in APP vs. WT, but doesn't show an age related reduction. This suggests hAPP genetic mutation overshadows the age factor and dictates the expression levels of PACAP.

Aim 3: This is still ongoing. We are going to determine whether a similar age-dependent PACAP decline exists in healthy human populations as is observed here in older rhesus macaques.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Longitudinal assessment of advanced multiparametric MRI biomarkers of Alzheimer's disease. Ashley M. Stokes, PhD, Leslie C. Baxter, PhD, Richard Caselli, MD, Marwan Sabbagh, MD. Barrow Neurological Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims: 1) Assess longitudinal changes in advanced MR imaging signatures that are phenotypical of each stage of AD, from no cognitive impairment to MCI to clinically diagnosed AD. While structural MRI is known to change with later disease progression, advanced MR imaging of perfusion (using arterial spin labeling (ASL)), cerebral microbleeds (using susceptibility-weighted imaging (SWI)), and molecular species (using chemical exchange saturation transfer (CEST)) might provide specific signatures of disease progression. We hypothesize that the corresponding vascular or molecular changes could be an early indicator of incipient MCI or AD, prior to morphological changes.

Background and Significance: The proposed research aims to establish the longitudinal trajectory of multi-parametric imaging signatures, which might permit identification of patients likely to benefit from early AD prevention trials. The data will also shed new insights into the underlying molecular and functional changes that occur in the earliest phases of AD. MRI is ideal for longitudinal studies, and combining structural MRI biomarkers (e.g., brain atrophy metrics) with more advanced MRI biomarkers could provide a more comprehensive understanding of the neuropathological changes that occur decades prior to a clinical AD diagnosis. Functional and molecular changes precede morphological changes and might be detectable in the earlier MCI phases, when intervention would prove most beneficial. The proposed set of MRI biomarkers provide unique and complementary functional information that reflects the underlying AD pathology, where each method was chosen for its sensitivity to a known abnormality related to AD. We previously received funding through the BNI / AARC pilot program to establish advanced MR imaging signatures in these groups for a single time-point; here, we are proposing to expand that study to include a longitudinal assessment in the same subjects. This longitudinal study will establish the biological trajectory of each imaging metric, while also increasing both reliability and statistical power. The asymptomatic and MCI phases represent a clear potential for early intervention, and the non-invasive methods developed here will permit identification of patients along the clinical trajectory of AD, and thus those most likely to benefit from earlier intervention.

Preliminary Data and Plan: Leveraging our previous AARC award (7/1/2016-6/31/2017), we have acquired multi-parametric data in 35 subjects (12 normal controls, 11 MCI, and 12 AD) at the baseline time-points. These subjects were recruited from the BNI neurology clinic (Marwan Sabbagh, Co-Inv), from the subject database in the BNI Human Brain Mapping Laboratory (Leslie Baxter, Co-Inv), and from the Alzheimer's Disease Core Center (ADCC) database (Richard Caselli, Mayo Clinic). 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.

As in the prior study, all previously recruited subjects will undergo cognitive testing using the Montreal Cognitive Assessment (MoCA) and functional assessment staging (FAST), followed by an advanced 1-hr MRI. 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 and advanced MRI will be acquired, and morphometric features will be quantified using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>). Longitudinal analysis will be performed on a per-subject basis. Previously recruited subjects that opt out of the follow-up scan will be replaced by newly recruited subjects, which will permit cross-sectional analysis of baseline data across both years of funding.

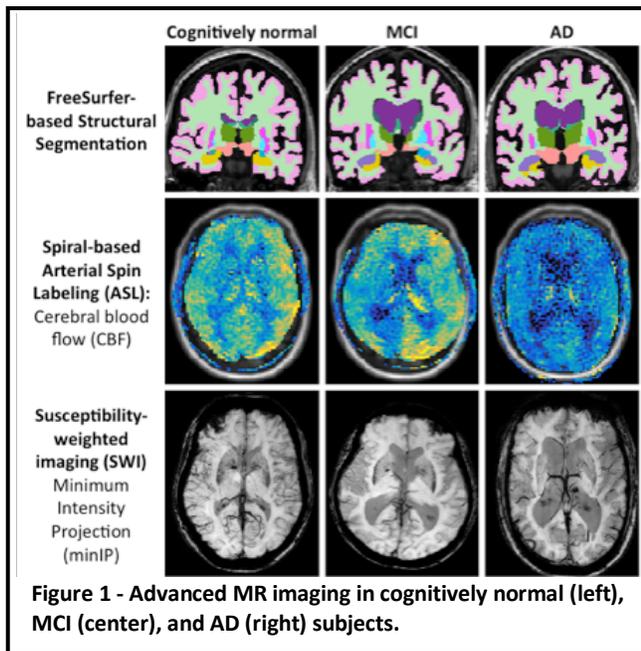


Figure 1 - Advanced MR imaging in cognitively normal (left), MCI (center), and AD (right) subjects.

Proposed One-Year and Long-Term Outcomes:

The prior year of funding has laid the foundation for this longitudinal study by establishing a baseline set of imaging phenotypes of AD progression. We anticipate publication of these initial results using a cross-sectional analysis, to be followed by the longitudinal results of the present study. The data obtained through this second year of funding will be used for a larger grant application through the National Institute on Aging (NIH/NIA). In particular, we will propose extending and continuing this longitudinal study to characterize the timeline of AD progression.

Year End Progress Summary (through March 1, 2018):

Aim 1: We have acquired longitudinal MRI data acquisition in 9 subjects thus far (of 11 possible subjects), along with cognitive testing using MoCA, clock draw, and FAST. The MRI data include high-resolution structural images, CEST, ASL, DWI, and SWI. The longitudinal post-processing stream has been initialized, and both cross-sectional and longitudinal data analysis are ongoing. This has allowed us to identify several regions-of-interest and to quantify longitudinal changes in our advanced functional biomarkers for blood flow and volume, molecular species, and iron deposition. 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. We have been invited to present these data as an oral presentation at the International Society for Magnetic Resonance in Medicine annual conference in Paris, France in June 2018. We are in the process of performing statistical analysis of our cross-sectional data, in preparation for publication.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Impact of $\alpha 7$ nAChRs in the hyper-synchronization of in mouse hippocampal slices. Jie Wu, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Collaborators:

Barrow Neurological Institute: Jiong Shi, MD
Arizona State University: Yunze Yang, PhD

Specific Aims: To evaluate role of $\alpha 7$ -nAChRs in hippocampal network hyper-synchronization in of APP mice

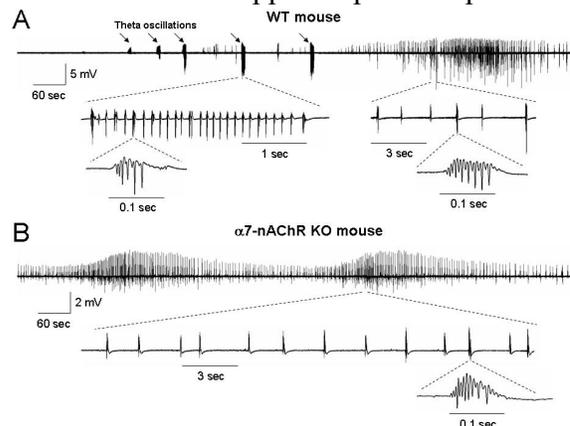
Rationale: Accumulating evidences suggest that in both AD animal models and AD patents (1) neural hyper-excitation and hyper-synchronization occur but underlying mechanisms are unknown; (2) $A\beta$ interacts on $\alpha 7$ -nAChRs, and $\alpha 7$ -nAChR expression level (mRNA and proteins) is significantly enhanced. We reason that $\alpha 7$ -nAChR is an important target to mediate $A\beta$ -induced hyper-synchronization in AD models.

Background and Significance: In Alzheimer's disease (AD) patients, the incidence of epilepsy is significantly higher than that in age-matched, non-AD controls. Epilepsy is an important phenotype of AD, and $A\beta$ accumulation induces aberrant neuronal hyper-excitation could be a primary upstream mechanism leading to cognitive deficits both in humans and animal models. However, the genic mechanisms of the neural hyper-excitation in AD are largely unknown. Recently, we demonstrate that $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ -nAChRs) play an important role in mediated chronic $A\beta$ exposure-induced neural hyper-excitation in primary hippocampal cultured neurons. In this pilot proposal, we will extend our study to evaluate the roles of $\alpha 7$ -nAChRs in hippocampal neural-network hyper-synchronization using hippocampal slices. We will test a novel central hypothesis that **$\alpha 7$ -nAChR is an important target for neural hyper-synchronization and neuro-pathogenesis in AD models.**

Preliminary Data and Plan:

1) Comparison of CCh-induced ictal and interictal events WT and $\alpha 7$ KO mice

Field potential recordings were performed in the CA1 cell layer using a glass electrode filled with 2M NaCl. During recordings, the recording chamber was set to 33°C. Hippocampal field potential ictal and interictal oscillations were induced by bath application of 50 μ M carbachol (CCh) for 10-20 min, as previously described. As shown in Fig. 1, in the continuous presence of 50 μ M CCh, there were typically three types of oscillations, slow (delta: 0.5 ± 0.06 Hz, n=18), theta (6.3 ± 0.46 Hz, n=23) and super-fast (146.1 ± 7.0 Hz, n=19) oscillations in WT hippocampal slices (Fig. 1A). However, in $\alpha 7$ -nAChR KO hippocampal slices, the same CCh only induced two types of oscillations, slow (delta: 0.6 ± 0.15 Hz, n=10) and super-fast (153.7 ± 7.2 Hz, n=7)



oscillations (Fig. 1B). while the typical theta band ictal events were lack. The statistical analysis showed that the difference in frequencies of slow or super-fast oscillations between WT and $\alpha 7$ -nAChR KO mice was not significant ($p > 0.05$, T-test). These results suggest a lack of theta-band ictal oscillations in $\alpha 7$ -nAChR KO slices.

Fig. 1 CCh-induced field potential oscillations in hippocampal slices prepared from wild-type (WT) and $\alpha 7$ -nAChR KO mice. A: A typical trace of 50 μM CCh-induced field oscillations in a WT slice. 50 μM CCh was continuously present during recording. The theta-band ictal events are indicated by arrows. Insets show the expanded time scale for ictal (theta) and interictal (slow oscillations). Further expanded time scale shows the high-frequency oscillations of each interictal event. B: A representative trace of CCh-induced field oscillations in a $\alpha 7$ -nAChR KO slice. 50 μM CCh was continuously present during recording. Expanded time scale shows only slow oscillatory (interictal) events. Further expanded time scales show high-frequency oscillations of each interictal.

2) Comparison of CCh-induced ictal events between WT and 3xTgAD mice

CCh (50 μM)-induced field potential oscillations of interictal and ictal were recorded and compared in 5-month-old WT and 3xTgAD mice, respectively. Results showed that 3xTgAD mice exhibited stronger ictal events than WT mice, suggesting that in AD mice there is neural network hyper-synchronization.

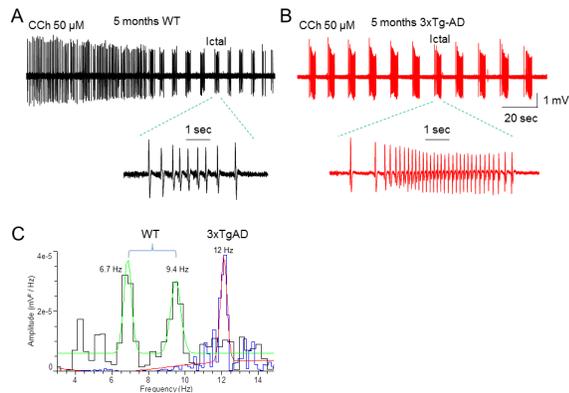


Fig. 2 CCh-induced ictal and interictal events in hippocampal slices from WT and 3xTgAD mice. The typical CCh-induced field potential oscillations (ictal and interictal events) were recorded from WT (A) and 3xTgAD (B) mice. Inset: the expanded time scale of ictal events. C: Further power spectrum analysis (Clampfit 10.6) showed that the hippocampal slices from 3xTgAD mice (red fitting curve) show stronger ictal synchronization than that from WT mice.

Effects of acute $\text{A}\beta_{1-42}$ (10 nM) on CCh-induced ictal events between WT and 3xTgAD mice

In these experiments, we examined the effects of acute perfusion of $\text{A}\beta_{1-42}$ (oligomer, 10 nM and co-application with 50 μM CCh) on ictal events in the hippocampal slices prepared from WT and 3xTgAD mice. Figure A and B showed a period of 70 sec recordings in the presence of 50 μM CCh and demonstrated 4 ictal-like events in either WT (A) or 3xTgAD (B) mice. Expanded time scale showed a low gamma-band (21 Hz) oscillations and a high-frequency (160 Hz) oscillations in WT hippocampal slices (A,C), while in 3xTgAD mouse hippocampal slices, the ictal-like events are consistent of a long-lasting high frequency oscillations. Power spectrum analysis showed that the co-applications of $\text{A}\beta_{1-42}$ and 50 μM CCh induced much stronger ictal-like events, suggesting that 3TgAD mice exhibit stronger network synchronization.

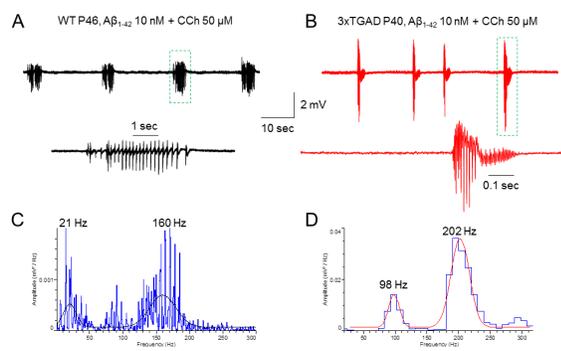


Fig. 3 Effects of acute $A\beta_{1-42}$ on CCh-induced field potential oscillations in hippocampal slices prepared from WT and 3xTgAD mice. Field potential recordings for 70 sec periods showed the ictal events in WT (A) and 3xTgAD (B) mice. WT slice showed longer event duration (A inset), while 3xTgAD slice showed more stronger amplitude power (B inset), suggesting a high degree of network synchronization. Power spectrum analysis demonstrated that WT slice exhibited two frequency peak, around 20 Hz and 160

Hz (C), while 3xTgAD slice exhibit higher frequency peak, around 100 Hz and 200 Hz.

3) Comparison of electrical stimulation-evoked gamma oscillations between WT and $\alpha 7$ KO mice

We have compared the acute electrical stimulation (100 Hz for 200 ms with maximal stimulus intensity)-evoked gamma-band field potential oscillations in the hippocampal slices from WT (Fig. 4A) and $\alpha 7$ KO (Fig. 4B) mice. In WT slice, a power spectrum analysis showed a predominant frequency peak at 73 Hz (high gamma), while in $\alpha 7$ KO slice, spectrum analysis showed two frequency peaks at 37 Hz (A inset) and at 52 Hz. (B inset), respectively. $\alpha 7$ KO slice demonstrated a remarkable weak of oscillation frequency power (around 0.002 mV^2/Hz) compared to WT slice (around 0.03 mV^2/Hz), suggesting the genetic deletion of $\alpha 7$ KO impairs hippocampal neural network synchronization. In addition, we compared the frequency-dependent feature of evoked synaptic potential (given maximal single stimulus intensity) between the hippocampal slices prepared from WT (Fig. 4C) and $\alpha 7$ KO (Fig. 4D). Unexpectedly, we found that the deletion of $\alpha 7$ nAChRs reduced the ability of hippocampal synaptic ability to follow high frequency (100 Hz) stimulation compared to WT slices. Figure 4E fitting the stimulation number-dependent reduction of evoked synaptic potential (fEPSPs) using a single exponential fitting program (Prism 5.0) and found that the $\alpha 7$ KO slices exhibited faster decline of evoked fEPSPs (Fig. 4D and E) compared to WT slices (Fig. 4C and E). These results demonstrate that the $\alpha 7$ KO slices show the weaker network synchronization, suggesting that $\alpha 7$ nAChRs might play an important role in participate in the formation of hippocampal gamma oscillations.

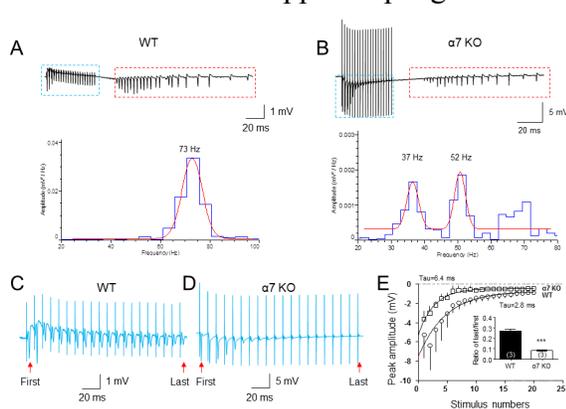


Fig. 4 Comparison of high frequency (100 Hz for 200 ms) stimulation-induced gamma oscillations in hippocampal slices prepared from WT and $\alpha 7$ KO mice. Typical traces of electrical evoked gamma oscillations in hippocampal slices prepared from WT (A) and $\alpha 7$ KO (B) mice. Spectrum analysis showed the reduced oscillatory frequency and amplitude power occurred in $\alpha 7$ KO (B, in set) mice. During high frequency stimulation (100 Hz, 200 ms), the evoked fEPSPs were not well followed the stimulation frequency compared to WT mice (C-E). E inset: Bar graph compares the ratio of last/first of

fEPSPs and showed a significant reduction in $\alpha 7$ KO mice.

Proposed One-Year Outcomes:

1. Continue to work on proposal to test acute and chronic AB on hippocampal synchronization and evaluate the effects of $\alpha 7$ nAChR antagonists on seizure activity in hippocampal slices.
2. Developing this proposal to form a NIH (e.g., R21) proposal for submission.
3. Complete a research paper to report our exciting findings in this project.

Project Progress Report

Critical Path Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Update of a regulatory-endorsed clinical trial simulator for Alzheimer's disease: new data incorporation, statistical modifications, and user-friendly graphical user interface development. Jackson Burton, Daniela Conrado, Stephen Arnerić, Roberta Diaz Brinton, Klaus Romero, and the CPAD Modeling and Simulation Team. Critical Path for Alzheimer's Disease (CPAD) [previously: Coalition Against Major Diseases (CAMD)], Critical Path Institute; University of Arizona; Pfizer; Merck; Novartis; Lilly; Arizona Alzheimer's Consortium.

Specific Aims: 1) Use contemporary patient-level data of mild-to-moderate Alzheimer disease (AD) from the Critical Path for Alzheimer's Disease (CPAD) database containing APOE-ε4 allele counts and concomitant medication use and patient-level data in the Alzheimer's Disease Neuroimaging Initiative (ADNI) to develop an analysis subset, i.e., a subset taken from the totality of variables collected in the different studies, used for formal analysis; 2) Utilize the analysis subset to update the statistical framework of an existing regulatory-endorsed clinical trial simulator (CTS) for mild-to-moderate AD; and 3) Develop a graphical user interface (GUI) for the updated CTS.

Background and Significance: Evaluation of the efficacy of potential medical products for the treatment of AD depends strongly on efficient clinical trial design. Designing such trials requires a thorough understanding of the underlying natural disease progression to allow optimized patient enrollment for an efficient evaluation of new drug candidates. CPAD, a consortium led by the Critical Path Institute (C-Path) in partnership with several industry and academic members, have integrated and standardized a database of patient-level data for AD. Additionally, the ADNI study, which contains patient-level data of individuals with different stages of AD, as well as normal controls, was utilized as a key dataset to quantify the natural disease progression of AD. Leveraging the power of the integrated patient-level data, in 2013, C-Path completed the development of the first regulatory-endorsed clinical trial simulator (CTS) for mild-to-moderate AD. This CTS was endorsed under the Fit-For-Purpose initiative within the FDA, a program designed to provide a pathway for regulatory acceptance of dynamic tools for use in drug development programs. In parallel, this tool was also endorsed with EMA through the Qualification of Novel Methodologies pathway. The purpose of the CTS is to address challenges associated with patient enrollment and evaluation of clinical outcome assessments through statistical analysis and simulation. In the past years, the CPAD database, as well as the ADNI study have expanded to include additional patient-level data. The expansion reflects the evolving nature of AD drug development. In particular, with added granularity on APOE-ε4 allele counts and concomitant medication use, further validation of the CTS tool, based on the expanded dataset can be performed, to expand the knowledge base of their effects on disease progression [1]. These additional data prompt an update to the CTS that utilizes the new information to provide key additional insights in the progression of AD and aid in the new treatment paradigms.

Data management: The success of developing the CTS was heavily due to the application of therapeutic area standards for AD, developed by CPAD, in partnership with the Clinical Data Interchange Standards Consortium (CDISC) to the diverse data sets integrated for this effort. Under these standards, data in their original form from the different contributors undergoes a remapping phase to the CDISC standards. Afterwards, judicious quality checks are performed on the data, and corrections are made through collaborative interactions with the contributors. An

updated version of the CDISC standards for therapeutic areas of AD has been developed since the endorsement of the CTS tool by FDA and EMA [2]. Such standards will need to be applied to the current ADNI and CPAD databases. Updating the databases with the new standards is critical for an updated statistical analysis.

Clinical Trial Simulator: The CTS is a quantitative tool that has two components: 1) The statistical model that analyzes the data, and 2) The simulation component that produces theoretical patient-level data, based on the statistical estimates of the first component, and uses it to analyze clinical trial scenarios. Within the statistical model, which is formulated as a nonlinear mixed effects model, AD progression is described as a combination of three components: 1) natural progression, 2) placebo effect, and 3) drug effects. The utility of the model lies in its ability to measure the significance of several covariates, i.e., potential explanatory variables, which here include baseline age, baseline severity, sex, number of APOE- ϵ 4 alleles, and concomitant medication use. The model quantifies the variability associated with each covariate on overall AD progression, providing users with the ability to inform decision-making for clinical trial design and assessment. For example, the CTS could be used for analyzing new treatment data to differentiate the efficacy of a drug candidate from the placebo effect and natural progression. In order to increase the usability of the CTS, the development of a GUI to increase user accessibility without the need training in the R statistical programming language is performed. Such a GUI will provide all members of clinical development teams and AD researchers direct access to the capabilities of the CTS without the need for training in the R statistical programming language. It will also provide the groundwork for developing an analogous tool for preventative trials conducted in the pre-symptomatic stages of AD. As the next step in achieving this goal, CPAD is currently developing a tool for mild-cognitive-impairment using the CDR sum of boxes as an endpoint.

Preliminary Data:

Table 1: Details of the data added to the CTS tool.

Co-Variates	Original CTS Tool	Updated CTS Tool	% Increases
Individuals	3255	4575	40.6
% Females	55.1	55.4	0.3
Years since diagnosis	2.07	2.46	18.8
Individuals with APOE- ϵ 4 status	1486	1895	27.5
Individuals on stable medication	2483	3271	31.7

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:

The one-year-outcome will be increasing the statistical framework of the CTS, and the development of a fully-functioning GUI to facilitate the use of this drug development tool for all AD clinical trialists.

There are several long-term outcomes for this project: 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 statistical framework of the CTS to include studies on mild cognitive impairment aimed at earlier disease intervention, with the goal of regulatory endorsement; and 3) Increase accessibility to the CTS through refinements to the GUI platform as well as providing training materials for clinicians and other healthcare professionals involved in clinical trials.

Year End Progress Summary:

Aim 1: An analysis subset was developed from the ADNI database which contained all variables previously included in the CPAD analysis subset that was used for the original CTS tool. Criteria were established to include only mild-to-moderate individuals from the ADNI dataset based on MMSE scores and CDR sum of box scores at baseline. Rules to determine concomitant AD medication use were developed to derive binary status of stable background medication. Number of APOE- ϵ 4 alleles were calculated and included. The completed analysis subset was merged with the CPAD database and a thorough curation process was performed. Observations with missing values and less than two observations were removed entirely.

Aim 2: The combined (CPAD and ADNI) dataset was utilized for statistical analysis with the aim of updating the previously developed CTS tool. Several considerations regarding the original CTS model structure were taken into account prior to the start of the work. The interpretability of the parameters and the assumptions of the original model prompted a decision to use a new base model, namely a logistic regression model. While it is similar to the original model, it addresses some of the limitations of the previously used model. The model uses generalized logistic function which is more versatile in describing nonlinear progression. Similar to the previous model, it uses beta-distributed residuals that allows for predictions of scores within the bounds of the ADAScog scale. Additionally, baseline severity is intrinsically accounted for in the model since rate depends on the score at each time point. The subsequent model building process took place as follows: The model was fitted to the ADNI dataset only to derive parameter estimates for natural disease progression in the absence of any placebo effects. These parameters were then utilized as prior information in a Bayesian framework to estimate the placebo effect within the clinical trial data of the CPAD data. The mean trajectories by studies in the CPAD database are shown in **Figure 1**, indicating an early placebo response. A series of diagnostic and optimization procedures were

performed to address model convergence issues and decrease the run time of parameter estimation. Parameter estimates were achieved to account for the placebo effect. Covariates (baseline age, sex, number of APOE- ϵ 4 alleles, and concomitant medication use) were then included one at a time, and their effect measured, to ensure that their corresponding effect was significant. Estimation is ongoing to ensure proper fitting of parameters. Visual predictive checks were used as a model diagnostic (**Figure 2**).

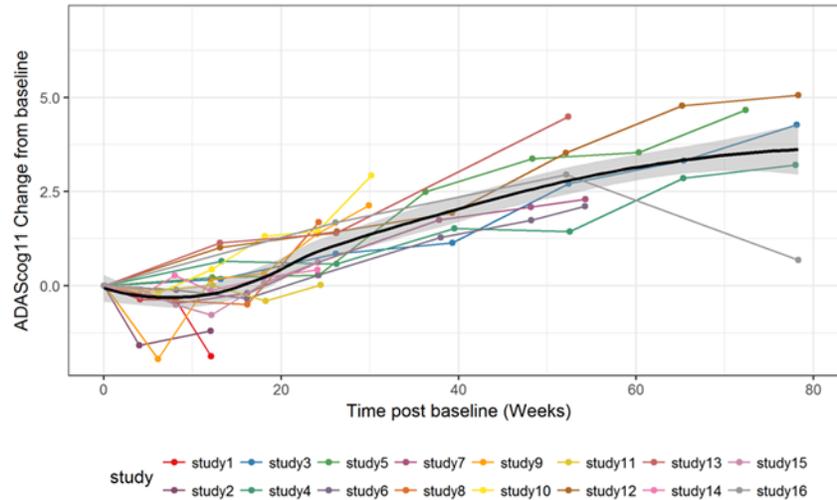


Figure 1: Mean trajectories over time of studies in the CPAD database (studies 1-15) and the ADNI study (study 16). Black solid line is the loess line.

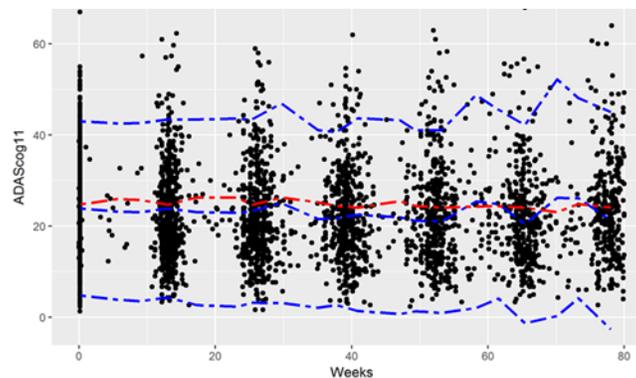


Figure 2: Visual predictive check. Blue lines represent 95% confidence intervals for virtual patient populations generated from parameter estimates. Red line is the mean of the observed data. Study 4 is shown for reference.

Aim 3: In parallel with Aim 2, work was initiated for the development of a graphical user interface (GUI) for the updated CTS tool. The *R-Shiny* package, part of the statistical programming language *R*, was chosen to develop the GUI since it is open source and widely known to the community as a high functioning platform. The layout of the user interface is in strategic development aimed at being accessible and user friendly for a non-technical audience.

Project Progress Report

Mayo Clinic Arizona

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 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.

Collaborators: This project also provides core resources to the Consortium and other studies. Data and over the years biospecimens have been provided to Sierks (ASU), Shi (BNI), Baxter (BNI), Reiman (BAI), Wang (ASU), Geda (Mayo Clinic Arizona), Taner (Mayo Clinic Florida), Rademakers (Mayo Clinic Florida), Huentelman (TGen), Grecus (Stanford), Nielsen (Stockholm University), and Knopman (Mayo Clinic Rochester).

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

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 including 451 APOE e4 noncarriers, 240 e4 heterozygotes, and 97 e4 homozygotes. Of these, 609 have completed two or more epochs of testing, with follow-up 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).

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

Year End Progress Summary:

We have completed our 2017-2018 goals:

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).

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Predicting cognitive decline in cognitively unimpaired individuals. Cynthia M. Stonnington, MD, Kewei Chen, PhD, Eric M. Reiman, MD. Mayo Clinic Arizona; Banner Alzheimer's Institute; 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 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 but are still cognitively unimpaired.
2. 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.
3. To preprocess MRI scans using cortical thickness, i.e., Freesurfer, and grey matter volume, i.e., SPM, methods. Compare region of interest and whole brain differences between decliners and nondecliners for each of the methods.
4. 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.

Preliminary Data:

1. 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.
2. 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.

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.

We will first 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.

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.

Budget Justification:

Principal Investigator (6% Salary and Benefits). Cynthia Stonnington, MD Associate professor of Psychiatry will oversee all aspects of this study including procurement of scans, image analysis, coordination of data acquisition and analysis from the APOE cohort with Dr. Caselli, preparation of presentations, manuscripts, and progress reports, and compliance with all institutional and ethical guidelines.

Other budgetary items overlap with the project, Normal and Pathological Aging.

Progress report:

1. We have completed specific aim #1 and #2 as noted above in preliminary data section. We continue to track and update groups regarding diagnosis of MCI.
2. For aim #3, we worked with Yalin Wang at ASU to develop a method that we can then apply to the APOE cohort for the purpose of specific aim #4. This uses a fine-grained surface analysis, which revealed significant differences in the ventricular regions close to the temporal lobe and posterior cingulate for MCI patients who later converted to AD. This method achieved good correlation with neuropsychological tests and FDG-PET.
 - a. Shi J, Stonnington CM, Thompson PM, Chen K, Gutman B, Reschke C, Baxter LC, Reiman EM, Caselli RJ, Wang Y, Alzheimer's Disease Neuroimaging Initiative. Studying ventricular abnormalities in mild cognitive impairment with hyperbolic Ricci flow and tensor-based morphometry. *Neuroimage*. 2015 Jan 1; 104:1-20. Epub 2014 Oct 05. PMID:25285374. PMCID:4252650. DOI:10.1016/j.neuroimage.2014.09.062.

- b. Using a novel ventricular segmentation algorithm. Professor Wang's lab studied the morphometry on hippocampus and lateral ventricle between stable control and declining control groups using our APOE cohort comparing 18 cognitively unimpaired (CU) subjects approximately 2 years (1.84 ± 0.77) before development of aMCI and 35 age and sex matched participants who remained CU for ≥ 4 years. We also compared another, APOE4 matched group of 20 participants who remained CU for ≥ 4 years. The findings on the hippocampus and lateral ventricles were consistent and showed that hippocampal and ventricular morphometry has significant potential as an imaging biomarker of preclinical AD
3. For aim #3 and #4, we examined the FDG PET and MRI data from the same 18 cognitively unimpaired (CU) subjects approximately 2 years (1.84 ± 0.77) before development of aMCI and 35 age and sex matched participants who remained CU for ≥ 4 years, as well as 20 APOE4 matched CU participants. FDG-PET and MRI regions of interest were used separately and in combination to examine the sensitivity and specificity in distinguishing the two groups using binary logistic regression technique, receiver operating curve and leave-one-out approach. Compared to non-progressors and regardless of APOE-matching, progressors had significantly reduced baseline MRI and PET measurements in brain regions preferentially affected by AD, and reduced hippocampal volume was the strongest predictor of an individual's imminent progression to the clinically significant memory decline stages of AD (79% sensitivity/78% specificity among APOE-matched cohorts). The results from this study are currently under review at Journal of Alzheimer's Disease
4. Professor Wang's group has recently also developed a patch-based sparse coding method to classify different stages of AD on hippocampal morphometry. The prediction result of progression to aMCI/AD was achieved with hippocampal surface MMS features with 100% accuracy, 100% sensitivity, 100% specificity, 100% positive and 100% negative predictive values for the APOE4 matched Arizona cohort. Using the same methods on data drawn from ADNI (18 progressors and 34 nonprogressors), the prediction result of progression to aMCI/AD was achieved with hippocampal surface MMS features, with 90% accuracy, 84% sensitivity, 94% specificity, 89% positive and 91% negative predictive values. We presented these results at AAIC in London, 2017 and are in the process of completing the manuscript for publication.
5. In order to test the generalizability of the patched-based sparse coding method to classify imminent clinically significant cognitive decline, we combined the data from our APOE cohort with the ADNI data, which is drawn from a different demographic. In the combined groups of 36 progressors and 54 nonprogressors, we achieved 93% accuracy with 90% sensitivity, 100% specificity, 100% positive and 80% negative predictive values. We will include these data in our manuscript. We now plan to use this method toward developing a tool that clinicians can use to predict clinically significant decline using MRI.

Project Progress Report
Midwestern University

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Investigating the differences between ape and human GFAP proteins involved in neurodegeneration. Nancy S. Bae, PhD, and Mark J. Swanson, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Collaborators:

Midwestern: Jason Artigas, Nivritti Kumaran, Alice Chow

Specific Aims: 1a) Determine whether the interaction between the telomeric protein RAP1 and the GFAP protein isoform δ is competitive or cooperative with the Alzheimer's Disease associated protein, presenilin 1 (PS1). 1b) Determine if there is a difference between these interactions when the ape isoform is used in place of the human GFAP δ . 2) Determine the effects of variants of GFAP δ and mutations in PS1 on the RAP1-PS1-GFAP δ association.

Background and Significance: Mutations in the genes coding for amyloid precursor protein (APP) and presenilins (PS1 and PS2) are frequently seen in familial AD. APP is cleaved by various secretases to form A β proteins. A β -40 and A β -42 proteins are products of A β precursor protein digestion by γ -secretase, the catalytic subunit of which is the PS1 protein. When the ratio of A β -40:42 favors the more soluble A β -40, the brain functions without AD-related pathology. Higher levels of A β -42 promote self-aggregation, resulting in the formation of senile plaques. Accumulation of A β -42 can be prompted by mutations in the gene encoding PS1 that cause it to preferentially produce the neurotoxic A β -42 over the innocuous A β -40.

Glial Fibrillary Acidic Protein (GFAP) is an intermediate filament protein predominantly expressed by astrocytes in the brain. Studies have implicated GFAP involvement in the injury response and protection of the brain, maintenance of the integrity of the blood brain barrier, myelination, synaptic plasticity and a host of other processes. Increased levels of GFAP are the most frequently noted change in astrocytes with aging, and the concentration of GFAP is inversely proportional to cognitive function. An increase in the GFAP protein will also lead to senescence in astrocytes, which plays a key role in the chronic inflammation associated with AD. Astrocytes preferentially express different isoforms of the GFAP protein in different areas of the nervous system. The GFAP δ isoform is expressed by neurogenic astrocytes in the sub-ventricular zone. GFAP δ contains a unique carboxy-terminus that specifically allows interaction with PS1.

The attrition of telomeric sequences with each round of cellular division is a form of cellular aging. When cells are not actively replicating, the shelterin protein complex protects telomeres from damage and degradation. The RAP1 subunit of this complex protects telomeres from illegitimate recombination. Our lab has recently discovered that RAP1 interacts with GFAP δ . We aim to determine the effect of RAP1 on the GFAP δ -PS1 complex.

Similar to humans, chimpanzees and other great apes build up amyloid plaques as part of the natural aging process. However, signs of aging in a 40-year-old chimp brain are relatively limited compared to the human equivalent of 80-90 years old. Comparing the sequences of RAP1, GFAP δ ,

and PS1 between humans and apes shows that there are few sequence differences. In the region of PS1 that interacts with GFAP δ , apes and humans are invariant. The RAP1 protein is conserved except for a single amino acid change at position 130, which is histidine in humans and leucine in apes. For GFAP δ , humans and great apes differ in the single amino acid residue at position 426. While the ape protein contains an invariable alanine residue, the human protein is polymorphic having a threonine 70% of the time, valine 21% of the time and alanine 9% of the time.

We propose that the interactions among RAP1, GFAP δ , and PS1 modulate the accumulation of amyloid deposits, a characteristic of a human AD brain. Upon comparing the protein sequences of GFAP δ proteins, human GFAP δ exhibits a polymorphism in one specific residue while ape sequences do not. This residue might play a protective role in apes, safeguarding them from neurodegeneration. We will explore the interactions among these proteins in greater depth, comparing the interactions between human and ape forms of the RAP1 and GFAP δ proteins. In addition, we will investigate the effects of AD-associated PS1 mutations on these interactions. Eventually, we hope to understand the molecular mechanism that might trigger the onset of AD, and use this knowledge to develop preventative drugs that can do more than delay clinical signs of AD.

Preliminary Data and Plan: Previously, we showed using primary neonatal human dermal fibroblasts that the natural shortening of telomeres correlated with a marked decrease in the abundance of the shelterin subunits, except for RAP1. We observed that RAP1 was not only found in the nucleus but also in the cytoplasm. The fact that older cells still maintained RAP1 in the cytoplasm even with greatly reduced telomeres indicates that RAP1 plays a role independent of its function at telomeres. When these cells were stressed by reactive oxygen species, more RAP1 was seen in the cytoplasm, showing that the telomere protein RAP1 responds to oxidative stress in cells by translocating to the cytoplasm to perform an additional function. To determine an additional, cytoplasmic function for RAP1, it was used as a bait protein in a yeast 2-hybrid screen to identify interacting proteins. Using a human fetal brain cDNA library, we identified the δ isoform of GFAP, isolated as four independent clones. No other forms of GFAP were isolated. We directly tested the most abundant form, GFAP α , but it did not show an interaction with RAP1, similar to PS1. We will continue to use the yeast two-hybrid system to explore further the interactions among these proteins, including species variants (for GFAP δ and RAP1) and AD-associated mutations (for PS1).

Proposed One-Year and Long-Term Outcomes:

1. We will determine whether the interaction among RAP1, GFAP δ and PS1 is cooperative or competitive in nature.
2. We will determine whether the ape variants of the RAP1 and GFAP δ proteins affect the interaction strength among the three proteins.
3. We will determine the effects of AD-associated mutations as well as more severe mutations on the interactions of these proteins.

The data we generate here will provide us with a platform to continue our studies. This preliminary data will be included in grant proposals so that we might investigate the effects of these interactions on the production of A β peptides. We will use the variants and mutations in a reconstituted γ -secretase system in yeast to determine the effects of the interactions on A β production. The yeast

system is attractive since yeast do not express any of these proteins naturally, providing a “clean” system that is easily manipulated. Eventually, we will move into human cells. In addition, we might find that the specific allele of GFAP δ expressed in a human individual might have some bearing on the formation of A β plaques and might even be a novel AD-effector to be considered.

Year End Progress Summary:

Aim 1a: We have had to switch our yeast two-hybrid system to one that can accommodate the expression of three proteins. This system uses typical two hybrid proteins (one fused to a DNA binding domain and one fused to an activation domain) to detect interactions by expression of reporter genes. A third protein (that can associate or compete) is expressed from a promoter that can be regulated so that it can be turned on and off to compare interactions with and without the protein. Since both PS1 and RAP1 interact with the same domain of GFAP δ , we will test RAP1 expression on the PS1-GFAP δ interaction and PS1 expression on the RAP1-GFAP δ interaction. All of the genes have now been cloned into the appropriate plasmids, and we are transforming yeast to test the interactions. Preliminary data indicates that the RAP1-GFAP δ interaction is stronger than the PS1-GFAP δ interaction comparing the results of binary interaction tests.

Aim 1b: The GFAP δ variant that was obtained from the yeast two-hybrid screen was determined to be the allele encoding threonine at amino acid position 426. We have mutagenized this clone so that it encodes alanine at position 426. We have cloned this variant into the yeast two-hybrid plasmids, and we are now transforming the yeast reporter strains. We have mutagenized the human RAP1 clone we have so that the histidine at amino acid position 130 has been replaced by leucine, which is found in the ape sequences. This version of RAP1 has been cloned into the two-hybrid plasmids, which are being introduced into yeast.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Cerebrovascular function in APOE3 and APOE4 targeted-replacement mice. Delrae Eckman, PhD, Carleton 'Buck' Jones, PhD, Jessica Powell, PsyD., Johana Vallejo-Elias, PhD, T Bucky Jones, PhD, Tom Virden, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Collaborator:

Midwestern: Brikena Hoxha

Specific Aims:

Aim 1. Determine whether MCA mechanical characteristics and/or vessel wall composition is altered in young (3-month) and aged (18-month), male and female APOE3 and APOE4 mice.

Aim 1.1. Assess whether the APOE3 and/or APOE4 phenotype alters MCA arterial wall thickness, distensibility and stress/strain relationships.

Aim 1.2. Determine the relative contribution of elastase and collagenase to active and passive vascular wall structure and function.

Aim 1.2. Using molecular and immunohistochemical techniques, determine whether APOE3 and APOE4 phenotype alter MCA expression of elastin and/or collagen.

Aim 2. Determine whether myogenic tone (MT) is altered in the MCA in young (3-month) and aged (18-month), male and female, APOE3 and APOE4 mice.

Aim 2.1. Assess the pressure-response relationship in endothelium-intact MCA from young and aged, male and female mice using stepwise increases in intraluminal pressure from 10mm Hg to 140mm Hg.

Aim 2.2. Assess the contribution of NOS and COX to MT in MCA from young and aged, male and female mice.

Aim 2.3. Assess relative contributions of NOS, COX, and Caveolin in young and old, male and female, APOE3 and APOE4 mice.

Background: Apolipoprotein E (APOE) is an apolipoprotein produced primarily in the periphery by the liver, and in the brain by astrocytes¹. Three isoforms have been identified in humans: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ (APOE2, APOE3, and APOE4) and are associated with varying risk of developing Alzheimer's disease (AD)³. APOE3 is the most common allele (79%) and carries a 'normal' risk for AD, while APOE2 (7% allelic frequency) is 'low' risk (OR = 0.621) and APOE4 (14% allelic frequency) is 'high' risk (OR = 3.68) (Alzforum, 2017). Based on these findings, a mouse model using targeted replacement of the murine APOE with human APOE3 or APOE4 was developed that provides an excellent model system for exploring the role of APOE4 in the pathogenesis of AD². The development of AD has been linked to vascular dysfunction in several clinical studies, and in humans the E4 allele is associated with increased plasma cholesterol and a greater risk of coronary artery disease (see review by Scheltens and colleagues)⁴. However, to our knowledge the interaction of APOE4 and vascular dysfunction in the pathogenesis of AD has not yet been explored. Thus, in this proposal, we plan to determine cerebrovascular function and cognitive status in aged APOE3 and APOE4 targeted replacement mice.

Impact: APOE4 is known to play a role in both cardiovascular dysfunction and AD pathology, however the mechanisms by which these occur is unclear. *The current project will be the first to examine the effect of the APOE4 allele on cerebrovascular function in the targeted replacement APOE4/APOE3 mouse model.* The data generated from this project will provide insight into potential relationships between APOE4 and cerebrovascular dysfunction. Importantly, the clinical signs of hypertension and cardiovascular disease typically manifest well before the first signs of cognitive decline in AD. Data generated from this proposal might therefore provide the basis for earlier detection of AD pathogenesis. This project is solidly in line with the thematic goals of the Arizona Alzheimer's Consortium by highlighting early pathogenic changes that might serve as potential diagnostic targets for early detection of AD.

Preliminary Data and Plan:

1. Establish a working team of investigators to assess the relationship between cardiovascular and cerebrovascular function in young and old APOE mice.
2. Assess cardiac, aortic and carotid artery function in APOE mice prior to assessing cerebral vascular reactivity in isolated middle cerebral arteries.
3. Assess cerebral vascular function as outlined in specific aims 1 and 2 above.
4. Submission of extramural grant using preliminary data collected using this funding mechanism to continue Alzheimer's disease/dementia research at MWU.

Year End Progress Summary:

We have made significant progress on this project and feel that we can address the goals outlined in the original project. To this end we have completed the following:

1. Established working team and submission for extramural funding.

Currently we have established a working group of seven individuals who have come together to form a functional research team for this current MAAC proposal, and to submit proposals for extramural research.

Delrae M. Eckman, PhD (PI): Responsible for all aspects of study design, execution of *in vivo and ex vivo* studies outlined in this MAAC proposal and pending support, data analysis and manuscript preparation. If ABRC grant (see pending grant information below, AZ NIA, Arizona RFGA ADHS17-00007401) is funded. Dr. Eckman will be mentored by Dr. April Ronca on all aspects of behavioral/cognitive studies (execution, study design, data analysis, and manuscript preparation).

Dr. Carleton 'Buck' Jones (Co-PI): Along with Dr. Eckman, Dr. Jones will be responsible for study design, data analysis and manuscript preparation. He will also assist with *in vivo and ex vivo* studies outlined in this MAAC proposal and pending support. If ABRC grant (see pending grant information below, AZ NIA, Arizona RFGA ADHS17-00007401) is funded. Dr. Jones will be co-mentored by Dr. April Ronca on all aspects of behavioral/cognitive studies (execution, study design, data analysis, and manuscript preparation).

Dr. Jessica Powell (Co-PI): Assist with *in vivo and ex vivo* studies outlined in this MAAC proposal and pending support, study design, data analysis and manuscript preparation. If ABRC grant (see pending grant information below, AZ NIA, Arizona RFGA ADHS17-00007401) is funded. Dr. Powell will be co-mentored by Dr. April Ronca on all aspects of behavioral/cognitive studies (execution, study design, data analysis, and manuscript preparation) and serve as co-team lead on

these projects. Because of Dr. Powell's clinical experience, she will work closely with Drs. Eckman and Jones on clinical translation of rodent studies.

Johana Vallejo-Elias, PhD (Co-PI): Assist with study design, data analysis, manuscript preparation and execution of *in vivo and ex vivo* studies, histological and molecular studies assessing smooth muscle and endothelial function outlined in this MAAC proposal and pending support.

T Bucky Jones, PhD (Co-PI): Assist with study design, data analysis, manuscript preparation and execution of *in vivo and ex vivo* studies, histological and molecular studies assessing neuronal function outlined in this MAAC proposal and pending support. Dr. T Jones is the PI of the APOE breeding colony and will be responsible for all aspects of animal husbandry and maintaining an adequate supply of animals required for completion of outlined projects.

Tom Virden, PhD (Co-PI): Assist with study design, data analysis, and manuscript preparation of all behavioral and cognition studies. Because of his clinical/psychology background, Dr. Virden will serve as co-team leader with Dr. Ronca on these projects.

April Ronca, PhD (Co-PI, NASA): We are pleased to have Dr. April Ronca, a senior scientist with NASA join our research team. Dr. Ronca is a Co-PI on the ABRC grant (see pending grant information below, AZ NIA, Arizona RFGA ADHS17-00007401) which was submitted as a continuation of this project. If funded, Dr. Ronca will be serving as the lead PI on all aspects of behavioral/cognitive studies (execution, study design, data analysis, and manuscript preparation). In addition, Dr. Ronca will be actively involved with the experimental design and translational aspects of *in vivo and ex vivo* studies.

2. Assess cardiac, aortic and carotid artery function in APOE mice prior to assessing cerebral vascular reactivity in isolated middle cerebral arteries.

We are in the final stages of collecting cardiac, aortic, and carotid artery function in APOE 3 and APOE 4 mice. These data have contributed to submission of two abstracts to the upcoming Experimental Biology meeting (EB 2018) and will also be presented at upcoming Arizona Alzheimer's consortium meeting. To date, we have focus our data collection on two aspects of healthy aging in the APOE mice.

Evaluation of cardiovascular structure and function in young and aged female APOE3 and APOE4 mice

In this study, hAPOE3 mice exhibited an age-related increase in bodyweight ($p < 0.05$) and hAPOE3 mice weighed significantly more than hAPOE4 mice at 18-20 months ($p < 0.05$). There was no age-associated increase in bodyweight in the hAPOE4 mice. CA structure and function was assessed by wall thickness (WT) and pulse wave velocity (PWV) respectively. Both hAPOE3 and hAPOE4 mice displayed an age-related increase in WT ($p < 0.05$). CA PWV was significantly greater in aged hAPOE4 vs young APOE4 mice ($p < 0.05$), however there was no age-related CA PWV increase in hAPOE3 mice. Both hAPOE3 and hAPOE4 mice exhibited an age-related increase in TA PWV ($P < 0.05$), but measurements of aortic structures: aortic annulus, sinus of valsalva, and sinotubular junction, showed no significant age-related changes. Cardiac output (CO) and stroke volume (SV) was higher in young- and aged- hAPOE3 mice compared to age matched hAPOE4 mice (CO: $p < 0.05$ and SV: $p < 0.05$). All other cardiac indices (e.g., stroke volume, ejection fraction, E/A ratio, etc.) were similar between groups. Finally, the systolic and diastolic BP values showed no significance difference between groups. These preliminary data suggest that female hAPOE3 and APOE4 mice exhibit age-related changes in C, TA and CA structure and function.

Cardiovascular characterization of young and aged, female and male APOE4 mice

In this study, young and old, female and male hAPOE4 mice exhibited similar bodyweights. CA structure and function was assessed by wall thickness (WT) and pulse wave velocity (PWV) respectively. Both female and male hAPOE4 mice displayed an age-related increase in PWV ($p < 0.05$), but only the female APOE4 mice displayed an age related increase in CA wall thickness (WT) ($p < 0.05$). Female and male hAPOE4 mice exhibited an age-related increase in TA PWV ($P < 0.05$), but measurements of aortic structures: aortic annulus, sinus of valsalva, and sinotubular junction showed no significant sex or age related change. Interestingly, except for a modest increase in mitral valve deceleration time with age in male hAPOE4 mice, there was no effect of age or sex on cardiac parameters assessed by U/S (e.g., cardiac output, ejection fraction, stroke volume, etc.). Finally, blood pressures were similar in female and male, young and old hAPOE4 mice with the only exception being an elevated pulse pressure in young male hAPOE4 mice vs young female APOE4 mice ($p < 0.05$).

The above preliminary data suggest that female and male, hAPOE4 mice, exhibit age-related changes in TA and CA structure and function. Additional studies and animals will be needed to determine whether hAPOE4 mice exhibit structural and/or functional changes similar to that seen in women and men. We have procured intramural funds to assist with these purchases.

3. Assess cerebral vascular function as outlined in specific aims 1 and 2 above.

We are actively collecting data on the mice used for the above cardiac, aortic and carotid artery studies. Briefly, we are the process of determining whether there is an age or sex related change in cerebral artery wall thickness, distensibility, stress vs strain, and myogenic tone. To better correlate the in vivo data with the functional data in isolated cerebral arteries, we have decided to assess the same mechanical characteristics in carotid arteries. Data from cerebral and carotid vessels from the same animal will be compared with each other to improve our understanding of how the APOE4 allele impacts large and small vessel structure/function.

Tissue is also being collected/preserved for histological assessment vascular and neuronal biomarkers outlined in the MAAC proposal. We are in the process of ordering molecular and histological antibodies now. We have observed that vessel isolation damages the surrounding tissue to an extent that histological assessment cannot be performed, therefore we will be ordering additional animals for histological studies.

We are in the process of ordering additional animals to address the specific aims outlined in our MAAC proposal. Currently, we are on track for completion of the functional data by June 30th, 2018 and the histological data shortly thereafter.

4. Submission of extramural grant using preliminary data collected using this funding mechanism to continue Alzheimer's disease/dementia research at MWU.

Our team has submitted one extramural proposal to the Arizona Biomedical Research Commission the ABRC grant (see pending grant information below, AZ NIA, Arizona RFGA ADHS17-00007401). If not funded, our team will rework this proposal and submit to NIH using the R15 format.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

The role of infection in the development and pathological features of Alzheimer's disease. Garilyn Jentarra PhD, Ping Chu, T. Bucky Jones PhD, Jason Kaufman PhD, Johana Vallejo-Elias PhD, Douglas Jones PhD, Fernando Gonzalez PhD, Tony Tullo MD, Alexandra Rogers, Shanika Kingston, Monica Castro, Ross Potter, PhD, Thomas Beach, MD PhD, Pamela Potter PhD. Midwestern University; Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Collaborators:

Midwestern University: Ariel Kerry-Gnazzo, Frans Honig

Specific Aims:

Aim 1: Determine if infection or microbial components can induce responses that lead to the formation of neurofibrillary tangles. **Aim 2:** Establish the presence or absence of microbial DNA/proteins/components in brain tissue from AD or mild cognitive impairment (MCI) patients, high pathology non-demented controls (HPC) and non-demented normal controls (ND-N). **Aim 3:** Assess whether *C. albicans* infection exacerbates neuropathology in AD triple transgenic mice (3xTg). Determine the effect of *C. albicans* inoculation on production of inflammatory cytokines in the brain and spleen of (3x-Tg) and apolipoprotein E4 (APOE4) targeted replacement mice.

Background and Significance:

The objective of this project is to address the potential role of chronic, low-level infection in the development of Alzheimer's disease (AD). AD pathology has largely been considered to result from an erroneous process rather than an intentional cellular action. In the interest of looking at the problem from a new perspective, we begin with the assumption that these pathologies are not the result of unintentional or accidental processes, but rather that they serve a deliberate purpose in the brain. Our hypothesis is that chronic infection and concomitant inflammation in the brain of AD patients provokes both the characteristic amyloid plaques and neurofibrillary tangles. We propose that the presence of microbes prompts an antimicrobial response in the brain, inducing production of A β which might act as an antimicrobial peptide. We also propose that the microbial presence prompts hyperphosphorylation of tau, producing neurofibrillary tangles. Reports have implicated a variety of microbes in AD, leading us to suspect that if AD is provoked by an infection, there might not be one single microbe associated with all cases of AD. Instead, symptoms and neuropathology might result from any number of microbes producing chronic subclinical infection in the brain and activating common cellular response pathways. Our **first** aim will explore a novel explanation for hyperphosphorylation of the microtubule associated protein tau (MAP-T), which is linked to formation of neurofibrillary tangles. The **second** aim will build on work we have been conducting on brain tissue from AD patients and control subjects which seeks to identify the presence of microbes in brain regions affected by AD pathology. The **third** aim will expand promising work that is underway in AD mouse models infected with a microbe that has previously been associated with AD pathology.

Preliminary Data and Plan:

Aim 1: Tau hyperphosphorylation is the precipitating event for formation of neurofibrillary tangles in AD, although the cause of hyperphosphorylation is unknown. Tau hyperphosphorylation results in loss of its microtubule-stabilizing activity, and subsequent collapse of the cellular microtubule

structure. GSK3 β is an enzyme implicated in tau hyperphosphorylation and known to be upregulated in both AD and during the infectious process. We will attempt to experimentally induce tau pathology using microbial infection or exposure to microbial components.

Cell culture analysis: Two cell lines commonly used in AD and Parkinson’s disease research, SH-SY5Y cells and Neuro2A cells, will be used. **Cell infection:** Cultured cells will be infected with HSV-1, *C. pneumoniae*, and *C. albicans*, microbes frequently reported in brain tissue of AD patients. **Cell treatment:** Cultured cells will be treated with microbial components or mimics including lipopolysaccharide (LPS), poly I:C (mimicking viral dsRNA), CpG DNA (mimicking bacterial DNA) and chitin. **Analysis:** The microtubule structure of cells following infection or treatment will be visualized using immunocytochemistry, which will also be used for comparison of relative levels of hyperphosphorylated tau and evaluation of the formation of hyperphosphorylated tau aggregates. Western blotting will also be used to evaluate changes in levels of hyperphosphorylated tau, as well as changes in GSK3 β levels.

Aim 2: There have been many reports of the presence of microbes in the brains of individuals with AD. The organisms identified include fungi (esp. *Candida*), HSV-1, and a variety of bacteria (*Treponema*, *C. pneumoniae*, etc.). Given the assortment of microbes identified, we hypothesized that the pathology observed in AD might be a non-specific response to any chronically infecting organism that enters or persists in the brain. We proposed that it is the presence of the microbes more than their actual identity which leads to pathology. We therefore designed a study which allowed for an unbiased survey of the bacterial DNA present in post-mortem brain tissue from AD patients, individuals with MCI, HPCs who had no cognitive impairment but did have AD pathology, and normal non-demented control subjects (Figure 1).

Aim 3: Given recent evidence that A β exhibits strong anti-microbial properties, there is reason to believe that its accumulation in the brains of AD patients might reflect a defense against infection. If A β is in fact an AMP, then AD-like pathology in the brain would develop earlier or at a greater level in infected mice susceptible to AD pathology compared to uninfected mice. The 3xTg-AD mouse model exhibits the major histopathological hallmarks of AD over a well-established time course. 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.

Proposed One-Year and Long-Term Outcomes:

1. We will compile data from the three aims to determine if they suggest a role for infection in AD. The data will be publishable regardless of whether it supports or fails to support the idea that microbes are involved in AD. Aims 2 and 3 will have generated sufficient data for 2 separate publications by the end of Summer 2018.

Alzheimer's disease				Mild Cognitive Impairment			
Case ID	Age	Sex	APOE	Case ID	Age	Sex	APOE
11-35	93	Female	3/3	12-06	74	Female	3/4
11-38	64	Male	3/3	12-28	80	Male	2/4
11-48	87	Male	3/3	15-73	84	Male	3/4
11-78	82	Male	3/3	05-20	75	Male	3/3
13-35	76	Female	3/3	07-52	90	Female	3/3
13-54	85	Female	3/3	09-04	93	Female	3/3
13-10	74	Male	3/4	10-57	90	Male	3/3
13-46	85	Female	3/4	11-08	96	Male	3/3
13-53	92	Female	3/4	12-41	97	Male	3/3
13-66	75	Male	3/4	13-39	91	Male	3/3
13-75	77	Male	3/4	13-61	86	Male	3/3
14-06	85	Male	3/4	15-18	101	Female	3/3
Average	81.25			Average	88.08		

Non-Demented Normal Controls				High Pathology Controls			
Case ID	Age	Sex	APOE	Case ID	Age	Sex	APOE
07-11	75	Female	3/4	08-47	91	Male	2/3
08-40	76	Male	3/4	11-102	93	Male	2/3
09-05	97	Male	3/4	09-44	97	Female	3/3
10-20	61	Male	3/3	11-04	88	Female	3/3
10-22	59	Female	3/3	12-44	80	Female	3/3
10-26	95	Female	3/3	14-02	86	Female	3/3
10-39	93	Male	3/3	14-16	99	Female	3/3
10-63	79	Male	3/3	14-20	93	Female	3/3
13-49	75	Female	3/3	14-42	92	Male	3/3
07-37	89	Male	3/3	08-35	87	Male	3/4
07-73	76	Female	3/4	13-55	90	Male	3/4
08-90	81	Male	3/3	14-24	87	Male	3/4
Average	79.67			Average	90.25		

Figure 1: Subject characteristics including age, sex and APOE status. AD and normal controls are age matched (p=0.5929). The higher pathology controls and MCI subjects are older on average than AD subjects (AD vs. MCI p=0.061, AD vs. HPC p=0.0043).

2. We have used data from Aims 2 and 3 to submit an R15 (AREA) proposal in February 2018. This proposal will substantially expand upon the work that is already underway.
3. We will utilize the outcomes of this study to design additional studies to further explore mechanisms which initiate and drive plaque and tangle pathology.
4. Continue analysis of the potential role of viral infection in AD by expanding analysis to include additional common viruses such as HSV-1, HBV, CMV and EBV. We will also expand the DNA analysis to include unbiased analysis of fungal DNA.

Year End Progress Summary:

Aim 1 is currently in progress. Data is not yet complete.

Aim 2: Results of 16S rRNA gene sequencing from brain tissue are shown in Figure 2. Data for each distinct bacterial sequence is reported as a percentage of total reads for that sample. Each column represents 100% of the reads for each sample with contaminating background sequences removed, leaving behind only reads that could be reasonably presumed to originate from the tissue samples. Each color block within the columns represents the percentage of those reads that was a specific non-background bacterium.

After removal of background sequences, the additive percentage of bacterial reads for normal subjects was 5% or less of the total reads, indicating that most reads from normal subjects came from background and only a small number represent bacterial DNA from tissue. In the HPC group, there was substantially increased variability with between 3% and 30% of reads attributable to non-background bacteria. For individuals with MCI, non-background reads were between 7% and 41% of total reads. Individuals with AD also showed a large degree of variability with non-background reads ranging from <1% to greater than 70%. The read numbers for this sample set ranged from a low of 469 to a high of >33,000. While the highest number of reads was in the AD group, that group also contained some low read numbers, and so that information was of limited use in

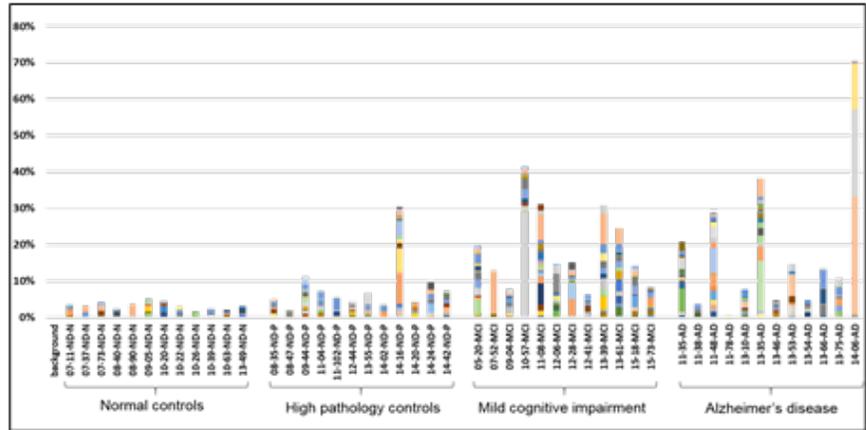


Figure 2: Percent non-background bacteria by subject

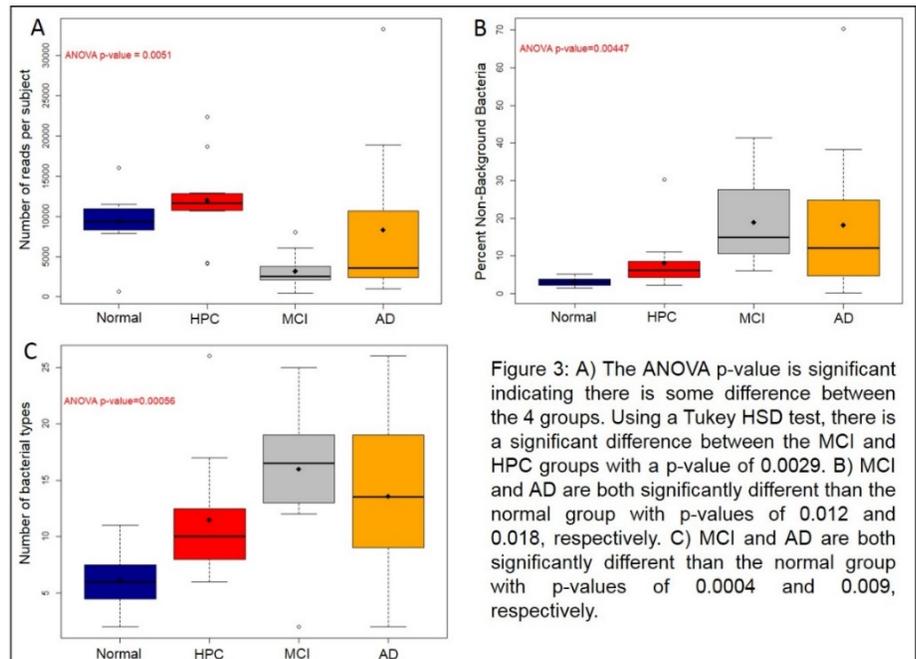


Figure 3: A) The ANOVA p-value is significant indicating there is some difference between the 4 groups. Using a Tukey HSD test, there is a significant difference between the MCI and HPC groups with a p-value of 0.0029. B) MCI and AD are both significantly different than the normal group with p-values of 0.012 and 0.018, respectively. C) MCI and AD are both significantly different than the normal group with p-values of 0.0004 and 0.009, respectively.

distinguishing the AD versus normal control group. The absolute number of reads in each subject group did differ for MCI versus HPC, but not between other groups (Figure 3A).

When comparing the numbers and percentages of varieties of bacteria between groups, there were clear significant differences, indicating that subject groups can be distinguished from each other based on the variety of bacteria present. When comparing the percent of non-background bacteria between groups, the MCI and AD groups were both significantly different than the normal control group (Figure 3B). Comparison of the number of types of different bacteria showed significant differences between the MCI and AD groups versus the normal controls (Figure 3C).

Aim 3: We have made significant progress in this aim. We proposed to examine the response of 3xTg-AD and control mice at 6 months and 12 months of age to intravenous infection with a *C. albicans*. We completed our inoculation of mice (3xTg-AD and C57BL/6 wild-type control; n = 100) and have begun analyzing the tissues (Figure 4). We have established that at 6 months of age, C57BL/6 mice had 100% survival compared with 75% survival of 3xTg-AD mice ($p = 0.06$). The rate of survival of WT mice at 12 months of age decreased to 67% ($p = 0.06$ versus 6 months of age) while the rate of survival of 3xTg-AD mice at 12 months of age did not change from that observed at 6 months ($p = 0.7$ versus 6 months). Collectively, these data suggest strain- and age-dependent effects on the response to fungal infection.

In Figure 5 we demonstrate marked splenomegaly in 3xTg-AD mice inoculated with *C. albicans* at 6 and 12 months of age compared with inoculated C57BL/6 mice (left panels; $p < 0.001$). Spleen weights continued to increase in 3xTg-AD mice as the mice aged ($p < 0.0001$), in contrast to C57BL/6 mice in which the spleen weights did not differ between 6 and 12 months of age (middle panels; $p = 0.2$). Organomegaly was seen mainly in males when compared to age-matched 3xTg-AD female mice (right panels; $p < 0.001$). Similar findings were observed in liver weights (data not shown).

In addition, we were able to re-isolate viable *Candida* organisms from all of the tissues surveyed. We are in the process of analyzing these data but our initial observations suggest that at six months of age, C57BL/6 mice are not as efficient at clearing the fungus as 3xTg mice, as indicated by the recovery of greater numbers of organisms from C57BL/6 tissues (data not shown).

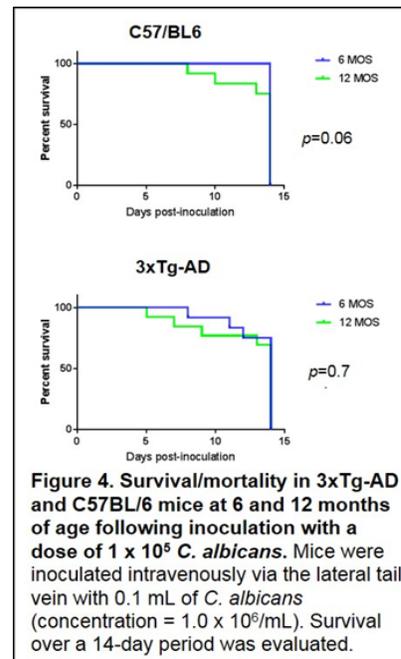


Figure 4. Survival/mortality in 3xTg-AD and C57BL/6 mice at 6 and 12 months of age following inoculation with a dose of 1×10^5 *C. albicans*. Mice were inoculated intravenously via the lateral tail vein with 0.1 mL of *C. albicans* (concentration = 1.0×10^6 /mL). Survival over a 14-day period was evaluated.

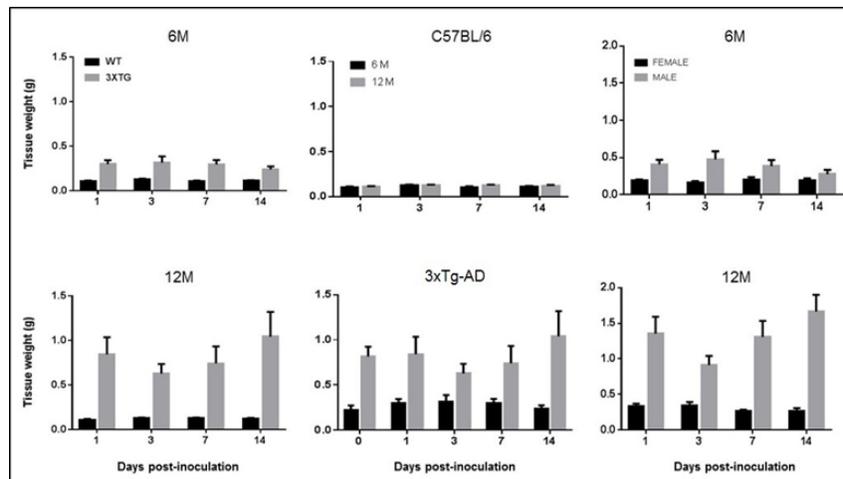


Figure 5: Age- and sex-dependent organomegaly in inoculated 3xTg-AD, but not C57BL/6 WT mice.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

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

Collaborators:

Midwestern University: Monica Castro, Tatum Banayat, Charles Schaeffer, Amy Fisher, Chaheylya St Aubin, Schuyler Rockwood, Bryan Lunt, Katerina Meassick, Saad Elaquad, Austin Hellings, Janelle Lopez

Specific Aims: Determine 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).

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) 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.

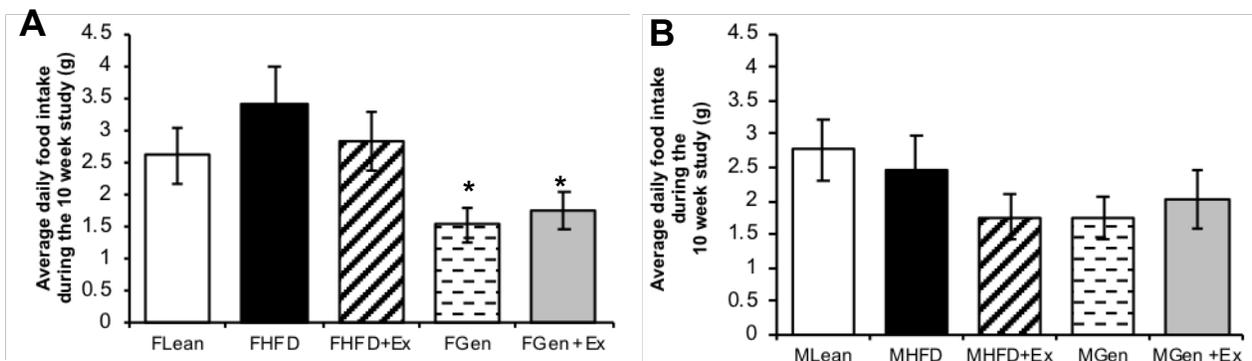


Figure 1. Effects on body food intake. A. Females: Mice fed HFD+genistein (Gen) and those fed HFD+Ex+Gen ate significantly less than the other groups. n=6/group. **B. Males.** There were no changes in food intake between the groups. Data are mean \pm SEM. * denotes significant difference from HFD, $P < 0.05$

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 will be collected at the conclusion of the 12-week diet and exercise study (during the weeks of March 5th and March 12th).

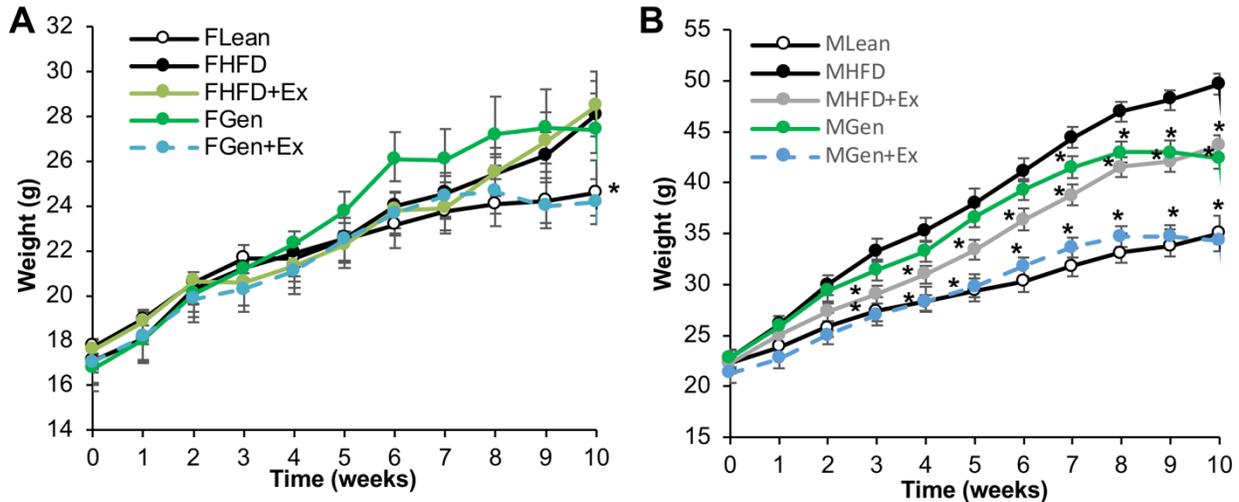


Figure 2. Effects on body weight. A. Females: Mice fed high fat diet (HFD) or HFD+exercise (Ex), HFD+genistein (Gen) weight more than the HFD+Ex+Gen. n=10/group. **B. Males.** Mice fed high fat diet (HFD) weight more than those in the HFD+exercise (Ex), HFD+genistein (Gen) groups. Those in the HFD+Ex+Gen group have the most beneficial effects on weight-gain. n=8-10/group. Data are mean \pm SEM. * denotes significant difference from HFD, $P < 0.05$

In female mice, we note that addition of genistein to the HFD and exercise treatment alone have no effect in female mice, whereas in combination (HFD+Ex+Gen) the result is a significant 4g difference in weight from HFD alone, at week 10 in the study (Fig. 2 A). We note an associated decrease in food intake in the HFD+Ex+gen female group (Fig.1A). In male mice the effects are quite different. We note significant weight loss in the exercise trained group after 3 weeks, and significant

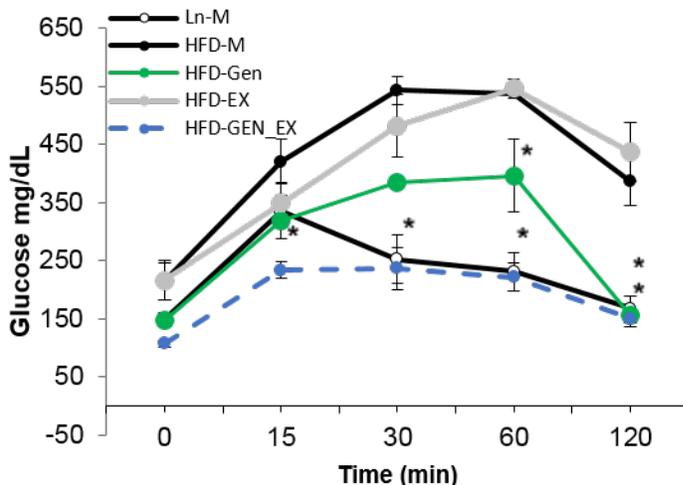


Figure 3. Effects on glucose tolerance test, GTT, in males. Lean control mice exhibit a typical robust GTT (open circles) after a glucose bolus of 2mg/kg mouse. Mice fed high fat diet (HFD) or HFD+exercise (Ex) demonstrate insulin insensitivity, with sustained elevated glucose levels. Those mice fed HFD+genistein (Gen, green circles) have a robust glucose response, returning to baseline levels after 120min. Those in the HFD+Ex+Gen group have the most beneficial effects on GTT, and are comparable to leans. n=3-5/group. Data are mean \pm SEM. * denotes significant difference from HFD, $P < 0.05$

weight loss with genistein treatment after 7 weeks. At weeks 8-10, the effects of genistein-alone or exercise alone are comparable, resulting in a significant 6g weight loss compared to HFD. However, in combination, both genistein+exercise result in synergistic significant benefits at week 3, resulting in a significant 15g weight loss compared to HFD (Fig. 2B). The significant effects of HFD+EX+gen on weight loss is not due to a decrease in food intake (Fig.1B).

We have performed glucose tolerance tests, GTT's on a subgroup of males during week 11 of the study. Data is shown in Figure 3, we are excited to note that genistein and exercise treatments combined with HFD, result in a "lean-like" GTT response, i.e. insulin sensitivity is rescued. We predict this will translate to comparable beneficial effects on our proposed outcome measures for serum, bone health and brain amyloid plaque formation.

The sex-dependent differences on weight gain are interesting, and we are excited to see if 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 counterpart.

Plan for tissue use for this 12-week diet and exercise study with the remaining funds:

Evaluation for differences between treatment groups in:

1. brain protein expression for markers of Alzheimer's pathology.
2. bone strength.

Project Progress Report
Translational Genomics Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Methods development for the utilization of archival fixed tissue specimens for RNA sequencing analysis. Matthew Huentelman, PhD, Ignazio Piras, PhD, Joshua Talboom, PhD, Thomas Beach, PhD. Translational Genomics Research Institute; Mayo Clinic Arizona, University of Arizona; Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

AIM 1: Assess the performance of the BioSpyder TempO-Seq approach on fixed free floating archival brain samples

AIM 2: Identify differentially expressed transcripts associated with Alzheimer's disease in multiple brain regions

Background and Significance: Traditionally, the analysis of RNA in tissue requires the use of rapidly collected and un-fixed specimens. As a result of this, fresh frozen tissue resources become high priority specimens for many researchers and therefore many brain regions become sample limited. Additionally, the requirement for high quality RNA as input for molecular analysis might severely limit total study size resulting in underpowered analyses and resulting conclusions that are difficult to independently replicate. To address these issues, we have been searching for RNA sequencing approaches that are able to utilize fixed free floating brain specimens as input. The use of such specimens would simplify the time constraints of fresh frozen tissue sampling as well as address the brain region availability issue thereby expanding the number of regions that might be evaluated per donor as well as the overall total study size and power. We recently identified a technology by BioSpyder Technologies (Carlsbad, CA) termed TempO-Seq that uses a targeted RNA sequencing approach and might work with high efficacy on fixed floating archival tissue specimens. During the course of the proposed work we will evaluate this approach across 100 donors and five brain regions (for a total of 500 samples) to assess if it will indeed facilitate the detailed RNA profiling of these banked specimens.

Preliminary Data: Unpublished data from BioSpyder suggests that TempO-Seq will perform well on fixed tissue specimens (the assay has also been shown to work on fixed and paraffin-embedded tissue as well). Whole transcriptome sequencing results were obtained from low input (e.g., single tissue "scrolls") specimens.

Experimental Designs and Methods: We will select a cohort comprised of the following:

- (1) Alzheimer's disease cases and closely demographic matched controls (N=50 in each group),
- (2) An equal sex mix in each group,
- (3) All individuals will be APOE 3/3 to permit us to examine the transcriptional changes in the absence of the APOE E4 allele, and
- (4) One fixed free floating specimen available from each of the brain regions; frontal association cortex (superior frontal gyrus) at the level of the genu of the corpus

callosum, temporal association cortex (fusiform gyrus) at the level of the pes hippocampus, putamen at the level of full development of the lenticular nucleus, substantia nigra, and cerebellar cortex. Of note, this includes a mix of regions important to the development of AD as well as control regions that are not involved in the disease and/or are important for other neurodegenerative diseases.

TempO-Seq will be performed for each tissue specimen using a whole human transcriptome capture library. 3M sequencing reads will be dedicated to each sample [note that this amount is lower than standard assayed due to the targeted nature of TempO-Seq]. Total genes detected in each sample will be determined and compared to other sample attributes such as brain region and age of specimen. Differential gene expression analysis will also be performed. Sex as a biological variable will be incorporated into the analysis.

Proposed One-Year and Long-Term Outcomes: At the end of this year we expect to do the following:

- (1) **Assess the ability of BioSpyder TempO-Seq to generate whole transcriptome RNA-Seq data on fixed free floating specimens.** This will be determined by calculating the number of genes quantitated in each specimen.
- (2) **Examine the differential gene expression between AD cases and controls across the sequenced brain regions.** We have selected regions that have already been assessed in the context of AD as well as additional regions of interest. Due to this design we will be able to assess if our approach replicates known findings already in the literature as well as generates new data for the field.

Successful execution of this work is expected to result in both a scientific publication and NIH grant application before the end of the year of funding. The grant application will expand both the brain regions examined as well as the number of donors utilized. The gene expression results will be provided freely and openly to the field as a resource.

Year End Progress Summary:

Aims 1 and 2: We have spent the majority of the funding period assessing the performance of TempO-Seq. As this is a new assay and chemistry approach we had to optimize several wet lab and bioinformatic parameters for analysis of the resulting data. On the wet laboratory side, we tested different input amounts of RNA as well as input quality. We determined that more RNA was necessary than suggested by the company for robust performance. The assay did work well on lower quality RNA – such as would likely be isolated from the fixed tissue scrolls. Informatically, we had to develop methods for analysis as the company-provided pipeline did not meet our needs for the study. We also had to develop methods for background correction due to contaminating DNA. These informatics issues have also been addressed. During the next months of the funding period we will perform the analysis of the AD case and control tissue as described.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Characterization of circular RNAs in the brain. Winnie S. Liang, PhD, Shobana Sekar, MS, Philip Geiger, MS, Lori Cuyugan, MS, Thomas Beach, MD PhD, Geidy Serrano PhD. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background and significance: Circular RNAs (circRNAs) are a novel type of endogenous, non-coding 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.

While our understanding of the functional roles of circRNA is limited, we performed bioinformatics analyses to detect circRNAs in RNA sequencing (RNAseq) data previously generated from microdissected astrocytes collected from the posterior cingulate (10 Alzheimer's disease [AD] subjects, 10 no-disease [ND] controls) [1], and hippocampus and substantia nigra (n=6 AD, n=6 controls for both regions) [2]. We implemented an ensemble approach for circRNA detection and used six separate prediction algorithms (find_circ, CIRI, DCC, Mapsplice, KNIFE, and CIRCexplorer) to identify circRNAs. Overall, 2,375 and 2,380 circRNAs were predicted across all tools in the AD and ND astrocyte samples, respectively (union across all tools). All six tools predicted 62 and 73 circRNAs in AD and ND PC samples respectively, 35 and 15 circRNAs in AD and ND HIPP samples respectively, and 15 and 20 circRNAs in AD and ND SN samples respectively. We additionally identified a number of circRNAs that are homologous to genes previously implicated in AD and other neurological diseases, and thus might potentially regulate micro-RNAs or transcripts derived from these genes. These include CDR1 (cerebellar degeneration-related protein 1), IGF2R (insulin like growth factor 2 receptor), FAIM2 (Fas apoptotic inhibitory molecule 2), and BPTF (bromodomain PHD finger transcription factor) [3].

Year-end progress summary: To expand on our previous analyses, we tested: (a) the incorporation of an RNase R treatment step prior to library preparation to remove linear RNAs and enrich for circRNAs, (b) the utility of performing an initial ribosomal RNA depletion step prior to RNase R treatment, and (c) two separate RNA library preparation kits (Kapa Biosystems' Stranded RNA Kit with RiboErase and Illumina's TruSeq Stranded RNA Kit with RiboZero). Following construction of test libraries and sequencing, we concluded: (a) that an initial rRNA depletion step was not necessary, and (b) that Illumina's TruSeq Kit performed the most consistently. We thus outlined an optimized protocol and used this approach to construct circRNAs libraries from fresh frozen control brain samples provided by Dr. Thomas Beach from BSHRI's Brain and Body Donation Program. We received fresh frozen cerebellum, inferior parietal lobule, middle temporal gyrus, occipital cortex, and superior frontal gyrus from six control subjects. We performed total RNA extractions, RNase R treatment, circRNA library preparation using the Illumina TruSeq Stranded RNA kit with RiboZero, and paired end sequencing on the Illumina HiSeq. We generated

a total of 3,329,267,162 million mapped and properly paired reads with a median of 98,416,405 million reads per sample after removal of UMIs (unique molecular identifiers).

Following circRNAs prediction, two subjects were dropped due to insufficient data. For the remaining four subjects and using all six circRNAs prediction algorithms, we identified circRNAs that were called by all six tools in each sample with circRNAs counts varying depending on the minimum number of supporting reads required. Requiring at least two supporting reads, the number of circRNAs detected ranged from 32 to 3138 (median=1526), whereas requiring at least 50 supporting reads reduced the number of detected circRNAs to a median of 41 across all samples. Differential expression analysis of identified circRNAs led to the observation that the cerebellum demonstrates the greatest number of differentially expressed circRNAs ($P < 0.05$) compared to the other brain regions.

Aside from these analyses, we have also completed circRNAs analyses on RNAseq data generated from our previous ADCC pilot for which we performed laser capture microdissection of astrocytes from the posterior cingulate of AD subjects and healthy controls (as described above). For our manuscript we focused on analysis using four separate tools, CIRI, CIRCexplorer, find_circ, and KNIFE, and identified a union of 4,438 unique circRNAs across all samples. Notably, because this is a historical data set, RNase R treatment was not performed but we were able to identify circRNAs. We also performed in silico predictions on the regulatory networks that might be impacted based on the circRNAs identified. We have submitted a manuscript on this study to *BMC Genomics*, are currently working on responding to reviewers' critiques, and are planning to resubmit our revision by March 2018.

Future directions: For our brain region analysis, we are currently performing transcription regulation prediction analyses using: (a) in silico predictions of microRNAs (miRs) that bind identified circRNAs, (b) mRNAs that are predicted to be regulated by these miRs, and (c) pathway analysis of identified mRNAs to evaluate the potential transcriptional regulatory impact of the identified circRNAs. We are also incorporating an in silico validation approach of performing de novo assembly to prioritize results from circRNAs detection. We will be submitting a manuscript for peer review in the spring of 2018 on these analyses. We had also extracted additional total RNA for small RNA and whole transcriptome analyses and will construct libraries and perform sequencing and analysis during the spring/summer of 2018 and compare these data against our in silico predictions.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Can single nuclei-based RNA-seq be utilized to categorize brain cells? Winnie S. Liang, PhD, Nicholas Banovich, PhD, Philip Geiger, MS, Jerry Antone, BS, Daniel Enriquez, BS, Jonathan Keats, PhD, Matthew Huentelman, PhD, Kendall Van Keuren-Jensen, PhD, Thomas Beach, MD PhD. Translational Genomics Research Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Goals:

- 1) Test storage and processing conditions on samples obtained from BSHRI's rapid autopsy program (fresh versus frozen samples).
- 2) Compare transcriptome sequencing between single cell nuclei and whole cells.
- 3) Establish methods and protocols that will maximize the utility of autopsy materials from different tissues.

Background:

We have an unparalleled opportunity, with collaborators across TGen and Banner Sun Health Research Institute (BSHRI), to develop efficient methods for single cell RNA sequencing (scRNAseq) which has gained increased adoption in genomics research. While various approaches to performing scRNAseq have been explored, 10X Genomics' Chromium platform provides a streamlined solution for scRNAseq. This platform enables the measurement of up to thousands of mRNAs from individual cells for up to tens of thousands of cells in a sample using barcoded gel-bead emulsions (GEM). This approach enables cell classification analysis to support the identification of sub-populations of cells that demonstrate correlative expression profiles. Given the valuable tissue samples available through BSHRI's Brain and Body Donation Program headed by Dr. Beach, the goal of this study is to identify and develop optimal approaches to generate scRNAseq data from fresh and banked samples.

Progress update:

To assess our ability to utilize this platform for cell population classification on the brain, we received samples from Dr. Beach for testing. These samples included:

- 1) Healthy elderly control subject
 - a. Frozen whole cell suspension from frontal cortex
 - b. Fresh frozen tissue from adjacent frontal cortex
- 2) Alzheimer's disease subject
 - a. Frozen whole cell suspension from frontal cortex
 - b. Fresh frozen tissue from adjacent frontal cortex

Using these samples, we performed four separate tests. For fresh frozen tissue samples, we tested and optimized an in-house cell dissociation protocol for scRNAseq analysis on the 10X, and adjusted parameters of wash steps and increased the BSA (bovine serum albumin) concentration to mitigate inter-cell adherence. Across the four tests we evaluated: (1) the feasibility of using frozen cell suspensions provided by BSHRI to perform 10X scRNAseq library preparation for whole cell or nuclei only preparations; (2) the feasibility of using an in-house tissue dissociation protocol that incorporates myelin removal on fresh frozen frontal cortex tissue to perform 10X

nuclei library preparation; (3) the feasibility of using frozen cell suspensions provided by BSHRI to construct 10X scRNA whole cell libraries using modified wash steps prior to library preparation; and (4) the feasibility of utilizing fresh frozen tissue samples and performing both an in-house TGen tissue dissociation protocol and construction of whole cell and nuclei preparations on the 10X.

We additionally evaluated if tissue processing for downstream whole cell or nuclei sequencing subjects the samples to transcriptome altering perturbations. To directly compare transcriptome sequencing of nuclei and whole cells in the absence of such perturbations, we used freshly isolated peripheral blood mononuclear cells (PBMCs). Briefly, fresh blood was collected from a volunteer and PBMCs were immediately isolated using a Ficoll gradient. Nuclei were isolated using a gentle lysis buffer in accordance with the 10X Genomics protocol. All other processing was performed in parallel and we generated both nuclei and whole cell RNAseq libraries for sequencing.

Year-end progress summary: Overall from this pilot analysis, we evaluated the impact of:

- (1) Fresh frozen brain suspensions prepared by BSHRI compared to TGen-dissociated suspensions from fresh frozen brain tissue provided by BSHRI
- (2) Whole cell versus nuclei preps from TGen dissociated fresh frozen brain tissue
- (3) Processing of fresh versus flash frozen or cryopreserved PBMCs on whole cell and nuclei preps

Based on sequencing, we concluded the following:

1. Nuclei preparations of fresh frozen brain, or fresh/cryopreserved PBMCs, are associated with a consistently higher number of detected genes.
2. Nuclei preparations of fresh frozen brain, or fresh/cryopreserved PBMCs, are associated with consistently higher total gene counts.
3. Whole cell preparations are associated with consistently higher fractions of mitochondrial transcripts.
4. Flash frozen PBMCs performed poorly, likely due to cell lysis, such that fresh or cryopreserved PBMCs are the most optimal material to perform scRNAseq on.

As there are currently no established protocols for whole cell or single nuclei sequencing of non-brain adult human tissue, we have also begun collecting and testing methods for sample processing and storage for five other non-brain tissues: pancreas, liver, lung, colon, and skin. We are investigating differences in the transcriptome between samples processed fresh, after freezing and after cryopreservation. Within each condition we are testing for transcriptional differences between whole cell and nuclei RNA sequencing. As of February 2018, we have collected samples from two autopsies, and initial work is aimed at optimization of sample processing to obtain viable cells and nuclei. We are currently working closely with 10X Genomics to optimize these protocols.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Identification of RNA modifications altered in Alzheimer's disease. Rebecca Reiman, Elizabeth Hutchins, PhD, Thomas Beach, MD PhD, Kendall Van Keuren-Jensen, PhD. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Project description:

Chemical modifications on proteins, such as phosphorylation of the tau protein, are critical to the development of Alzheimer's disease (AD) pathology. And there are changes in DNA methylation that might alter gene regulation and play a role in AD susceptibility (DeJager et al., 2014). It is also likely that there are RNA modifications that contribute to Alzheimer's disease pathology, yet this area is largely unexplored. According to RMBase, there are more than 100 types of RNA modifications, however, almost nothing is known about how they are regulated, or their function in health and disease (Sun et al, 2015). While the number of protein coding genes has remained relatively stable, the number of non-coding RNAs continues to grow each year. These newly detected RNAs highlight the complexity of the transcriptome and its ability to modulate, stabilize, and change cell functions. The brain is full of exquisite cell types that are unique and carry out exclusive roles. Cells near one another that appear to be similar cell types, have different functions and electrophysiological properties. Single cell sequencing has revealed new subtypes of neurons and glia (Usoskin et al., 2014; Zeisel et al., 2015, Darmanis et al., 2015). If the number of protein coding genes is relatively small, this diversity and regulation of neuronal and glial subtypes must come about through dynamic genetic tools, including the diversity of noncoding RNAs and RNA modifications.

It is well known that some types of RNAs are highly modified, such as tRNAs (Chan et al., 2016), rRNAs (Decatur et al., 2002), and snoRNAs (Meier 2016). There has also been an increasing interest in less abundant RNA modifications on mRNAs (Helm et al., 2017). With increasing advances in sequencing technologies, researchers are finding new ways to study RNA modifications. In this proposal, we want to establish competencies in studying RNA modifications, and use these new tools to reveal important information about AD pathology.

One of the main reasons that so few RNA modifications have been identified or studied, has been due to technical challenges. First of all, sequencing, qRT-PCR and most common methods for studying RNA require reverse transcription and conversion to cDNA. These processes strip the RNA of the RNA modifications. Also, RNA modifications often cause reverse transcriptase to fall off of the RNA molecule, causing shortened cDNAs for sequencing. Several papers in recent years have developed strategies to remove the modifications so that the samples can be sequenced and compared (Cozen et al., 2015; Zheng et al., 2015). These new techniques make use of enzymes that can cleave off the RNA modifications. Samples can then be sequenced with and without the enzymes, based on stops in the sequence, it can reveal the location of an RNA modification. We have written to two of these groups and have received the plasmids to grow and purify the enzymes that remove the RNA modifications. Both groups are willing to provide us with guidance as we

use these tools to study RNA modifications. We will use RNA isolated from several different tissues and biofluids, and we will first focus on tRNAs with many abundant, known modifications.

While the approach outlined above is the most straightforward, it is not the most revealing or efficient. The approach that would make the most significant advances in this area of RNA modifications, would be direct RNA sequencing. While very few laboratories currently do this, there are early access protocols available using the Oxford MinIon. This type of sequencer uses a nanopore, rather than the fluorescence and base building chemistry of Illumina. RNAs and DNAs can go through the nanopore which has an ionic current. Each base (G, A, T, C) has a specific disruption on the current and can be read. More importantly, each modification has a specific deflection of current that can also be read. We will take some of the tRNA information we study in the first part of this aim, with known modifications at specific sites, and we will train our ability to assess modifications passing through the nanopore. Oxford nanopore also has a direct RNA sequencing protocol that is in the early stages of testing and was just released. We will adapt this protocol and learn to sequence the RNA directly. We have already purchased the Oxford Nanopore.

Progress to date: With the help of collaborators at USC and expertise from Oxford Nanopore, we have been able to successfully run through the procedure and acquire data. We are working on ways to improve the data yields on the sequencer, and also how to bioinformatically interpret base modifications. We are hoping to have our methods stabilized and a paper out this summer on our findings from brain tissue. In addition, we are examining the PacBio for comparison of results and data on long read sequencing.

Project Progress Report

University of Arizona

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Patient recruitment and outreach for Alzheimer's disease and related-disorders. Geoffrey Ahern, MD, PhD, Steven Rapcsak, MD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: This proposal requests complementary support to enhance ongoing efforts for participant recruitment and outreach efforts as part of the UA site of the Arizona Alzheimer's Disease Center (ADC). The Arizona ADC is part of a multi-institutional state-wide consortium that links together the major research institutions in Arizona to advance efforts in the early detection, tracking of progression, and evaluation of treatments and prevention therapies for Alzheimer's disease (AD) and related disorders. As part of the Clinical Core of the Arizona ADC, Drs. Ahern and Rapcsak lead efforts in the participant recruitment for patients with probable AD dementia, mild cognitive impairment (MCI), and healthy elderly controls in the Tucson-metro area. In addition, they have been actively involved in the recruitment and clinical assessment of patients with other less common forms of dementia afflicting the elderly, including frontotemporal lobar dementia spectrum disorders and the occurrence of AD dementia with an early age-at-onset.

This proposal will support the following primary specific aims:

AIM 1) to recruit, enroll, and evaluate patients with dementia, cognitive impairment, and healthy controls for inclusion in the Arizona ADC;

AIM 2) to support Arizona ADC outreach efforts, providing the Tucson-metro area community with educational information on AD and related disorders and the opportunity to participate in related research, including clinical trials.

Background and Significance: The older adult population is expected to grow rapidly over the next two decades. In the United States, the number of elderly persons will reach over 70 million (US Census Bureau, 16), and public health programs will increasingly need to respond to this escalating growth. Associated with the dramatic increase in the elderly will be an increase in the occurrence of AD and associated cognitive decline. It will be essential to identify new effective treatments and prevention therapies to address the increasing needs of elderly adults with increased risk for dementia. The Arizona Alzheimer's Consortium is a state-wide, multi-institutional research center focused on advancing research to enhance early detection, tracking of disease progression, and evaluating potential treatments for AD. As investigators in the Clinical Core of the Arizona ADC since its inception, Drs. Ahern and Rapcsak have been actively engaged in research to advance understanding of the clinical effects of AD and other age-related neurodegenerative diseases as part of the Arizona Alzheimer's Consortium. Geoffrey Ahern, MD, PhD, holds the Bruce and Lorraine Cumming Endowed Chair in Alzheimer's Research and is Professor of Neurology, Psychology, and Psychiatry at the University of Arizona. Steven Rapcsak, MD is Professor in the Departments of Neurology, Psychology, and Speech, Hearing, and Language Pathology at the University of Arizona.

Proposed One-Year and Long-Term Outcomes: The primary one year outcomes for this project include increasing the number of new participants enrolled in the Clinical Core of the Arizona ADC as well as to continue to follow currently enrolled participants on a yearly basis to characterize and track changes in cognitive functions and behavior. In addition, we plan to continue and expand our participation in outreach efforts to support our ongoing patient recruitment goals and to provide information to the Tucson-metro area community concerning current research efforts on AD, dementia, and age-related cognitive decline. For example, Dr. Ahern provided a presentation on new directions in the treatment and prevention of AD at the 2nd Annual Conference on Successful Aging (ACoSA), a conference developed and organized by Drs. Alexander and Ryan, collaborating Arizona AAC investigators at the University of Arizona, to provide the most up to date information on aging and the risk for AD to community members in the Tucson-metro area. The focus of this ACoSA meeting was Successful Aging: Reducing your Risk for Alzheimer's disease, and planning for the next year's conference is underway. Similarly, Dr. Rapsak has given several lectures on Alzheimer's disease and related dementias at various community centers in the Tucson area and at Banner-UMC.

Year-End Progress Summary: We were successful in enrolling new study participants from the following diagnostic categories: AD, MCI, frontotemporal dementia (FTD), Parkinson's disease (PD), and normal controls with family history of AD. We have a number of individuals on the waiting list to join the study. In addition, we continued with the annual follow-up assessments of study participants. We have continued with our outreach efforts to neurological colleagues, including the Neuromuscular Division at the University of Arizona to recruit individuals with FTD/ALS and the Movement Disorders Group to recruit individuals with PD/Lewy Body Dementia. Dr. Rapsak has given several lectures on the topic of AD and dementia, including presentations at community events and conferences attended by medical professionals, and has given interviews for local TV stations and newspapers.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Influence of health & lifestyle factors on brain aging and the risk for Alzheimer's disease. Gene Alexander, PhD, Kewei Chen, PhD, Alex Hishaw, MD, Matthew Huentelman, PhD, Yann Klimentidis, PhD David Raichlen, PhD, Manoj Saranathan, PhD, Ted Trouard, PhD. University of Arizona; Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: This proposal requests support for a collaborative research project that will provide the essential pilot data and methodological developments in support of a larger multi-disciplinary research program with the goal of advancing our understanding of how common health-related factors and lifestyle characteristics in the elderly impact brain aging and the preclinical 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, neurology, neuroimaging, neuroscience, genetics, statistics and public health, biomedical engineering, and biological anthropology. This hypothesis-driven, research program will use "state-of-the-art" methods for testing cognition, imaging of brain structure, function, and connectivity, genetics, and behavioral measures of physical activity and sleep quality. This integrative research program will support efforts to investigate health-related factors, focusing on exercise/physical activity and sleep quality and how they interact with cerebrovascular risk to impact the neural systems supporting cognitive function during aging and the preclinical risk for AD. Our overall hypothesis is that health-related lifestyle characteristics, including exercise/physical activity and sleep quality, moderate the impact of cerebrovascular and other health risk factors to influence brain aging and the risk for AD by altering the structure and function of brain networks important for cognitive processes that depend on frontal and temporal brain regions and the integrity of connecting white matter.

To support this research program, the proposed pilot study will address the following primary specific aims: 1) to further develop, implement, and evaluate neuroimaging acquisition and analysis methods for optimal measurement of hippocampal subfield volumes to investigate the effects of healthy aging and the preclinical risk for AD and 2) to determine how exercise/physical activity and sleep quality characteristics influence cognitive performance and associated brain structure, function, and connectivity measures sensitive to cognitive aging and preclinical AD in older adults engaged in differing levels of regular physical activity.

Additional Goals: This study will provide substantial added value by 1) acquiring a battery of cognitive and neuroimaging measures to advance new multi-modal analysis methods to detect the earliest effects of preclinical AD, 2) exploring how genetic variation related to the risk for AD and cognitive decline influence brain aging and cognitive performance in the elderly, 3) developing and submitting new external collaborative grant proposals on brain aging and the preclinical risk for AD, and 4) supporting community outreach and recruitment with our Annual Conference on Successful Aging (ACoSA) and Southern Arizona Healthy Aging Registry (SAHAR).

Background and Significance: The population of older adults is expected to grow rapidly over the next two decades and public health programs will increasingly need to respond to this

escalating growth. Associated with this increase in the elderly will be an increase in Alzheimer's dementia and associated cognitive decline. One important and highly prevalent health risk factor for the development of cognitive decline in the elderly is hypertension. Hypertension is estimated to occur in almost two-thirds of those over the age of 60, is associated with brain changes, including increased white matter macrostructural lesions, and is associated with an increased risk for cerebrovascular disease and AD. It is well established that the risk for developing AD is greatly influenced by genetic factors that can increase the probability of developing dementia and cognitive decline over the lifespan. The most common susceptibility gene for late onset AD is apolipoprotein E with $\epsilon 4$ homozygosity conferring the greatest risk. There is, however, great need to evaluate how other genetic factors influence the overall risk for developing AD and the ability to test and replicate findings in very large datasets is needed to address this critically important question. In contrast to these health risks, exercise has shown promise as a way to help mitigate or improve cognition and brain function during the lifespan. Studies have shown that aerobic exercise can improve cognition during aging and might reduce the risk of AD. In older individuals, high levels of physical activity are correlated with increased brain volume and functional connectivity needed for cognitive processing. Studies investigating cognitive functions and brain imaging in older adults are critically needed to determine the potential for exercise in supporting healthy brain aging, while reducing the risk for AD. Studying individuals with high versus low levels of regular physical activity can help to identify the cognitive and brain-based benefits of exercise for healthy and pathological aging. In addition, the importance of sleep quality is an emerging area that might reflect an important factor influencing healthy aging and the risk for AD.

Preliminary Data: Preliminary results using a new automated white matter hyperintensity (WMH) lesion volume method implemented in Dr. Alexander's lab has shown that using multi-spectral processing for WMH probability maps provides an accurate and reliable approach for evaluating the effects of vascular risk factors, like hypertension, on white matter in healthy aging. In addition, we recently reported that self-report measures of cognitive function were related to memory performance differences in older adults with hypertension, but not in non-hypertensive elderly, suggesting that subjective complaints of cognitive difficulties might be an important early marker of cerebrovascular effects in aging. Furthermore, we applied a novel multivariate, multimodal neuroimaging approach for evaluating the effects of blood pressure differences in healthy aging by showing that greater expression of a network pattern of gray matter atrophy related to WMH volume was associated with poorer blood pressure control. Together, these findings support the use of MRI and especially measures of white matter lesion load and integrity to evaluate health and genetic risk factors for preclinical AD, an issue recently highlighted by Dr. Alexander in an invited editorial for JAMA Neurology. In addition, we recently proposed a new model, the Adaptive Capacity Model (ACM), suggesting that changes in lifestyle behaviors involving everyday cognitive and exercise activity might help to explain a source of individual differences in cognitive and brain aging. We found differences in resting state MRI between young adult endurance athletes and non-athletes, suggesting high levels of physical activity can lead to differences in brain connectivity that might enhance cognitive resilience in later life.

Proposed One-Year and Long-Term Outcomes: The one-year outcomes for this project include the opportunity to identify new findings on the effects of health factors like exercise/physical activity and sleep quality on cognition, as well as on brain structure, function, and connectivity in the context of aging. The plan to further develop and optimize acquisition and analysis methods

for hippocampal subfield volumes has the potential provide a sensitive neuroimaging marker for aging and AD collaborative research. In addition, this work will be leveraged to support planned complementary projects investigating genetic risk for AD and physical activity; as well as the effects of advanced aging in the oldest-old on cognition and brain structure and function. Together, these studies reflect collaborations focused on developing externally funded grant proposals, as part of larger multi-disciplinary, collaborative research program, to investigate how cerebrovascular risk factors, differing levels of aerobic fitness, and advanced successful aging 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 might either enhance or diminish the risk for dementia and age-related cognitive decline. It is expected that this dataset will provide essential pilot data to support new applications for external funding to NIH, NSF, and other external funding sources planned for submission next year. Specifically, this project will provide key data and methodological developments to support planned grant applications by the project investigators, including two NIH applications to investigate the effects of differences in exercise/physical activity and cognitive training on brain aging and cognitive function. It is expected that this work will also lead to an external grant proposal addressing the interactive effects of genetic risk and physical activity on AD among advanced elderly and what factors support successful aging. In addition, we plan to continue our efforts supporting ACoSA and SAHAR to provide for enhanced community outreach, education, and subject recruitment in for our ongoing studies of brain aging and the preclinical risk for AD, as well as outreach efforts of the Arizona ADC.

Year-End Progress Summary: We have made significant progress, in the past year, in our studies on individual differences in health factors and lifestyle characteristics for brain aging and the risk for AD. Analysis from our healthy aging cohort investigated the effects of hypertension status and white matter hyperintensity (WMH) volume on regional networks of white matter integrity in older adults, 50 to 89 years of age. In this study, we found that WMH volume was related to decreased white matter tract integrity measures assessed by diffusion tensor magnetic resonance imaging (MRI), whereas hypertension status was not associated with tract integrity differences. Together, these findings suggest that WMH volume might be an important vascular risk factor that is separable from hypertension status in the context of healthy aging. This work has been submitted for publication (Nguyen et al., submitted). In addition, we performed a preliminary investigation of differences in hippocampal subregions in healthy aging by studying healthy participants 50 to 89 years of age. For this study, we found a regional network with reductions in the vicinity of the dentate gyrus and relative preservation in CA3 associated with increased age; and further this pattern showed a higher expression in those with APOE ϵ 4, after controlling for age. The preliminary results from this work were presented at the Society for Neuroscience meeting (Alexander et al., 2017). Working with Dr. Saranathan, we have made significant additional progress in identifying and evaluating MRI sequences to optimize acquisition of MRI for hippocampal subregion measurements.

We continue to extend our human hypertension work with a translational research study currently underway using a transgenic rodent model of hypertension in a \$2.4M NIA-funded R01 grant (Multiple PIs: Alexander, Barnes, Coleman). This five-year study with AAC collaborators uses “state of the art” epigenetics, cognitive measures, and neuroimaging methods to evaluate the effects of hypertension on the molecular status of brain regions affected by brain aging. A

manuscript showing the first regional network gray matter covariance pattern in rodent brain MRI at 7.0T was submitted (Alexander et al., submitted), supporting the use of human neuroimaging methods in translational studies with small animal models of aging and neurodegenerative disease. Work from the current AAC study has also supported the ongoing development of a multi-site collaborative project funded by the McKnight Brain Research Foundation (Multiple PIs: Alexander, Cohen, Visscher, Wright) to study the effects of cognitive and brain function in generally healthy advanced older adults, ages 85 to 100+. This effort is currently underway and reflects ongoing collaborations between the University of Arizona, University of Florida, University of Alabama, and University of Miami. Preliminary findings from this work has shown that more consistent physical activity, assessed by actigraphy, is associated with greater cortical thickness in multiple frontal and temporal brain regions in a group successful aging, oldest old adults. This work also includes an additional funded proposal to enhance the development and implementation of novel cognitive measures to assess cognitive decline in this advanced elderly cohort (Multiple PIs: Alexander, Cohen, Levin, Wadley). This multi-site collaborative work has led to an externally funded five year \$5.7M NIA R01 grant, currently underway, conducted by the University of Florida, University of Arizona, and University of Miami to evaluate the benefits of cognitive training in older adults (UA Field Center PI: Alexander; UA Co-Investigators: Allen, Hishaw, Trouard). In addition, this multi-site effort has led to the development of plans for new intervention trial proposals to both the McKnight Brain Research Foundation and NIA to evaluate ways to enhance cognitive function in aging and those at risk for AD (Multiple PIs: Bowers, Alexander, Wood).

Drs. Raichlen, Alexander, and Klimentidis have continued to pursue implementing the acquisition of actigraphy to provide data on physical activity and sleep characteristics in our AAC studies. To support this effort, we have also initiated an analysis of a large actigraphy dataset to evaluate how individual differences in activity relate to age and mortality, as well as genetic factors. Manuscripts on this work have been submitted (Klimentidis et al., submitted; Raichlen et al., submitted), along with submission of a provisional patent on our novel method of analysis (Raichlen, Alexander, Klimentidis). We have plans to submit a new NIH grant proposal to expand on our very encouraging findings with exercise and brain aging.

In a collaboration with Dr. Judith Su in the Departments of Optical Sciences and Chemistry and Biochemistry at the University of Arizona, we are applying her novel technology to identify AD-related blood and cerebrospinal fluid biomarkers. This work reflects a collaboration with Dr. Tom Beach from the Sun Health Research Institute and the Arizona ADC Pathology Core, with an NIH R03 grant on this work recently funded (PI: Su; Co-Is: Alexander, Beach). During this year, Dr. Alexander (Core Leader), working with other members of the AAC, including Drs. Reiman (ADC PI), Chen (Core Co-Leader), Beach, Kuo, Baxter, Ahern, Ryan, and Trouard], submitted a \$3.7M NIA P30 Core Supplement grant to create a new Brain Imaging and Fluid Biomarkers Core for the Arizona ADC, which will make PET imaging of AD pathology and fluid biomarkers available for AAC researchers across the Tucson and Phoenix metro areas.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Daily thinking patterns in healthy and pathological aging. Jessica Andrews-Hanna, PhD, Matthias Mehl, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To develop a scalable mobile smartphone app to measure on- and off-task thinking in daily-life.

Aim 2: To explore age-related changes in the frequency, content, and consequences of daily thinking patterns.

Aim 3: To determine aspects of daily thinking that differentiate optimal from nonoptimal aging.

Aim 4: To develop collaborations with members of the Arizona Alzheimer's Consortium and plan a future study to explore on- and off-task thinking in individuals at risk for Alzheimer's Disease (AD).

Background and Significance: Adults spend nearly half their waking day engaged in off-task thought, and converging evidence (including work by P.I. Andrews-Hanna), suggests that such thoughts are associated with a variety of costs and benefits. Whereas off-task thinking can disrupt task performance and fuel distress or unhappiness, it can also make us better equipped to confront future challenges, solve problems, and navigate the social world. Although growing interest lies in understanding off-task thoughts and in characterizing the factors that promote their adaptive and maladaptive consequences, existing behavioral studies are limited by their use of laboratory-based paradigms in small uniform samples, or retrospective self-report questionnaires known to be influenced by memory biases and distortions. Consequently, how on and off-task thoughts unfold in real-world contexts as individuals go about their day-to-day lives remains poorly understood.

Another significant gap in our understanding of off-task thinking is how it changes in healthy and pathological aging. This question is particularly relevant because of important links between off-task thinking and many constructs known to become altered in old age, including memory, executive function and well-being. For example, older adults are vulnerable to depression and social isolation, constructs which can both be fueled by dysfunctional styles of off-task thinking and increase risk for dementia by 65%. Thus, understanding the ways in which off-task thoughts change in healthy and pathological aging might yield important insight into predictors of optimal versus nonoptimal aging, and risk factors for depression and AD. These topics are also relevant in light of a growing appreciation that the brain's default network (DN) is at the core of off-task thinking, aging, AD, and depression.

To address these gaps, we propose to develop an innovative mobile smartphone tool to measure on- and off-task thoughts in real-world settings at random moments throughout the day. Overall, the data yielded from this project will inform our understanding of the most intimate and arguably the most vulnerable aspect of human cognition – how humans think and feel in daily life.

Preliminary Data: P.I. Andrews-Hanna is in an excellent position to lead a project of this nature because of her extensive prior work exploring the psychological and neural underpinnings of

internally-guided thought. Her team has recently developed a free Android smartphone app, called *Where's My Mind?* that seeks to explore daily thinking patterns in diverse groups of individuals in daily life. However, this app could use significant improvements to its user interface and can only reach Android users – two limiting factors when it comes to older adults. As such, although there are 638 consistent users of the app, only 18 are over the age of 60. In a different ongoing study, P.I. Andrews-Hanna developed a trait questionnaire to assess daily thinking profiles, and a retrospective self-report questionnaire to assess thought content during a 5 minute resting state paradigm. Across our current sample of 42 young and 115 older adults (>60 years), older individuals reported less frequent internally-focused off-task thoughts, greater distraction by irrelevant external stimuli, greater present-focused and reduced past-focused content, and biases toward positive and other-focused thoughts. Among older adults, better well-being was associated with fewer internally-focused off-task thoughts (especially negative thoughts), fewer external distractions, and more goal-oriented content and imagery.

Proposed One-Year and Long-Term Outcomes: By the end of year 1, this project will yield a flexible, freely downloadable iOS smartphone app with potential to reach a diverse group of users across the world, scaling to sample sizes in the thousands. In conjunction with an already-existing Android app recently developed by the PI's team, both tools will make it feasible for the PI and her collaborators to examine longitudinal daily thinking patterns (and other variables of interest) in subsequent clinical research studies. As such, we expect this app will be viewed as a significant advantage when applying for external funding to support such larger studies at agencies such as the NIA, the Alzheimer's Association, and the Dana Foundation. In addition to these many future research opportunities, P.I. Andrews-Hanna and members of her team will present findings from this project at the 2018 AAC retreat and at other conferences, and also prepare relevant preliminary findings for publication.

Year-End Progress Summary: The PI and her team continue to make progress on the proposed research. Of relevance to Aims 1-3, the Android version of our *Where's My Mind?* app has been updated and development of the iPhone version of the *Where's My Mind?* app is underway in collaboration with two software development teams at UA. An iOS platform is being developed by Ami Buczek, Principal Application Systems Analyst of the University of Arizona's Central Information Technology Services and Hagan Franks, Manager of Software Engineering in Data7: UA's Interdisciplinary Data Science Institute. PI Andrews-Hanna has been in communication with the Alzheimer's Prevention Registry (APR; endalznw.org), who have agreed to include the proposed study in their registry of ongoing research projects, reaching a database of >290,000 users once the iPhone version is complete. Many of the users in the APR database are older adults and iPhone users. Relevant to Aims 2 and 3, PI Andrews-Hanna presented a poster at the annual *Society for Neuroscience* conference assessing age-related changes in the frequency, content, and neural underpinnings of mind-wandering with a novel trait questionnaire, and collaborated with Dr. Muireann Irish at the University of Sydney on two manuscripts currently under review at *Psychological Research* and *PNAS* documenting similar findings during a novel behavioral laboratory-based task, and extending investigation of mind-wandering frequency to older adults with Alzheimer's disease, Frontotemporal Dementia, and Semantic Dementia. Although neither of these studies make use of the *Where's My Mind?* smartphone app to assess thinking patterns using an ecological momentary assessment approach in daily life, the findings are promising and converging, with important implications for mental health. These studies reveal age-related

reductions in the frequency of mind-wandering, and document more positive, less negative, less self-focused, more socially-focused, and less past-oriented off-task thoughts in older as compared to younger adults. The last two collaborations have led to a chapter currently underway exploring the neural underpinnings of age-related changes in internally-guided cognition. PI Andrews-Hanna has also forged new collaborations with faculty within the department of Psychology at UA, resulting in 1) submission of a collaborative grant to the Arizona Alzheimer Core Center to investigate depression as a risk factor for Alzheimer's disease, and 2) a chapter under review exploring dysfunctional internally-guided thinking in mental health disorders, and mechanisms of therapeutic change⁵. Further collaborations with researchers outside of the Psychology Department will be forged at the March 2018 Arizona Alzheimer Consortium retreat. Finally, PI Andrews-Hanna has participated in public outreach pertaining to her work on internally-guided thought, aging, and brain network function, including a talk at Sun City retirement community "Aging Gracefully: Insights from Neuroscience Research," an article in Arizona Daily Star Science Times "UA Researchers Develop Mind's Fitness Tracker," and a TV news interview on KGUN-TV.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Primate models of age-related memory impairment: tests of agents approved for other indications that are safe and might be successful cognitive enhancers. Carol A. Barnes, PhD, Lalitha Madhavan, MD, PhD, Carolyn Harley. University of Arizona; Newfoundland University; Arizona Alzheimer's Consortium.

Specific Aims: The overall goal of this project is to determine whether the alpha-2 noradrenergic receptor agonist guanfacine can mitigate multi-tasking deficits known to occur in older humans, nonhuman primates and rodents. It has been demonstrated that guanfacine can enhance working memory in sustained attention tasks that require monkeys to focus on a single stimulus in a field of distractors, or to split attention between two separate stimuli. Another distinct form of attentional control is the ability to switch attention between different streams of behaviorally-relevant information, a process referred to as flexible attention. The ability to use this form of attention is also known to deteriorate with aging. The Aim of this experiment is to determine whether guanfacine will also enhance flexible attention, as it does other forms of prefrontal cortex-dependent executive functions such as sustained attention.

Background and Significance: Noradrenergic modulation of forebrain neuronal networks alters the encoding, processing and storage of sensory information through heterogeneous actions across multiple anatomical regions and receptor subclasses. Dense noradrenergic afferent projections from the locus coeruleus distribute across the mammalian prefrontal cortex reaching a constellation of brain regions that support cognitive functions, including working memory, sustained and divided attention. During normative aging, many prefrontal cortex-dependent behaviors become impaired, resulting in a reduction of an individual's ability to comprehend and manipulate incoming sensory stimuli and act appropriately. Recent evidence suggests that locus coeruleus cell densities positively correlate with cognitive function within age populations, implicating this system as a promising target for pharmacological enhancement of mental abilities in older humans.

Within the prefrontal cortex, the neural circuits thought to underlie flexible attention reside in regions more dorsolateral to those involved with sustained attention, which are found more medially. Furthermore, the relative abundance of the different types of noradrenergic receptors varies between these regions of the prefrontal cortex. For these reasons, it is uncertain whether increasing the function of the alpha-2 receptor will result in the same improvements in cognition as was observed for sustained attention tasks.

Preliminary Data: We have trained 6 young and 5 old bonnet macaques to perform a task requiring attentional switches from a primary recognition memory task to an unrelated task and back (requiring "flexible attention"). We were able to show that this multi-tasking paradigm disproportionately disadvantaged the older animals.

Proposed One-Year and Long-Term Outcomes: The data collected from this experiment will form the basis for a rationale to use guanfacine during prefrontal cortical single cell recordings

that will be performed in these animals. While single cell recordings have been conducted in frontal cortex in the presence of iontophoresis of guanfacine near the recording electrode, and guanfacine has been given to monkeys while performing a behavioral task, the physiology and behavior have not been conducted simultaneously, nor has this form of flexible attention been examined. If we demonstrate that we can improve cognition with this treatment, we will go on to conduct the full physiology/behavior study.

Year-End Progress Summary: We have made excellent progress towards the goals of the work proposed for the Arizona Alzheimer's Consortium state-funded project. First, we have successfully used an imaging-based approach for removing auto-fluorescing elements that accumulate in aged neural tissue, often creating significant artifacts in neuroanatomical experiments. The use of this linear unmixing technique will significantly reduce contamination from fluorescent artifacts in our tissue. Second, we have worked with the manufacturer of our confocal microscope, Zeiss, to create custom software that moves the microscope stage in a way that randomly samples within a user-defined region of tissue. This is a necessary component to achieve unbiased stereological estimations of cell density. Third, we have identified locus coeruleus-containing brain tissue from all of our monkeys. Fourth, we have obtained advice from an expert (Lalitha Madhavan) on how to implement systematic random sampling strategies, which is a second necessity to achieve unbiased estimates of cell density. Finally, we have successfully tested and finalized the immunofluorescent protocols for five different antibodies specific for the cell-types of interest in this study. We are currently initiating tissue staining, confocal imaging and stereological analysis.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Exploring the microbiome-gut-brain axis: impact of microbial communities and their genes on cognition in aging. Carol A. Barnes, PhD, John Konhilas, PhD, Lee Ryan, PhD, Betty Glisky, PhD, George Watts, PhD, Dean Billheimer, PhD, Greg Caporaso, PhD. University of Arizona; Northern Arizona University; Arizona Alzheimer's Consortium.

Specific Aims: The overall goal of this pilot project is to determine whether there is an association between the level of cognition in younger and older rats and humans and the species and functional composition of a given individual's gut microbiome. The goal is to discover those microbial properties that are correlated with brain health and cognitive status of individuals. Most of the mechanistic details of the gut-microbiome-brain connection remain to be established, but these studies could eventually lead to microbe-based therapies for optimizing cognitive health. There are two Specific Aims of the current proposal. Aim 1 is to assess cecum bacterial diversity in young (6mo), middle-aged (15 mo) and old (23 mo) male, F344 rats who have been individually characterized on a large cognitive test battery and have been assigned to one of three groups: "high functioning", "average functioning" and "low functioning" for each of the 3 ages examined. The results of this experiment will guide our hypotheses in the second aim. Aim 2 is to assess fecal samples from healthy older individuals in a cohort of cognitively-characterized individuals that Glisky and Ryan have followed longitudinally, and who have been determined to be either: a) high-functioning in both the temporal lobe and frontal lobe test batteries, 2) or low-functioning in both the temporal lobe and frontal lobe test batteries.

Background and Significance: There is substantial variation in the impact of aging on cognition in healthy older adults, even those who are unlikely to go on to develop Alzheimer's or vascular dementias. In fact, there is substantial variation in the impact of aging on cognition even in genetically 'inbred' strains of rats whose environmental experience in terms of exposure to pathogens, nutritional and social environments are apparently very similar. This suggests that animal models will contribute important insights into the mechanisms underlying individual differences that result in successful rather than unsuccessful aging phenotypes across species.

Barnes is the PI of a funded RO1 that supports the conduct of an integrated set of experiments designed to assess mechanisms underlying differential cognitive trajectories observed over the lifespan of the F344 rat. These variables include cognitive test batteries over different domains, high resolution MRI imaging, behavior-driven single cell gene expression imaging and brain region- and cell-specific whole transcriptome analysis of brain regions relevant to the behaviors tested. The cognitive test battery used in the large rodent study is conducted to identify rats on the basis of possessing behavioral performance scores that are "high", "average" or "low" with respect to performance distributions from young adult, middle-aged and older adult rats. The behaviors include assessment of hippocampus-dependent spatial memory, motor behaviors, spatial search strategies, visual, general motivational factors, and simple and compound discrimination tests. Other tasks assess ventral visual stream/perirhinal cortical function, frontal cortex-dependent working memory, interference and temporal order tasks. The range of memory tested in these behavioral tasks are analogous to a number of the cognitive tests given in humans in Aim 2.

Although not a ‘funded’ component of this grant, at the time we sacrifice our young, middle-aged and old rats (3 levels of cognitive aptitude in each age group), we also collect gut samples. Konhilas has trained us to dissect the gut into 7 distinct components, and to collect contents and epithelial scrapings from each of these levels for rapid freezing. We can then extract the DNA, and Watts performs the bacterial DNA isolation and 16S gene amplicon generation and rRNA gene sequencing. Following this, Billheimer and Lussier will apply computational biology approaches they have developed to these datasets.

Detailed analyses of the gastrointestinal (GI) tracts of these rats will allow us to determine whether different distributions of microbiota in the GI system are related to the way in which individual rats segregate along a cognitive competence continuum throughout life. The answers we obtain from these rats, using technologies that cannot be used in humans at present, will allow direct predictions to be made for our human studies. To begin to explore human cognition we will continue to obtain stool samples from cognitively-characterized older individuals from the Glisky/Ryan cohort to begin to explore what characteristics of the microbiome might be advantageous in human populations, and to develop hypotheses about critical brain-immunological interactions for optimizing cognitive health throughout the lifespan.

Preliminary Data: We have obtained cognitive data in both the temporal lobe and frontal lobe domains in both the rats and human participants that will contribute to these studies. We prepared samples from 49 rats for gene sequencing in the past year, and these data have been given to Billheimer and Lussier to evaluate using their statistical models. We have also collected samples from 12 of our targeted 20 human participants for this study.

Proposed One-Year and Long-Term Outcomes: The data collected in these two aims will give us preliminary data to be used to request a supplement for funds to analyze the remaining data in the rodent study, and as preliminary data for an RO1 for a larger human experiment.

Year-End Progress Summary: We have made good progress on the gut project over the past year. We have given 83 samples total to the Genomics Core at the Cancer Center, where George Watts is completing the 16SrRNA sequencing on contents and epithelial scrapings from the cecum. All of these rats have gone through a cognitive test battery and have been judged to be either low or high performing at young and old ages. We are also doing quantitative PCR validation of the bacterial species of interest from the sequencing method. We have now obtained all the control DNA templates for this species and are awaiting the primers for the qPCR analysis. Once we get the PCR confirmation or disconfirmation of a significant effect of age and cognition on these bacteria, we will either have confidence that we found a potentially significant microbiome brain interactions – if we do not confirm, we have several options. Our colleague, Greg Caporaso at NAU, has a number of additional levels of analyses that we could go on to perform, should it be necessary.

We have collected samples from 15 total cognitively characterized human participants, with a composite memory score that was high (n = 8) vs low (n = 7). We are continuing to collect samples with the hope of 12 in each group. To begin, we will perform targeted analyses of microbiome species composition, dependent on the outcomes of the rodent experiments.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

APOE4: Accelerator of bioenergetic aging in female brain and risk of Alzheimer's disease.
Roberta Diaz Brinton, PhD, Nan-Kuei Chen, PhD, Ted Trouard, PhD, Fei Yin, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: While Alzheimer's disease is not unique to the female, women constitute the majority of persons with the disease. Discovery of at risk endophenotypes in women and their underlying mechanisms could potentially lead to the early identification of those at greatest risk of developing Alzheimer's (AD) and interventions to prevent the disease. Given the aging of the U.S. population, including a projected 45 million women over age 55 by 2020, the timing of this research is crucial. The goal of our proposed project is to discover biological transformations in brain that occur in the female brain that lead to endophenotypes predictive of risk for Alzheimer's disease (AD). To achieve this goal, our analyses are designed to identify the mechanisms by which these transformations occur and to translate these discoveries into strategies to prevent conversion to an at-Alzheimer's-risk phenotype. The proposed program of research builds on our discovery that the perimenopause is a neurological bioenergetic transition state in the female that shifts the brain from utilizing glucose as its primary fuel to utilizing ketone bodies as an auxiliary fuel¹ (Fig. 1). Further, we have discovered that the adaptive reliance on ketone bodies puts the brain at risk for catabolizing its own white matter lipids for fuel. Outcomes of our mechanistic to clinical to global population program of research could provide insights into the increased burden of the ApoE4 gene and risk of AD in ApoE4 positive women.

In this program of research, we propose that: Females positive for ApoE4 gene experience three strikes that result in accelerated bioenergetic aging in brain. Strike one for ApoE4 positive females, is the genetic risk conferred by the ApoE4 genotype. Strike two is chronological aging. Strike three is the bioenergetic transformation of the endocrine transition of the perimenopause. Collectively these act as an accelerator to generate three hallmarks of Alzheimer's disease in brain, hypometabolism, beta amyloid deposition and hippocampal atrophy.

To test this hypothesis, we have developed a set of integrated specific aims that span mechanistic discovery in ApoE4 animal models to clinical neuroimaging in ApoE genotyped perimenopausal and postmenopausal women to a global population through the ENIGMA network of neuroimages, clinical data and ApoE genetics (<http://enigma.ini.usc.edu/about-2/>). Further, we have created an interdisciplinary team that spans basic, clinical, multimodality human brain imaging, and big data expertise.

Aim 1: Mechanistic Discovery: Determine ApoE4 genotype regulation of the perimenopausal bioenergetic, inflammatory and lipid metabolism transitions in brain and their association with Alzheimer's pathology. Determine modulatory factors that reduce or exacerbate the impact of ApoE4 genotype.

Hypothesis: APOE4 allele accelerates and exacerbates bioenergetic transition in female brain to increase development of Alzheimer's pathology.

Aim 2: Clinical Translation: Determine impact of perimenopause and the APOE4 genotype on brain metabolism, burden of Alzheimer's pathology, structural integrity and cognitive function in perimenopausal and postmenopausal women. Extend analyses of ELITE cohort (600 postmenopausal women) to determine impact of ApoE4 genotype on metabolic cluster membership and longitudinal cognitive function.

Hypothesis: APOE4 genotype accelerates and magnifies perimenopausal bioenergetic brain aging evidenced by hypometabolism, beta amyloid deposition and loss in hippocampal volume. Further, these brain imaging markers will be predictive of cognitive impairment.

Aim 3: Global Population Translation: Determine the impact of the APOE4 genotype and menopause on the lifespan trajectories of 5000 women derived from 10,000+ MRI derived brain volume metrics, genetics and clinical data available through the ENIGMA network. 33,195 subjects (men and women) with MRIs and genomes will also be investigated using a meta-regression model for the effect of age, ApoE4 and other genotypes on significant brain atrophy.

Hypothesis: APOE4 genotype shifts the postmenopausal endophenotype of brain volume and lifespan trajectory to the left (i.e., interaction between ApoE4 and menopause will be evident earlier as evidenced by glucose hypometabolism in brain accompanied by hippocampal atrophy).

Background and Significance: The greatest risk factors for Alzheimer's disease are age, the ApoE4 allele and female sex. Postmenopausal women constitute >60% of the affected Alzheimer population and are those who will bear the greatest burden of the disease. Twenty years, 2 decades, ago Farrer and colleagues reported a sex difference in the lifetime risk of AD in women. In his seminal report, women with a single copy of the ApoE4 allele was sufficient to increase disease risk associated with two copies of the ApoE4 gene in men. This finding was confirmed a year later in a subsequent report by Payami, Schellenberg and colleagues who found that ApoE4 heterozygote men had lower risk than ApoE4 homozygotes; there was not significant difference between epsilon4 heterozygote males and those without epsilon4. In contrast, epsilon 4 heterozygote women had the same significant twofold increased risk as homozygote men. Barnes, Bennett and colleagues found an even greater sex difference in the impact of pathology and risk of AD. Each additional unit of AD pathology was associated with a nearly 3-fold increase in the odds of clinical AD in men compared with a more than 22-fold increase in the odds of clinical AD in women. Increasing evidence links ApoE4 genotype and female sex with increased risk and severity of AD although not all studies find the female sex ApoE4 interaction. The earliest etiological factors that ultimately lead to late-onset Alzheimer's disease, when prevention is still possible, remains unresolved for the primary casualties of the disease, postmenopausal women.

Preliminary Data: Collectively, our mechanistic discovery findings, replicated in mouse, rat and translated to human, indicate that the perimenopause transition can lead to a bioenergetic crisis in the brain that activates a cascade of adaptive responses that ultimately lead to multiple features consistent with AD risk, including glucose hypometabolism in brain, development of a ketone body dependent brain, neuroinflammation, white matter degeneration and deficits in synaptic transmission. Further, dysregulation of metabolism in the human female is associated with significant cognitive decline²⁷. In brief, those findings are:

1. A natural aging rodent model of human female endocrine aging reveals two distinct aging programs, one chronological and the other endocrine. The aging program precedes endocrine aging and appears to initiate the endocrine aging program.
2. The glucose dependent bioenergetic system of the brain – including glucose transport, associated gene and protein expression, enzyme activity and mitochondrial respiration – all decline during the perimenopausal transition and remain decreased thereafter
3. Mitochondrial gene expression declines during the perimenopause and remains decreased thereafter.
4. Surprising to us, the ketogenic system also decreased during the perimenopausal transition¹ and subsequently recovered at the menopause. However, this adaptive bioenergetic pathway was time limited as it dissipated with age.
5. The perimenopausal decline in glucose metabolism is associated with a significant decline in synaptic transmission evidenced by decreased long-term potentiation¹.
6. Rise in inflammatory signaling pathways also occurred during the perimenopausal transition and were sustained thereafter¹.
7. Decline in genes required for β -amyloid degradation occurred subsequent to endocrine aging.
8. Astrocytes undergo a transcriptional shift in expression of estrogen receptors with an increased ratio of the nuclear receptors ER α : ER β . DNA methylation of the ESR2 (ER β) UTR correlates with differences in ER β expression suggesting that epigenetic factors might be related to perimenopause-related change in ER expression and loss of transcriptional response to E2.
9. Efficacy of hormone therapy in reducing A β accumulation and improving behavioral outcomes in female 3xTg-AD mice is (i) linked to its ability to suppress microglial activation, (ii) absent in middle-aged mice that have completed the ‘perimenopause’ transition, (iii) diminished in obese mice.
10. A widespread shift in neural estrogen responsiveness following perimenopause transition that likely contributes to the observed loss of hormone therapy efficacy in postmenopausal women.
11. Clinical translational validity of our bioenergetic hypothesis of perimenopause and its concomitant risk for cognitive decline was supported²⁷. Postmenopausal women with a clinical profile consistent with a risk of metabolic dysfunction (clinical profile at the limits of normal) exhibited significant decline in cognitive function relative to women of the same age whose metabolic function was well controlled. A rapidly deployable and economically feasible biomarker panel was developed to identify women at risk for developing late onset of Alzheimer’s⁷.
12. Lastly, glucose bioenergetic crisis initiated during the perimenopause activates a genomic and biochemical cascade in brain required to catabolize white matter lipids necessary to generate ketone bodies to fuel generation of acetyl-CoA.

Proposed One-Year and Long-Term Outcomes: Outcomes of our mechanistic program of research will provide insights into the molecular and genetic mechanisms underlying the increased burden of the ApoE4 gene and risk of AD in the female aging brain. Data derived from the proposed AAC analyses will support federal and philanthropic funding opportunities. We anticipate that findings from the proposed analyses will integrate with and expand upon those of the analyses of *APOE* ϵ 4 carriers conducted by Reiman and colleagues. While our analyses focus on the aging *APOE* ϵ 4 female brain, we anticipate that mechanistic insights derived from this accelerated aging model will inform our understanding of the increased risk of AD in the *APOE* ϵ 4 male.

Year-End Progress Summary: Our longitudinal study in the humanized APOE4 rat model revealed a significant interaction between age, APOE genotype and sex. APOE4 female rats exhibited lower brain glucose metabolism accompanied by elevated plasma ketone body and triglyceride levels at all three ages (9-10, 12-13 and 15-16 month-of-age) compared to males. The APOE4 effect on brain glucose metabolism was evident only in females and only at their post-menopause stages whereas in male brains glucose uptake was preserved across ages. These data indicate that APOE4 exacerbates glucose hypometabolism in females to accelerate utilization of ketone bodies as an auxiliary fuel.

Our findings from a multimodality brain imaging study in a cohort of clinically and cognitively normal women and age-matched men (Mosconi et al., 2017) are strikingly consistent with the rodent study and strongly support the translational validity of our preclinical model of female brain aging. Compared to pre-menopause (control) women and to men, perimenopause and menopause women exhibited increased indicators of AD endophenotype, including hypometabolism, increased A β deposition, and reduced gray and white matter volumes in AD-vulnerable regions. AD biomarker abnormalities were greatest in menopause group, intermediate in perimenopause group, and lowest in the control women. Moreover, glucose hypometabolism and A β deposition was exacerbated in APOE4-positive menopause women relative to the other groups, suggestive of APOE4 acceleration of the emergence of endophenotypes of late-onset AD risk upon endocrine transition.

Collectively, our pre-clinical and clinical studies suggest that the prodromal AD endophenotype that occurs early in the aging female brain coincides with perimenopause endocrine transition and is worsened by APOE4 allele.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Validating a new measure of cognitive aging and decline in Down Syndrome. Jamie Edgin, PhD and Katharine Hughes, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: The NIH Down syndrome working group has called for the development of cognitive measures that are valid and reliable for use in Down syndrome across the lifespan. In this study, we validate the use of a novel iPad-based cognitive assessment designed by the laboratory, across individuals with DS with differing profiles of genetic and cognitive risk who are >35 years of age and at risk to develop AD.

Aim 1. Employ the Arizona Memory Assessment for Intellectual Disability in 20 adults with DS >35 years, examining the psychometrics of the measure (i.e., floor effects) as well as the preliminary results comparing aging and young individuals with DS (using concurrent data from our NIH funded work).

Aim 2. Compare the measure between aging individuals with DS at varying levels of genetic and cognitive risk, including APOE 4 allele carriers (n = 5) vs. non-carriers (n = 5), and those with a clinical diagnosis of dementia (n = 5) vs. no diagnosis (n = 5).

Aim 3. 3-5 experts in DS and AD will provide written feedback about the use of the measure in future clinical trials.

Aim 4. In total, alongside our efforts in our funded NIH work, these results will help guide design and software modifications to the measure.

Background and Significance: Memory impairments are one of the most prominent deficits associated with DS, posing severe constraints on learning, language acquisition, and adaptive behavior. Impairments in memory function and executive control are also important indicators of cognitive decline in DS. We have been recently funded by the National Institutes of Health to design and validate a comprehensive battery of touch-screen assessments of memory for children with DS. This battery has three forms and can be completed in under an hour, allowing for what we hope will be an efficient and reliable assessment that minimizes fatigue effects. We have noted fatigue effects are present in some recent clinical investigations and could impact the ability to detect positive drug effects. While we are funded to validate this measure in children, suitable measures also are required at the other end of the lifespan, as cognitive capacities begin to decline and many individuals with DS start to demonstrate the symptoms of AD. To address these broad needs, the Edgin lab developed the Arizona Memory Assessment for Preschoolers and Special Populations (A-MAP) and an analogous version for older individuals with DS called the A-MAID (Arizona Memory Assessment for Intellectual Disability). Given the extensive evidence for an uneven profile of memory impairment in DS, the A-MAID incorporates subtests designed to assess specific components of memory and executive function linked to these neural regions. Only by assessing these discrete components of memory can we best identify early indicators of age and AD-related decline in individuals with DS. Our funded NIH grant focuses on validation of memory measures that would be useful for younger children. Currently, the NIH is not funding the use of

this battery in older adults with DS that are at risk for dementia, but we anticipate that a NIH supplement or renewal might include aging groups.

Preliminary Data: In our first report of the measure, adolescents and adults with DS show a profile of performance that would be expected based on mouse models of DS and from validation studies (Clark et al., 2017, *Hippocampus*). That is, participants with DS perform poorly on measures of temporal and spatial binding thought to be reliant on the hippocampus, whereas they perform relatively well on measures of item and spatial recall. Preliminary data collected by Marwan Sabbagh's lab in collaboration with us suggested a previous version of the task was well-tolerated in older adults with DS.

Proposed One-Year and Long-Term Outcomes: Data from the current project will be used to help modify the A-MAID measure and as proof of concept of the use of this measure in older adults with DS. Attempts to obtain external funding will be made to the NIH.

Year-End Progress Summary:

Aim 1. To date, we have initiated testing in 5 aging adults with DS >35 years, and testing is fully completed with 3 participants. 21 individuals have been identified for testing. All participants have tolerated the battery well and completed the tasks in a timely manner. In this small number of first participants, we have observed that the individuals stay engaged throughout the entirety of the assessment. The variety of tasks represented in the different phases kept the participants interested in what is next and focused on the task at hand. However, we have also noticed that many of the individuals in the adult age group have not been exposed to tablet technology prior to their visits and have no experience with computers or touch-technology. Because of this, we are implementing methods to get the person comfortable with the technology. When they return for their second and third visits, we have noticed significant improvements in using the tablet and their comfort levels with the technology.

Aim 2. We have recruited 4 participants >35 years (1 female, 3 males) without dementia and 1 participant (male, age 58 years) with a clinical diagnosis of dementia.

Aim 3. We have gathered feedback from experts in the field, including Dr Nancy Lee-Raitano, Dr Dagmara Dimitrou, Dr Carolyn Mervis, Dr Rene Pierpont, and Professor Mark Good. These individuals are experts in developmental disorders including Williams syndrome, ASD, DS; clinical psychologists; pediatric neuropsychologists; and experts in animal models of hippocampal dysfunction including AD. An expert in dementia in DS, Sharon Krinsky McHale and a clinical trial company CSO (Jeannie Visootsak) are also currently reviewing the measure.

Aim 4. We do not yet have sufficient data to draw conclusions about what features of the assessment might require alterations for the older population. However, we have identified participants for the required sample size; therefore, we expect to be able to interpret the data to inform design alterations for older individuals by the end of summer 2018.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Calibrating the function of the aged circadian clock with high-precision light. Fabian Fernandez, PhD, Michael Grandner, Norman Ruby. University of Arizona; Stanford University; Arizona Alzheimer's Consortium.

Specific Aims: As we age, the temporal organization of our mind and body strays from the Universal Time (UT) that is set with the Earth's rotation. The brain's internal clock can no longer maintain a coherent schedule aligned to the movement of the sun and the sun's two timekeeping stamps: dawn and dusk. This loss of circadian function directly interferes with our ability to store memory and can be a harbinger of neurodegenerative diseases to come such as Alzheimer's.

Our lab seeks ways to artificially engineer the light spectrum to treat age-related circadian dysfunction. In the current AAC project, we will use an animal model to deconstruct the circadian effects of a continuous 15-min light pulse delivered at areas of the night bookending dusk and dawn. We will determine how this light pulse can be whittled down so that a similar magnitude of response is achieved—but with the fewest photons possible—and will ask whether this logic is conserved in aging clocks (**Specific Aim 1**).

In the second arm of the project, we will characterize how those brief intermittent episodes can be broken-down (still) further into a secondary temporal structure that optimizes communication between the spaced pulses (**Specific Aim 2**). This secondary temporal structure will be comprised of discrete bins of millisecond light. Here, we will quantify the phase-shifting effects of high-speed LED flashes (0-120ms) in younger animals, compare them to constant equiluminous light, and will assemble a larger data set that tunes these flashes for color temperature, intensity, and delivery schedules. We will then quantify how the circadian pacemaker of older animals responds to these specialized sequences, establishing whether older clocks use the same photic information as younger clocks when calculating a phase-shift. The rule-sets we establish in this short-term project will ultimately filter into a larger programming language of photic stimulation we are developing to rehabilitate the brain's aging clock when the clock is having trouble entraining to the solar day.

Background and Significance: Developing patterns of precision light delivery that will kick-start circadian rhythmicity is not a monolithic endeavor. To expedite the steps in this process, we will turn to a model organism that has a strong, successful track record of uncovering general principles of light resetting: *Drosophila*. Every major facet of the circadian system now known to operate in humans was first demonstrated in insects such as flies. Like humans, these animals are tasked with entraining to the solar light-dark cycle and tend to use the same “software” logic to do so despite some obvious differences in nervous system hardware. More likely than not, the steady replay of twilight over millennia has led to an evolutionary convergence for what photic information the circadian clock favors to track time passage. In that sense, it is not surprising that *Drosophila* have been pioneers in pacemaker research, providing the first accurate estimation of the pacemaker's

sensitivity to light and one of the first indications in the animal kingdom that the action spectrum for circadian resetting was weighted towards shorter, “bluer” wavelengths.

Preliminary Data and Plan: To obtain the most generalizable picture possible on how light fractionation and millisecond pulses differentially affect the younger versus older pacemaker, we will quantify light-induced phase resetting of locomotor activity rhythms in *Drosophila ananassae*, a *particular* cosmopolitan species of fruit fly that co-evolved with human society. *Ananassae* form highly-structured domesticated populations around humans, rarely establishing homes in more natural habitats such as fields or apple orchards. Because of this background, the flies show a unimodal pattern of locomotor activity during the day—and consolidated sleep at night—that mimics the diurnal sleep/wake patterns of people and offer a particularly relevant model of human circadian behavior. Importantly, we have found that the phase shifts that *ananassae* exhibit after nighttime light administration map perfectly onto the amplitude of the responses seen in other animals and people. In all cases, light exposure occurring within the 1-2 h of the night bookending dawn (lights-on) or dusk (lights-off) results in activity shifts commensurate in magnitude with the difference in timing between the photic stimulation and the onsets/offsets of the light schedule.

Proposed One-Year and Long-Term Outcomes: All data from the current project will be maintained on secure lab servers and will be submitted for publication in peer reviewed journals. Attempts at outside external funding will be made to the NIH, as well as a number of private foundations dealing with aging and Alzheimer’s disease such as the Alzheimer’s Association. Dr. Fernandez is currently seeking funds from the Beckman Foundation for aspects of the proposed work. One important long-term outcome of the current project will be to isolate characteristics of the internal clock that might inform efforts focused on rehabilitating circadian function and memory with LED light.

Year-End Progress Summary:

Aim 1: Our results suggest that the pacemaker is impacted by the frequency with which light is alternated with darkness. For example, as expected, the average resetting response achieved with 15s of light delivered on-the-minute for 15 min—representing 225s of total stimulation—was significantly smaller than that achieved with an unbroken 15-min pulse (900s of total stimulation). However, the information drive of this 225s exposure could be significantly improved by condensing the fifteen 15s pulses into longer duration stimuli separated by incrementally larger relaxation intervals (a “golden” ratio of about 1:3 between stimulation and relaxation was particularly effective). This improvement elevated the shift profile of the exposure so **that it was on par with steady luminance** in younger *ananassae*. These data suggest that there is a wider logic the pacemaker uses to integrate light exposure into phase-shifting drive. We are in the process of extending our fragmentation studies to flies > 40 days old (> 40 years of age in humans) and are evaluating how their responses to steady and intermittent light are the same/different from those of younger animals.

Aim 2: We have just completed an exploratory survey of the effects of millisecond LED flashes on *ananassae* activity rhythms (30 separate administration protocols, > 1000 animals). For the first time, we can confirm that this form of high-precision light stimulation impacts the *Drosophila*

circadian system the same way it has been reported to impact the rodent and human system. The maneuver is evolutionarily conserved in *ananassae*, which can now be used as a two-way translational bridge to develop LED flash paradigms that can reach and steer the function of the aged human pacemaker. So far, we have made a few important observations. First, phase-shifting responses can be elicited in younger animals by visible spectrum flashes **tuned to twilight levels of intensity and lower** (ideal for not waking a person with light treatment during sleep). Second, the pacemaker will engineer phase shifts in response **to extremely small levels of UVA light with a photosensitivity that exceeds its photosensitivity to visible RGB light**. The result is striking because it suggests that the dose of incident light that survives filtration through the human lens (~2%) might actually be relevant for circadian timekeeping. We are in the process of creating a comprehensive parameter space with which to investigate monochromatic LED flashes in younger and older flies to determine how the logic for optimal phase-shifting changes across age.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Memory and executive function in normally-aging older adults. Elizabeth Glisky, PhD, Gene Alexander, PhD, Aurelio Figueredo, PhD, Lee Ryan, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: This proposal will support the completion, analyses, and publication of two projects that have been ongoing for some time. Data collection and data management were previously supported partly by the AAC and the McKnight Brain Institute. 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 second project compares older to younger adults with respect to various sub-components of executive function. The well-characterized participants from the longitudinal study have served and continue to serve as participants in numerous other experimental studies past and present, serving as a normative group for comparison to patient populations and as a baseline against which to assess levels of neurocognitive function in newly enrolled participants. The database now comprises data from over 800 adults aged 65 and over, and includes numerous demographics, a variety of 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. The analyses of the data will be focused on identifying the variables associated with normal aging, abnormal aging, and exceptional aging. Analyses will include regressions, factor analyses, structural equation models, hierarchical growth curve analyses, etc.

Specific Aim 1: To document changes over time in episodic memory function and executive function in normally-aging older adults aged 65+, and to assess the effects of demographic, genetic, health, neural, and neurocognitive variables on change trajectories.

Specific Aim 2: To validate an executive function battery for older adults, looking at 3 different sub-components of executive function—updating, inhibition, and shifting—that have previously been identified in young adults. We will directly compare factor structures of executive function in older and younger 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 other brain regions, particularly the prefrontal cortex, also contribute significantly to memory performance. Several studies have suggested that prefrontal brain regions might show earliest declines in normal aging, although medial temporal regions are also affected. We have collected neuropsychological test data associated with two independent factors: one reflecting medial temporal/episodic memory processes and the other capturing prefrontal/executive function processes. We have followed changes in these two composite measures longitudinally for the past several years. At the same time, we have collected data on several other variables that might mediate or moderate changes in these functions. Preliminary analyses suggest that memory and executive function change differentially over time and are differently affected by the other variables. Although cognitive measures taken at a single time point have for the most part not been able to discriminate between

people who will age normally and those who will develop MCI or AD, changes over time within the normal range, might be more sensitive and provide an early indicator of AD.

Specific Aim 2: Although much of the past literature has treated frontal function as if it was a unitary construct, recent literature suggests that there are multiple prefrontal functions that might be differentially affected by aging. Using factor analysis and structural equation models, Miyake et al. (2000) identified three such factors in young adults—shifting, updating, and inhibition—but attempts to replicate these findings in older adults have been inconsistent. However, no studies have compared young and older adults on the same set of measures. We completed a study using a subset of the same tests used by Miyake et al. in younger and older adults but failed to completely replicate the findings of Miyake et al. (see also Friedman et al, 2006) in young adults. We submitted our findings for publication, but (likely because it is a failure to replicate) reviewers have suggested several further analyses and possibly additional data collection to strengthen our case. We have been working on new analyses and have tested (and will test) additional participants to strengthen our findings.

Preliminary Data: In the longitudinal study, we have data on 300 older adults with at least two time points and 174 older adults (aged 65+) with data from three or more time points, for a total of 895 observations on each of the composite measures of memory and executive function. For the executive function battery, we currently have complete data on 152 older adults (aged 60+) and 100 younger adults (and have added to this recently). Data for this project came from three labs (Alexander, Glisky, and Ryan).

Proposed One-Year and Long-Term Outcomes: The one-year outcome is expected to be two peer-reviewed publications. Data will also be presented at conferences. The databases, however, will continue to support other studies requiring well-characterized older adult samples. Current projects recruiting older adults from our sample include the microbiome project (Barnes) and studies exploring the effects of genetic risk for AD on memory and emotion (Grilli). Data from these projects are supporting current grant applications (Grilli) and are expected to support future grant applications (Barnes).

Year-End Progress Summary: Work to date has focused on further data collection and analyses for the Executive Function Battery (Specific Aim 2). Based on previous analyses that indicated that one of our neuropsychological tests was not contributing to the confirmatory factor analysis, we were able to add 95 new older adults who had completed the other 5 tests, raising our total older adult sample size to 247. Currently we are collecting additional data on younger adults (previous sample size was 100) to strengthen our findings in this group, which failed to replicate other studies in the literature (a major reason for rejection of the paper). The novel findings in the younger group are critical to our theoretical interpretations because they provide the critical contrast to the older people. We anticipate re-submitting the paper this spring.

We have also been collecting additional data on older adults in support of Carol Barnes' microbiome project.

We have made no significant progress on the longitudinal study (Specific Aim 1) except for data cleaning, organization, and preliminary analyses. We are continuing with this project and hope to finish analyses this spring.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Forgetting one's past: episodic autobiographical memory in $\epsilon 4$ carriers. Matthew Grilli, PhD, Lee Ryan PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: To reveal that episodic autobiographical memory (EAM) retrieval mechanisms are compromised in healthy middle-aged and older adult $\epsilon 4$ carriers of the apolipoprotein E (APOE) gene. We hypothesize that EAM retrieval mechanisms, including scene construction, episodic detail binding, object-spatial associative memory, autobiographical fluency, and autobiographical content search, will be sensitive to $\epsilon 4$ status.

Specific Aim 2: To demonstrate that poorer EAM retrieval is associated with greater abnormality in structural integrity and intrinsic functional connectivity of the medial temporal lobe (MTL) and its cortical connections in $\epsilon 4$ carriers and non-carriers. We hypothesize that worse EAM retrieval abilities will be correlated with reduced MTL volume, reduced MTL-cortical white matter structural integrity, and disrupted MTL-cortical resting-state connectivity.

Background and Significance: The onset of Alzheimer's disease (AD) eludes clinical detection for years. The discovery of earlier cognitive and neural warning signs of AD would advance our understanding of disease progression and have the potential to improve the success of interventions. Prior research has revealed that the structural and functional integrity of the episodic memory neural network, which consists of the MTL and its cortical connections, is commonly disrupted in cognitively healthy middle-aged and older adult $\epsilon 4$ carriers relative to non-carriers. The central hypothesis of this proposal is that cognitive mechanisms that tax the functional limits of the episodic memory MTL-cortical network will reveal cognitive abnormalities in $\epsilon 4$ carriers. Guided by cognitive neuroscience theory, in this proposal we focus on EAM, a type of memory that has been shown to be highly dependent on the episodic memory neural network. Our preliminary results strongly suggest that, consistent with our hypothesis, EAM is impaired in cognitively healthy $\epsilon 4$ carriers. The present proposal will build on these preliminary results and investigate different mechanisms that support EAM retrieval with the goal of further characterizing this impairment. We also aim to identify the structural and functional neural correlates of this episodic memory impairment.

Preliminary Data: We completed a preliminary study in which we assessed EAM in cognitively normal (based on a comprehensive neuropsychological battery) middle-aged and older adults, including 18 $\epsilon 4$ carriers and 17 non-carriers who were matched to the $\epsilon 4$ carriers on age, education, and gender. The findings indicated that cognitively healthy $\epsilon 4$ carriers tend to generate fewer episodic details relative to non-carriers when describing both remote and recent autobiographical memories. These results are under review for publication. We have also completed development and piloting of the new cognitive measures for Aim 1, and we are on pace with new recruitment for Aims 1 and 2, with 42 participants completing behavioral sessions and MRI scans.

Proposed One-Year and Long-Term Outcomes: Our one-year goal is to continue to investigate and understand why EAM might be compromised among $\epsilon 4$ carriers, using novel cognitive measures and neuroimaging measures. If we are able to identify AD risk cognitive-neural marker profiles, our next step will be to determine how impaired EAM retrieval mechanisms relate to other markers suggestive of AD across various stages of the disease. Long term, we hope to develop novel neuropsychological tests that have the potential to be more sensitive to early AD. We also have plans to incorporate EAM testing into grants to NIA proposing to measure a combination of multiple genetic/familial risk (APOE, family history), CNS biomarker (CSF, amyloid imaging), and longitudinal cognitive/neuropsychological variables in healthy young, middle-aged, and older adults.

Year-End Progress Summary:

Aim 1: We completed the development and piloting of our cognitive measures of scene construction, episodic detail binding, object-spatial associative memory, autobiographical fluency, and autobiographical content search. In the past year, we have collected data on 157 participants, including piloting for the new cognitive tasks and their roll out for $\epsilon 4$ carriers and non-carriers. We have presented data at the International Neuropsychological Society Annual Meeting, and we have initial papers from this work under review and in preparation.

Aim 2: We have completed MRI scans for 42 individuals who have completed genetic testing and behavioral measures from Aim 1.

Long term outcomes: We have made good progress with refining our behavioral tasks into more precise measures that have potential to become brief neuropsychological tests. We have submitted a grant proposal to the Alzheimer's Association and an R03 application to NIA and will continue to develop research plans around the data collected through Aims 1 and 2.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Amelioration of neurodegenerative changes in spSHR by Mas agonists. Kathleen Rodgers, PhD, Kevin Gaffney, PhD, Carol Barnes, PhD, Meredith Hay, PhD, Tally Largent-Milnes, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) To evaluate the ability of novel Mas agonists to reduce cognitive changes observed in a rodent model of cardiovascular failure previously shown to cause cognitive impairment
- 2) To evaluate the ability of novel Mas agonists to reduce amyloid and Tau pathology in the brain tissues as well as bone marrow regenerative capacity in this rodent model

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 , leading to their accumulation. In fact, cardiovascular disease has a strong, positive correlation with neurodegenerative diseases. Hypertension in one's 40s, 50s and 60s and heart failure significantly increased the chance of developing AD later in life pointing to the cumulative degenerative hypoperfusion and hypoxia can have on the brain.

Angiotensin receptor blockers (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 (AT₁R) by the hypertensive peptide angiotensin II (A-II). While RAS is widely known for its renal actions in regulating blood pressure, research has shown the presence of RAS localized and integrated into a number of other tissues including the brain and neurovascular system. (**Figure 1**) In the brain, AT₁R is localized in brain stem and forebrain 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. Persistent activation of the A-II/AT₁R axis results in extensive cerebrovascular remodeling, inflammation, and oxidative stress (OS) leading to neurovascular uncoupling and disruption of the blood brain barrier (BBB). The ability of ARBs to decrease AD risk could result from blocking these detrimental processes.

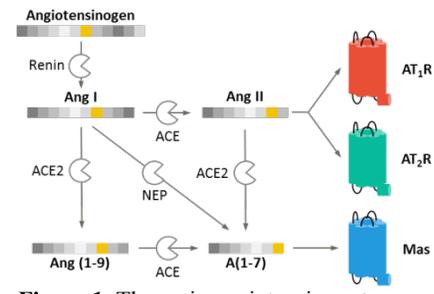


Figure 1. The renin angiotensin system

While the results on ARBs in AD are compelling, the protective arm of RAS holds an even greater potential to treat AD. The protective arm of RAS is comprised of the Mas receptor, its endogenous agonist angiotensin II (1-7) (A(1-7)), and ACE2, the enzyme that produces A(1-7) from A-II, as well as the less well characterized the angiotensin II type 2 receptor (AT₂R). Mas and A(1-7) were first characterized for their ability to counter regulate of the pathological actions of A-II and AT₁R such as decreasing inflammation and OS and increasing cerebral blood flow reactivity. However, a number of Mas-specific activities including the ability to activate regenerative process and stimulate stem cell proliferation have become well characterized. The effects of Mas agonist on

stem cells include increases in bone marrow and circulating mesenchymal stem cells (MSCs), a stem cell population currently in Phase II in AD patients.

Preliminary Data: As a result of these synergistic effects discussed above (**Figure 2**), a number of labs have begun to investigate the role of the ACE2/Ang-(1-7)/Mas axis in AD. Interestingly, in AD patients, the activity of serum ACE2 was found to be reduced compared to control subjects.¹⁷ Additionally, ACE2 activity was ~50% lowering in post-mortem brain samples from AD patients compared to age-matched controls. In these samples, ACE2 was inversely correlated to A β 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 Ang-(1-7) were found to be low while brain tau hyperphosphorylation levels were found to be significantly elevated, a trend also seen in P301S mice, a model of pure tauopathy.¹ These findings suggest that Ang-(1-7) might be implicated in the etiology and progression of AD. The effects of Ang-(1-7) treatment on AD was tested in the 5xFAD mouse model of AD which develops amyloid deposition and cognitive deficits at as early as 2 months of age.² Intracerebroventricular (ICV) infusion of Ang-(1-7) significantly ameliorated cognitive impairment on the Morris Water Maze and increased cerebral blood flow reactivity. Additionally, ICV treatment of spSHR 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.²

Over the past three years we have developed orally delivered Mas agonists: small molecules RASRx1902 and RASRx1911. In order to understand the potential of these Mas agonists as therapeutics for AD, we originally proposed to conduct the study with the spSHR rats on a high salt diet. In the interim, it was found that these molecules had a shortened half-life in rats. Therefore, we are conducting the proof of concept study in a mouse model of trans-aortic constriction, a model of cardiovascular disease which was shown to reduce cognitive function and to increase amyloid/tau pathology in the brains of surgical animals.

Year-End Progress Summary: Since the initiation of funding, we have received IACUC approval to conduct the study, have ordered the animals and performed the surgery and are in the midst of the treatment component of the study. All animal survived the surgery and have shown not observable adverse events either from the surgery or surgery combined with the Mas agonist treatments. Further, we have collaborated with cognitive behavioral laboratories (those of Drs. Carol Barnes, Meredith Hayes and Tally Largent-Milnes) to learn novel object recognition and Morris water maze procedures (tests shown to have deficit in the mouse model). 6-8 weeks after surgery, echocardiography will be conducted on these animals and 10-12 weeks after surgery, the animals will undergo cognitive testing. The treatment groups (n=12 per groups) include sham surgery controls treated with saline, TAC surgery controls treated with saline, TAC surgery animals treated with A(1-7), TAC surgery animals treated with RASRx 1902 and TAC surgery animals treated with RASRx 1911. When cognitive testing is complete, the animals will be euthanized and the brains, blood, and bone marrow (BM) will be harvested. The brains will be cryopreserved for sectioning and microglial, tau, & A β staining. Blood will be analyzed for ACE2 activity and MSCs. BM MSCs will be measured CFU-F assay.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Perirhinal cortical structure and function in older adults and its role in memory. Lee Ryan, PhD, Matthew Grilli, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1. To determine the relationship between object discrimination and object recognition and age-related perirhinal (PRC) changes in cognitively normal older adults.

Aim 2. To determine the relationship between measures of PRC structure and function and hippocampally-mediated memory including paired associate memory and pattern separation.

Aim 3: To determine the impact of genetic risk for Alzheimer's disease (apolipoprotein e4 allele) on PRC structure and function.

Background and Significance: The perirhinal cortex (PRC) plays an important role in object discrimination and object recognition, two functions that allow animals to function within, and navigate through, their environment. 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 object discrimination on hippocampally-mediated memory such as pattern separation and associative memory. Furthermore, recent studies suggest that postrhinal cortex (POR) remains relatively intact in older adults, suggesting that context – scenes and spatial information integrated with objects – might be utilized by older adults to compensate for poor object discrimination.

Recent studies of object discrimination suggest that aging results in decreased object discrimination efficiency. Aged rats and monkeys have difficulty identifying novel objects compared to younger animals in a spontaneous object recognition task when the objects shared multiple features, even at very short delays. Ryan et al. tested healthy older adults on a novel object discrimination task with two levels of feature overlap. While young and older adults performed similarly on the task when feature overlap was low, most older adults were impaired relative to young participants when the number of overlapping features increased. fMRI suggested that older adults do not engage bilateral anterior PRC to the same extent as young adults, and performance on the complex object matching performance was predicted in older adults by the degree to which they engaged left anterior PRC. These results provided the first direct evidence for human age-related changes in PRC function that impact complex object discrimination.

It is unclear how decreases in PRC function relate to age-related memory impairment. There is growing evidence that older adults are impaired on visual “pattern separation” tasks that rely on the ability to differentiate between previously experienced objects and objects that are similar, but not identical, to objects that have been previously experienced. Pattern separation is assumed to rely on intact hippocampal function. 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 degraded quality of object representations being supplied to the hippocampus via PRC, rather than hippocampally-mediated pattern separation. If correct, then other memory tasks that rely on comparisons across two visual

inputs, or a visual input and a preexisting representation, might also be affected. These might include paired associative memory tasks such as objects in scenes.

In this project, we will explore age-related changes in function and structure of the PRC, and how PRC structure/function relates to hippocampally-mediated forms of memory. We also will investigate whether PRC structure and function, or the related hippocampal function of pattern separation, are sensitive to APOE e4 status and thus might constitute preclinical markers of AD risk.

Proposed One-Year and Long-Term Outcomes:

1. We will write a review of the current literature on age-related changes in PRC functioning, and how these tasks might impact hippocampally-mediated memory functions.
2. The proposed study can be completed within the year and the results submitted for conference presentations and publication.
3. Based on our preliminary data and the results of the proposed study, we plan to submit an RO1 grant proposal that will further elucidate the age-related changes to the structure and function of the PRC, and how PRC relates to hippocampally-mediated forms of memory.

Year-End Progress Summary: We have now completed testing with 20 older adult participants on several PRC-sensitive behavioral and fMRI paradigms, which will be added to data from 40 older adults who were tested on the same paradigms in the previous year. The project is on schedule to be completed by June 30th. Analysis of behavioral data is underway. MRI data will be analyzed after data collection is complete.

One aspect of the project has already been published (Memel & Ryan, 2017) demonstrating that an integrative encoding strategy benefits associative memory in older adults. fMRI data from the project demonstrated that this strategy increases reliance on recollective processes rather than familiarity, shifting neural mediation from PRC to the parahippocampal gyrus and posterior hippocampus. In collaboration with researchers at the University of Florida Gainesville and University of Alabama Birmingham, we published a review paper in the journal *Trends in Neuroscience* (Burke et al., *Trends in Neuroscience*, in press) that presents a new innovative model of PRC functions and interactions with medial temporal lobe structures mediating memory. The model and supporting data from various laboratories will be presented at a major symposium at UC Irvine in April 2018.

Also in April, researchers collaborating on the project will be meeting at University of Alabama Birmingham to share data and discuss two potential grant submissions to NIA. We hope to have those submitted in fall, 2018.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Ultra-sensitive and label-free detection of Alzheimer's disease biomarkers using microtoroid optical resonators. Judith Su, PhD, Gene Alexander, PhD, Thomas Beach, MD, PhD. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Institute.

Specific Aims: We have recently developed a technique known as FLOWER (frequency locked optical whispering evanescent resonator) (Figure 1) that can detect low concentrations of molecules down to the single molecule limit without requiring the use of labels such as fluorescent or radioactive tags.¹⁻³ We plan to evaluate the ability of FLOWER to test for the Alzheimer's disease (AD) biomarker amyloid beta 42 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 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.

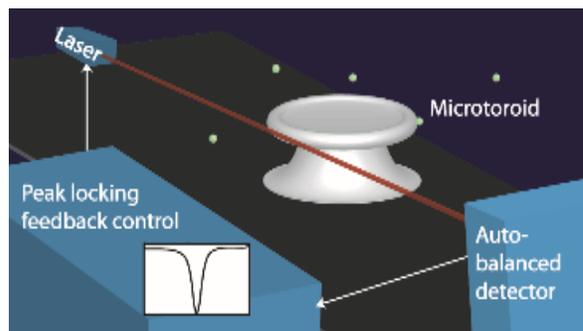


Figure 1. FLOWER schematic. In the FLOWER detection scheme, microtoroid optical resonators are used in conjunction with frequency-locking feedback control and balanced detection to improve the signal-to-noise ratio of the system. As a result, single-macromolecule detection becomes possible.

Aim 1: Fabricate devices. 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.

Aim 2: Establish surface chemistry protocols. We will covalently bind anti-amyloid beta uniformly to the surface of the microtoroid to serve as capture agent. We will use confocal microscopy with fluorescently tagged amyloid beta to confirm that uniform binding has occurred.

Aim 3: Evaluate the sensitivity of FLOWER for detecting different levels of amyloid beta 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 amyloid beta 42. 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-amyloid beta bound to the surface of the toroid as well as by attempting to bind amyloid beta to anti-interleukin-2 bound to the surface of the microtoroid. Interleukin-2 was chosen as it shouldn't bind to anti-amyloid beta. 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.² 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 amyloid beta 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. At the end of the project, we plan to submit an R01 proposal. This data could support new publications to aid detection of AD pathology in CSF and potentially plasma.

Year-End Progress Summary: We have successfully fabricated microtoroid optical resonator sensors and have demonstrated successful binding of antibodies to the surface of these resonators by using fluorescently tagged antibodies and confirming their presence on the microtoroid's surface using confocal microscopy. We have established the correct concentration of antibodies which will enable binding of proteins to our sensor without degrading its performance. We are currently performing experiments using several different protein targets, in particular tau and amyloid beta. In addition, we have fabricated a microfluidic flow cell which will enable us to perform more repeatable biomarker detection measurements. On the basis of these results, we have obtained an NIH R03 grant from the National Institute of Aging on this topic.

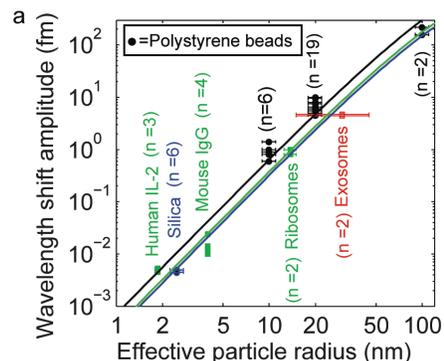


Figure 2. Summary of particle detection data using FLOWER. A wide range of particle sizes with radii from 2-100 nm were detected. The solid lines are theoretical predictions based on the different dielectric constants of the particles being detected.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Advanced diffusion and perfusion MRI methodology. Ted Trouard, PhD, Maria Altbach, PhD, Nan-kuei Chen, PhD, Lee Ryan, PhD, Gene Alexander, PhD, Gloria Guzman, MD, Craig Weinkauff, MD, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: In this project, we propose to develop acquisition and analysis methodology for two MRI techniques that will advance a number of neuroimaging studies being carried out at the University of Arizona.

Specific Aim 1. Develop and evaluate acquisition protocols and analysis techniques for advanced diffusion MRI including: Mean Apparent Propagator (MAP), neurite orientation dispersion and density imaging (NODDI), and high angular resolution diffusion imaging (HARDI).

Specific Aim 2. Develop and evaluate acquisition protocols and analysis techniques for Pseudo-Continuous Arterial Spin Labeling (PCASL) MRI.

Background and Significance: Since its inception over 40 years ago, magnetic resonance imaging (MRI) has progressively developed into an essential technology for neuroimaging and neuroscience research. The capacity to extract structural data combined with concurrent information regarding functional information is unique to the MRI domain. That MRI operates within parameters of highly controlled energy radiofrequencies and magnetic forces has yielded a highly safe technology. The fact that MRI can be carried out in both humans and animal models make it a fantastic translational technique that can be used to study a variety of neurological function and pathology. Although MRI is a well-established neuroimaging tool, it is continually advancing, with new techniques continually being introduced that are able to non-invasively interrogate the brain in new ways and provide new types of information on brain structure and function. Advanced techniques, however, are rarely trivial to implement and evaluate and require a development of expertise in the specific methods to be implemented.

Diffusion MRI (dMRI) refers to a class of techniques that use MRI to measure the microscopic random motion (diffusion) of water molecules in living tissue. The ability to measure the diffusion of water has made major contributions in a variety of areas including the clinical evaluation of acute stroke, pre-surgical planning for tumor resection, evaluating changes in white matter in response to normal development and aging as well as in neuropathological conditions. Recently, a class of diffusion MRI techniques has been proposed that take advantage of newly available rapid imaging methods to collect large dMRI datasets and analyze results using sophisticated modeling techniques. Among these new techniques are Mean Apparent Propagator (MAP) MRI which uses a new mathematical basis set for interpreting dMRI data that has been collected with different levels of diffusion weighting, i.e., b-value) in many different directions. MAP MRI was developed in the lab of Dr. Peter Basser at the National Institutes of Health, where Adam Berstein, and MD/PhD student in Dr. Trouard's lab has studied. Another technique, neurite orientation dispersion and density imaging (NODDI), uses similar datasets to model the density and orientation of neuronal structures as well as intracellular volume fraction and free water fraction. These parameters are suggested to reflect the microstructure of brain tissue and provide important evaluation of brain tissue. High Angular Resolution Diffusion Imaging (HARDI) refers to the analysis of dMRI data collected with multiple and many directions. The analysis uses Constrained Spherical Deconvolution (CSD) techniques to predict orientation distribution functions (ODFs)

that describe complex water diffusion in each imaging voxel. The ODFs can be used to carry out high-resolution tractography in the brain and provide information on the structural connectivity of the brain through its white matter tissue.

Arterial Spin Labeling (ASL) refers to a class of MRI techniques that try and use endogenous signal from flowing blood to measure the perfusion of tissue. ASL techniques are often applied in the brain to evaluate cerebral blood flow (CBF). Most of these studies are done qualitatively where only relative CBF measurements can be made. Recently, methods have been developed to do this in a quantitative manner, where CBF in mL of blood per mg of tissue per minute can be calculated. Pseudo-continuous ASL (PCASL) has emerged as the most promising ASL technique, but rigorous evaluations of its reliability are needed.

Proposed One-Year and Long-Term Outcomes: The methodology developed in this project will be implemented in studies planned at the UA including those from NIH and ABRC grants that are in progress as well as projects that are proposed to start in the next fiscal year. The techniques will be included into new grants using MRI in studies of humans and animal models.

Year-End Progress Summary: Methodology for acquisition of MAP MRI and HARDI diffusion data have been established on the Research dedicated 3T Siemens Skyra at the University of Arizona. The diffusion acquisition has been implemented in new research protocols. Analysis pipelines have been established for analysis of MAP MRI and HARDI data. These have been implemented on a high-performance computing (HPC) cluster at the University of Arizona. Example microstructural parameter maps are shown in Fig. 1 and connectivity analysis is shown in Fig. 2.

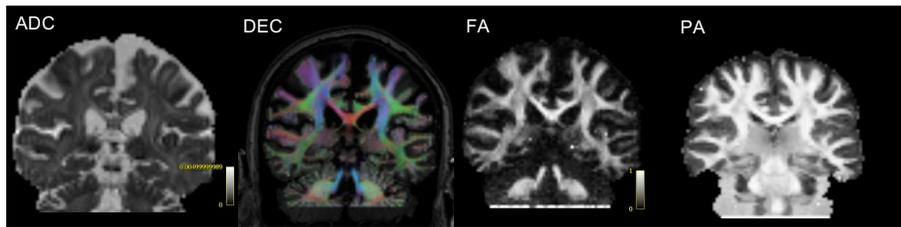


Fig. 1. Apparent Diffusion Coefficient (ADC), Directional Encoded Color (DEC), Fractional Anisotropy (FA) and Propagator Anisotropy (PA) maps generated from HARDI and MAP MRI developed in this project.

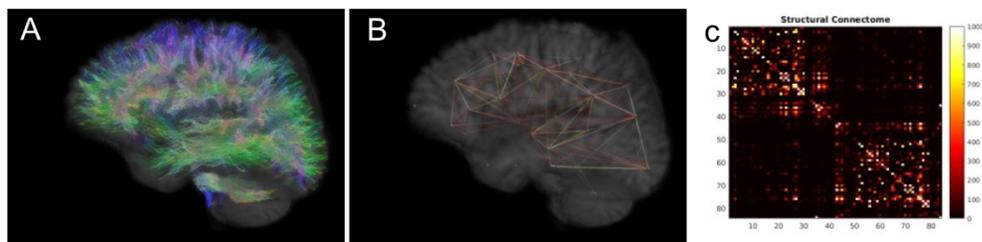


Fig. 2. Sagittal projections of whole-brain tractography (A) and connectivity (B). Structural connectivity matrix (C) quantifies connectivity between 86 different brain regions.

These capabilities are being incorporated into research projects and being included into new grant submissions. Commercial ASL sequences have been evaluated and found lacking and therefore a new PCASL sequence is being obtained through a collaboration with Siemens and University of Southern California (ASC). We expect the new ASL sequence will be available for evaluation in March 2018.

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Sex differences in translational animal models of human LOAD risk factors. Fei Yin, PhD, Robbie Brinton, PhD, Joanne Berghout, PhD, Ted Trouard, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: Late onset Alzheimer's disease (LOAD) is a complex neurodegenerative disease with four well-established risk factors: age, female sex, APOE4 genotype, and maternal history of AD. Each risk factor is characterized by complex specific and intersecting systems biology risks, making LOAD a complex systems challenge. These risk factors are often investigated as single variates, however, in reality they never occur in isolation. The proposed program of research is designed to test: *LOAD risk is dependent on the sex-differentiated, endocrine driven bioenergetic aging of the brain that interacts with chronological age, APOE genotype and maternal mitochondrial DNA inheritance.* This proposal will investigate the individual and combined mechanistic impact of the four major LOAD risk factors (sex, age, APOE4 and mtDNA variance) by developing a new translational *APOE-mtDNA* model that addresses maternal inheritance from the perspective of varying mitochondrial bioenergetic capacity.

Aim 1: To characterize the sex differences in AD at-risk endophenotypes across chronological and endocrine age.

Aim 2: To determine the impact of APOE gene load on the sex-differentiated trajectories of brain aging and AD risk.

Aim 3: To assess the combination of biparental- (APOE) and maternal (mtDNA) genetic risk factors with sex and age on LOAD risk.

Background and Significance: The greatest risk factors for AD are age, APOE4, and female sex. Greater than >60% of those affected by AD are postmenopausal women, and we have shown that the peri-menopausal transition involves major changes to brain bioenergetics, resulting in ketone body utilization rather than exclusively glucose fuel. Maternal – and not paternal - inheritance has also been associated with increased AD risk further linking deficits in mitochondrial respiration and glucose metabolism indicative of early aging to AD. The mitochondrial genome (mtDNA) is exclusively maternally inherited and mtDNA haplotype variation has been shown to modify bioenergetic and respiratory phenotypes, at both cellular and system biology levels. Consistent with the multifactorial nature of aging, LOAD risk and AD, mtDNA haplotype variance was also found to interact with risk factors such as APOE*4 genotype and chromosomal sex. Neuroimaging studies indicate an early hypometabolic phenotype in both cognitively normal people who carry the APOE4 allele or those with a maternal history of AD (controlled for female sex and APOE4 genotype). Therefore, an emphasis on mitochondrial and other metabolic processes is a promising therapeutic avenue to advance precision medicine in AD across multiple LOAD risks.

Preliminary Data: Our earlier study in female rats suggested that the perimenopausal transition is characterized by a decline in brain glucose metabolism, mitochondrial respiration, and long-term potentiation (16). We also observed a significant decline in glucose transport and metabolism followed by decline in mitochondrial function just prior to the transition into reproductive senescence in the 3xTG-AD mouse models prone to AD and non-transgenic colony controls (non-

Tg) (17). Our study in non-Tg mice at 6-, 9-, 12- and 15-months-of-age revealed substantial sex disparities in the trajectory of brain aging, including adaptations to energy and amyloid metabolism. In non-Tg females, the most substantial change was observed when comparing brains of 6mo mice to those at 9mo (18). Downregulated genes enriched those involved in bioenergetic processes and amyloid-related genes were upregulated. In contrast, major transcriptional changes in normal male brains occurred much later as mice transitioned from 12 to 15 months, with upregulation to mitochondrial, fatty acid and redox homeostasis processes observed as the mice age.

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 seek additional external, non-state funding from NIH to support our efforts to characterize the sex-differentiated risk factors for LOAD.

Year-End Progress Summary:

Aim 1: Our study in the AD prone 3xTg-AD mice suggested significant sex differences in brain bioenergetic function and amyloid metabolism. At 12 month-of-age, females exhibited impaired mitochondrial respiratory capacity and elevated A β load relative to age-matched males. These data indicate that female brains undergo endocrine age-related changes earlier than male brains, thereby activating sex differences in onset of the prodromal AD endophenotype.

Aim 2: With age-matched female and male ApoE4 and ApoE3 mice, we characterized their peripheral metabolic profile at 6- and 16 month-of-age, as well as their brain hippocampal transcriptome at 16 month-of-age. Our results indicated that ApoE4 genotype elicited significantly lower plasma levels of glucose (in both females and males) but higher levels of ketone bodies (only in females) mice compared to age-matched ApoE3 mice at 6 month-of-age, and this pattern persisted to 16 month-of-age. Also at 16 month-of-age, the females had higher total triglyceride levels relative to genotype-matched males while ApoE did not elicit a difference. Together these data suggested a potentially earlier shift in bioenergetic fuels in female brains due to glucose hypometabolism (Aim 1), with the ApoE4 genotype accelerating such a shifting process. Moreover, RNA-seq analysis of the transcriptome of these mice suggested distinguished impact of ApoE genotype and sex on regulating the hippocampal gene expression. In terms of differentiated expressed genes (DEGs) affected, variation in ApoE genotype alone led to a more significant change than that of sex alone, and when these two factors combined, the most DEGs were identified. Currently, a pathway-centric bioinformatic analysis of these transcriptomic changes is undergoing, aiming to delineate and differentiate the biological pathways being affected by sex and ApoE genotype, and to identify any commonly affected mechanisms by ApoE and sex.

Aim 3: The novel humanized ApoE mouse carrying different mtDNA haplotype variances (ApoE-mtNDA) is currently being developed in collaboration with Dr. Michael Sasner at the Jackson Laboratory and once generated, this highly translational LOAD model that incorporates the four major human LOAD risk factors – sex, age, ApoE4 and mtDNA variance, will be characterized.

Project Progress Report
University of Arizona
College of Medicine – Phoenix

ARIZONA ALZHEIMER'S CONSORTIUM

2017-2018 Scientific Progress Report

Modulation of the peripheral immune Response using remote ischemic conditioning (RIC) to improve chronic outcomes of traumatic brain injury (TBI). Maha Saber, PhD, Rachel Rowe, PhD, Jonathan Lifshitz, PhD. UA College of Medicine, Phoenix; Barrow Neurological Institute; Phoenix Children's Hospital; Phoenix Veterans Administration Healthcare System; Arizona Alzheimer's Consortium.

Background and Significance: According to the NIH, approximately 7 million 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 and affects over 5.4 million Americans and cost the US \$203 billion dollars in the year 2013 alone (Alzheimer's Association). There is currently no way to prevent, stop, or reverse Alzheimer's disease. Though there is no cure for AD, many risk factors for the disease have been identified. 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. The proposed research will not only be significant in bringing new information to the field but might reveal therapeutic strategies to reduce the likelihood of TBI patients developing neurodegenerative diseases, such as AD and chronic dementias. In our Translational Neurotrauma Research Program, we investigate consequences and potential therapeutic targets to treat and prevent chronic outcomes of TBI. In our rodent models, we are able to apply mechanical forces to induce brain injury, follow neurological function over time, and evaluate interventions to reduce neuroinflammation and cognitive deficits. The long-term goals of these projects are to determine a mechanism for age related neurological disorders associated with TBI and an intervention to reduce these conditions. Remote Ischemic Conditioning (RIC) is the transient restriction of blood flow to a limb that alters peripheral inflammatory populations, with the potential to disrupt inflammatory signaling and its impact on cognitive performance in murine models of both TBI and vascular dementia.

Specific Aims:

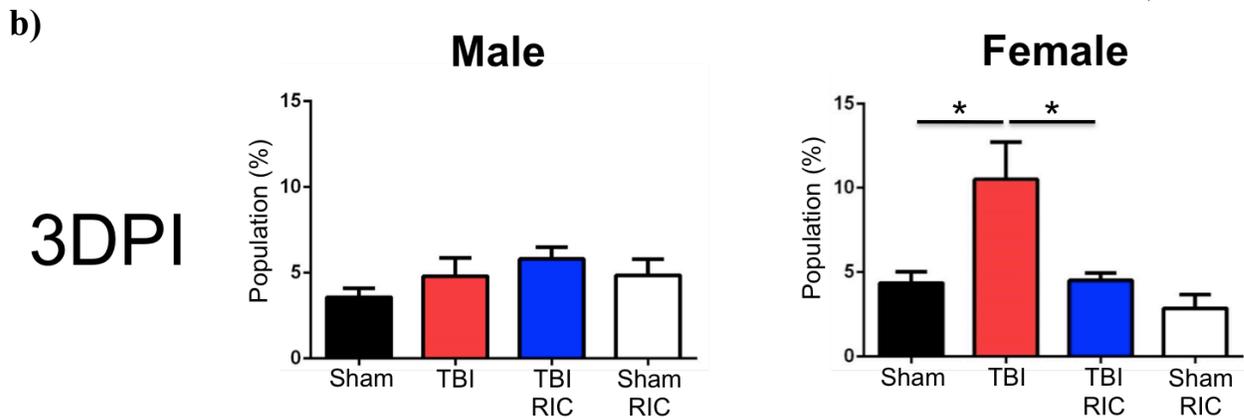
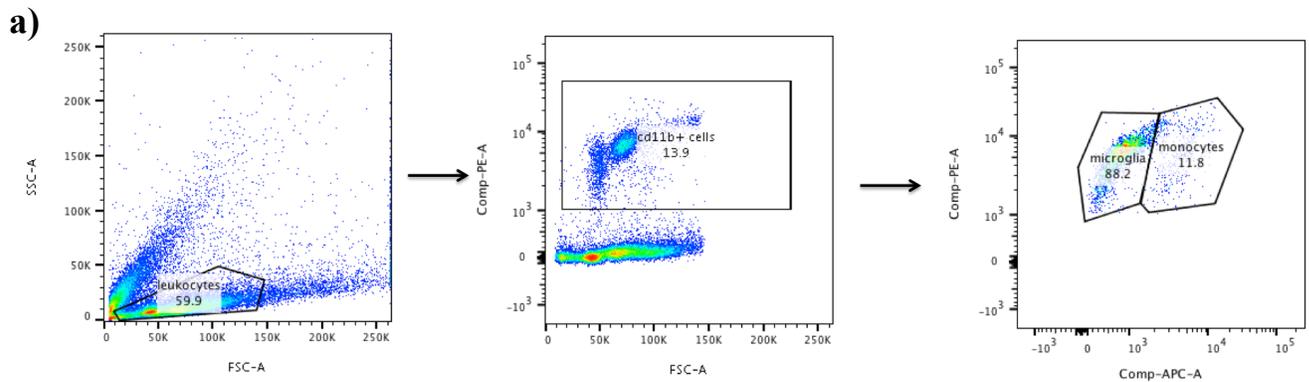
Specific Aim 1: To determine the acute and chronic inflammatory effects of RIC after TBI. 2-month-old mixed sex mice received diffuse TBI by midline fluid percussion injury (mFPI) or a sham injury. After 1 hour, half of the mice in both the injured and sham group received 4x5 minute sessions of RIC with 10-minute reperfusion between each session. Mice were euthanized at 3 DPI, 7 DPI, and 120 DPI (days post-injury), respectively. Spleens, cardiac blood, and brains were collected. Immune cells were quantified by flow cytometry focusing specifically on macrophages and monocytes. *We hypothesized that RIC treatment reduces neuroinflammation by modulating peripheral inflammation after TBI.* We found that RIC did, in fact, change the peripheral immune response and reduced the number of peripheral monocytes in the brain of female mice only at 3 DPI. Male mice did not show an increase in peripheral monocyte infiltration after brain injury at 3 DPI or any changes in peripheral monocyte expression after TBI or RIC treatment (see **Figure 1**).

Specific Aim 2: To determine the therapeutic efficacy of RIC for TBI-induced impairments in chronic cognitive and anxiety related behaviors. Primary outcome measures for cognitive

testing were the novel object recognition and Y-maze. Secondly, anxiety related behaviors were assessed using elevated plus maze and open field. Mice were tested on rotarod both acutely and chronically to measure and control for fine motor performance at 1, 3, 5, 7, 29, 59, 89 DPI. For anxiety-like behaviors, elevated plus maze was performed at 30 DPI and open field at 60 DPI. To assess chronic cognitive performance, novel object tasks were evaluated at 31 DPI and 90 DPI, with the Y maze evaluation at 60 DPI and 120 DPI. *We hypothesized that mice treated with RIC would exhibit less TBI induced behavioral impairment.* Data are currently being collected as cohorts reach their predetermined endpoints for analysis. Preliminary data suggest that additional acute behavioral assessments are necessary to discern whether RIC treatment is beneficial in attenuating injury-induced behavioral impairments. With the sex differences found in **Specific Aim 1**, new studies need to assess sex differences in behavior and chronic outcomes, where females might show therapeutic benefit from RIC treatment than males.

Preliminary Data:

These pilot studies add initial data on the potential for a peripheral immune response after an isolated central nervous system injury and practical interventions to dampen this response. Success in Specific Aim 1 required a rigorous gating strategy for use in flow cytometry to distinguish peripheral macrophages from resident microglia (a). Peripheral macrophages in male and female mice at 3 DPI showed a significant sex difference, where male mice had no increase in the percentage of peripheral monocytes in response to TBI. Female mice had a significant increase in the percentage of peripheral macrophages in the brain at 3 DPI that was reduced down to sham levels with RIC treatment (*p<0.05).



Impact: The impact of the results in the current work relates to the chronic conditions of TBI, one of the leading causes of death and disability worldwide. Conduct of these specific aims has developed experimental techniques for brain flow cytometry and RIC, which were applied to rigorous study designs that explore injury pathology and therapeutic intervention. There are currently no treatments that are known to prevent neurological disorders, neurodegeneration, or age related TBI pathologies. Our studies propose not only a mechanism for how brain injury can lead to neurodegeneration through peripheral inflammation, but also explore potential treatment to reduce neuroinflammation, peripheral inflammation, and behavioral deficits through a non-invasive, practical therapy of RIC. Upcoming studies resulting from these funded projects include the refinement of RIC treatment in terms of modulating inflammation and TBI-induced pathologies and behaviors. By attenuating injury-induced pathology, the goal is to control the risk for multiple neurodegenerative and age related diseases.

Remainder of proposed work: The Arizona Alzheimer's Consortium support for the UA College of Medicine – Phoenix has fostered an expansion of investigations into TBI-induced inflammation and chronic outcomes. The aspects of peripheral inflammation as an amplifier of neuropathology provides an opportunity to intervene prior to irreversible anatomical or neurological damage. To this end, RIC provides a personalized, dose-controlled, rapidly administered approach to mitigate risk for late onset morbidity. For the remainder of the funding period, additional cohorts of animals and data analysis continue.

Proposed One-Year and Long-Term Outcomes: At the conclusion of the funding period, data from both Specific Aims will be published in a peer-reviewed manuscript. Where possible, data models can identify correlations between the acute change in peripheral macrophage infiltration with RIC treatment and performance in behavioral evaluations. These pilot data have been incorporated into an NIH F32 NRSA for Dr. Saber on this topic. The techniques refined in conducting these studies are shared among investigators at UA College of Medicine – Phoenix and being incorporated into study designs to evaluate the role of microglia and sleep in the acute and chronic pathology of TBI. To this end, the existing data and data to be completed will contribute to NIH and other extramural funding applications focused on neuroinflammation in acquired neurological injury.

Year End Progress Summary:

Specific Aim 1: The acute time points for this aim have been completed. All flow cytometry data for 3 DPI and 7 DPI have been analyzed and a manuscript is in preparation. Animals used for the chronic cohort (120 DPI) are waiting to be processed.

Specific Aim 2: Chronic behavioral studies for this aim are ongoing and cohorts are maturing. However, a final cohort will be added to power our study to look at sex differences. Behavioral tasks will be analyzed using two way ANOVAs with repeated measures for tasks such as rotarod. Post hoc tests will be performed to determine group differences.

2017 – 2018

Publications, Manuscripts, & Grants

2017 Publications and Manuscripts

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Current and Pending Grants

Current Grants

<p>Caccamo, Antonella (PI) Project #: AARG-17-503765 Alzheimer's Association Title: Molecular mechanisms of cognitive decline in Alzheimer's disease</p>	<p>3/1/2017-2/28/2020 \$150,000 Annual DC</p>
<p>Caccamo, Antonella (PI) Arizona Alzheimer's Consortium Title: Assessing the role of necroptosis in Down syndrome</p>	<p>7/1/2017-6/30/2018 \$23,894.00 Annual DC</p>
<p>Wynne, Clive (PI) Petsmart Charities Converging Evidence for Behavioral Indicators of Welfare in Shelter Dogs</p>	<p>1/2017-7/2018 \$9,842</p>
<p>Mastroeni (PI) AARGD-17-529197 Alzheimer's Association Gender Effects on identified cell population in Alzheimer's Disease</p>	<p>2018-2021 \$175,000</p>
<p>Mastroeni (Co-PI) Department of Defense Probing the Mechanistic Role of Vascular Dysfunction and Vascular Inflammation in TBI-Mediated Cognitive Dysfunction</p>	<p>2018-2021 \$100,000</p>
<p>Mastroeni (PI) ADCC: Arizona Alzheimer's Research Center The effect of hormone status on synaptic transcripts in aging and Alzheimer's disease</p>	<p>2016-2018 \$35,000</p>
<p>Mastroeni (PI) AARC: Arizona Alzheimer's Research Consortium Determining whether we can use peripheral leukocytes to predict brain inflammation in Alzheimer's disease</p>	<p>2017-2018 \$38,000</p>
<p>Heather Bimonte-Nelson (PI) R01 Grant R01 AG028084 Renewal Variations in hormones during menopause: effects on cognitive and brain aging</p>	<p>9/01/13-5/31/18</p>
<p>Heather Bimonte-Nelson (PI) R01 Grant, Diversity Supplement R01 AG028084-09S1 Variations in hormones during menopause: effects on cognitive and brain aging</p>	<p>5/17-4/19</p>

Eric Reiman (PI) 7/1/01-6/30/21
Co-Directors of the Research Education Component: Heather Bimonte-Nelson (ASU) and Yonas Geda (Mayo)
NIH 2P30AG19610
Alzheimer's Disease Core Center Grant (Arizona)
Arizona Alzheimer's Disease Core Center

Heather Bimonte-Nelson (PI) 7/17-6/18
State of Arizona (ADHS14-052688) and NIH (5P30AG019610-13)
Alzheimer's Disease Center (Arizona)
Surgical menopause in a mouse model of Alzheimer's Disease: effects of duration of ovarian hormone loss

Jason Newbern (PI) 7/1/2016-5/31/2021
Co-Investigator: Heather Bimonte-Nelson
R01 Grant: R01 NS097537
Functions of ERK/MAPK Signaling in GABAergic Circuit Development

Bimonte-Nelson (Co-I) 9/26/2017-8/31/2022
R01 Grant (Olive PI)
R01 DA043172
Characterization and reversal of neurocognitive dysfunction produced by long-term synthetic cathinone use

Carol Barnes, Paul Coleman, Eric Reiman (Co-PI) 5/01/2016-4/30/2021
Associate Directors: Heather Bimonte-Nelson, Matthew Huentelman
Postdoctoral T32 Training Grant: NIA (NIH) T32AG044402
Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease

Juliana Kling (PI) 1/1/2017-6/31/2019
Co-Investigators: Heather Bimonte-Nelson, Virginia Miller, Cynthia Stonnington, Leslie Baxter, Anita Mayer, Paru David, Julia Files, Dona Locke, Yonas Geda, Hamy Temkit
Mayo MEGA Award
Cognitive effects of ovarian hormones in menopause

Heather Bimonte-Nelson; Julia Files (Co-PI) 2/1/2017-1/31/2018
Anita Mayer; Marcia Ko, Rosy Krajmalnik-Brown
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) Faculty Mentors: Heather Bimonte-Nelson and Paul Whiteaker Arizona Biomedical Research Commission (ABRC) Early Investigator Award (Mentor) Amyloid beta-induced homeostatic neuronal instability in basal forebrain cholinergic neurons	10/31/14-6/31/18
Velazquez, Ramon AARFD-16-442710 Alzheimer's Association Pim 1 inhibition as a therapeutic strategy for Alzheimer's disease (ASUF 30007328)	10/1/2016-9/30/2019 \$62,256.00
Caccamo, Antonella AARG-17-503765 Alzheimer's Association Molecular mechanisms of cognitive decline in Alzheimer's disease (ASUF 30007546)	3/1/2017-2/28/2020 \$45,454.00
Oddo, Salvatore R01 AG037637 HHS-NIH-NIA Molecular interplay between A tau and mTOR: Mechanisms of neurodegeneration	6/1/2016-5/31/2021 \$150,000.00
Oddo, Salvatore R21 NS096375 Tau conditional knockout mice to elucidate the function of tau in the adult brain	7/15/2016-6/30/2018 \$150,000.00
Oddo, Salvatore NSF-SBE1606833 Elucidating the molecular mechanisms linking maternal choline supplementation to healthy cognitive aging	8/15/2016-7/31/2018 \$71,995.00
Oddo, Salvatore YR1 UofA NRSA Postdoctoral Training Grant #425243 University of Arizona	6/1/2017-5/31/2020 \$41,383.00
Oddo, Salvatore OAF FY18: Oddo: Arizona Alzheimer's Consortium Arizona Alzheimer's Consortium	\$30,870.00
PI: David Brafman Department of Defense Biomanufacturing of Cells in the Neuroectoderm Fate Space	03/01/2018-08/31/2019 \$1,387,138
PI: David Brafman Department of Defense / BioFab USA Towards comprehensive online certificate and degree programs in regenerative medicine	11/01/2017-10/31/2018 \$146,588

PI: David Brafman R21 AG056706 NIH-NIA Generation and characterization of isogenic hiPSC lines with various APOE genotypes	09/15/2017-04/30/2019 \$409,034
PI: Brafman R01 GM121698 NIH-NIGMS Investigating the mechanisms of a multi-state model of Wnt signaling	04/01/2017-03/31/2022 \$1,518,984
PI: David Brafman 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
PI: David Brafman R21 EB020767 NIH-NIBIB Synthetic substrates for the expansion and differentiation of hPSC-derived NPCs	06/01/2016-05/31/2018 \$418,921
PI: Coon, David US Administration for Community Living US Administration on Aging Alzheimer's Disease Initiative-Specialized Supportive Services (ADI-SSS) Arizona Dementia Capable System Expansion	06/01/2016-05/31/2018 \$418,921
PI: Coon, David National Institute on Aging EPIC: A Group-Based Intervention for Early-stage AD Dyads in Diverse Communities	05/15/2016-06/30/2021 \$3,600,000
Core Leader: Coon, David National Institute on Aging Outreach & Recruitment Core Arizona Alzheimer's Disease Core Center P30	07/01/2016-06/30/2021 Total Award: \$8,800,000 Core Leader: \$459,230
PI: Coon, David Phoenix Symphony & BHHS Legacy Foundation Music and Memory II	10/01/16-09/30/17 \$85,000
Co-PI: Coon, David Arizona Alzheimer's Disease Consortium Development & Evaluation of Social Media-based Testimonials Targeting Potential ADRD Research Participants within the Latino/Hispanic Community	07/01/16 – 06/30/17 ASU Budget: \$61,002
Co-PI (Subcontract): Coon, David HHS-HRSA Empowering Caregiver Self-Care	07/01/15 – 06/30/18 ASU Budget: \$61,002

PI (Subcontract): David Coon U.S. Administration for Community Living U.S. Administration on Aging Creating and Sustaining Arizona's Dementia-Capable Service System	10/01/15-09/30/17 ASU Budget: \$251,572
PI: Coleman, Paul Arizona Alzheimer's Research Consortium Early Nuclear Loss of H3k4me3 Affects Synaptic and Mitochondrial Pathways in Alzheimer's Brain.	2017-2018 \$19,000
Co-PI: Coleman, Paul R01 Renewal Gene expression in brain regions of a rat hypertension model	2013-2018
Co-PI: Coleman, Paul R01 Renewal Gene expression in stroke brain	2016-2021
Smith, Brian H (PI) R01 GM113867 HHS-NIH-NIGMS Multiscale Model of Exploration-Exploitation Tradeoff: From Genes To Collectives	9/1/2015-5/31/2019 \$1,918,606
Smith, Brian H (PI) NSF-BIO 1556337 Ideas Lab Collaborative Research: Using Natural Odor Stimuli to Crack the Olfactory Code	11/1/2015 - 10/31/2018 \$900,000
Smith, Brian H (PI) Human Frontiers Science Program Odor-background Segregation and Source Localization Using Fast Olfactory Processing	7/1/2015 - 6/30/2019 \$337,500
Smith, Brian H (co-PI) USDA-NIFA Evaluation of the dose-response of honey bees to carboximide and strobilurin fungicides: from cellular mechanism to integrated management	3/15/2017 - 3/14/2020 \$932,284
Federico Sanabria (co-PI) R01NS097537 NIH Functions of ERK/MAPK signaling in GABAergic circuit	7/1/2016-6/30/2021 \$1,247,099
Reiman EM (PI) 5 P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center	09/30/01-06/30/18 \$1,628,650 Annual DC

Reiman EM (Site PI) P01 AG052350 (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 Annual DC
Reiman EM (PI) 2 R01 AG031581 (Reiman, Caselli) NIH/NIA Brain Imaging, APOE, & the Preclinical Course of Alzheimer's disease	05/01/08-03/31/19 \$1,110,690 Annual DC
Reiman EM (PI) 3R01AG031581-17S1 (Reiman) NIH/NIA Administrative Supplement to Brain Imaging, APOE & the Preclinical Course of Alzheimer's Disease	06/15/16-03/31/19 \$352,478 Annual DC
Reiman EM (PI) 1UF1AG046150-01 (Reiman/Tariot) NIH/NIA Alzheimer's Prevention Initiative APOE4 Trial	09/20/13-08/31/18 \$22,280,073 Total Project DC
Reiman EM (PI) TGEN (Reiman) TGen Professional Services Agreement Translational Genomics Research Institute	07/01/08-12/31/18 \$30,330 Annual DC
Reiman EM (Site PI) 4UH3TR000967-02 (Strittmatter/Van Dyck) NIH/Yale University Fyn Inhibition by AZD0530 for Alzheimer's Disease	06/18/13-05/31/17 \$92,943 Annual DC
Reiman EM (Site PI) U01NS093334-01 (Cummings/Reiman/Shenton/Stern) Boston University via Mayo Clinic Arizona Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course and Risk Factors	12/15/15-11/30/22 \$436,318 Total Project DC
Reiman EM (PI) Alzheimer's Association/GHR/FBRI (Reiman/Tariot/Langbaum) Alzheimer's Prevention Initiative APOE4 Trial	01/01/16-12/31/20 \$10,000,000
Reiman EM (PI) Flinn Foundation (Reiman/Tariot/Langbaum) Alzheimer's Prevention Initiative	01/01/14-12/31/18 \$357,473 Annual DC

Reiman EM (PI) 1UG3OD023171-01(Ojo, Reiman, Theodorou) NIH/ University of Arizona University of Arizona-Banner Health Precision Medicine Initiative Cohort Enrollment Center	07/01/16-06/30/21 \$674,750 Annual DC
Reiman EM (Site PI) 5U01AG051406-02 (Handen) NIH via University of Pittsburgh Neurodegeneration in Aging Down Syndrome (NiAD): A Longitudinal Study of Cognition and Biomarkers of Alzheimer's Disease	09/30/16-04/30/2018 \$263,470 Annual DC
Reiman, EM (PI) 1R01AG055444-01 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/17-03/31/22 \$1,654,577 Annual DC
Reiman EM (PI) NOMIS Foundation (Reiman) NOMIS Foundation via Banner Alzheimer's Foundation	9/1/07-8/31/21 \$1,240,381 Annual DC
Reiman EM (Site PI) 1R01AG054671-01A1 (Quiroz) NIA/NIA via Harvard University Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease	09/01/17-5/31/22 \$33,040 Annual DC
Reiman EM (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 \$473,520 Annual DC
Chen K (Site PI) 5 P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center	09/30/01-06/30/18 \$1,628,650 Annual DC
Chen K (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 Annual DC
Chen K (Co-I) 3R01AG031581-17S1 (Reiman) NIH/NIA Administrative Supplement to Brain Imaging, APOE & the Preclinical Course of Alzheimer's Disease	06/15/16-03/31/19 \$352,478 Annual DC

Chen K (Project PI) Arizona Alzheimer's Research Consortium State of Arizona Advanced Image Analysis Techniques for the Detection and Tracking of Alzheimer's disease and its prevention	7/1/2011-6/30/2018 \$75,000 Annual DC
Chen K (Project PI) Arizona Alzheimer's Research Consortium State of Arizona Statistical and Neuroimaging Core Resources Serving the Consortium members for the Alzheimer's disease and prevention related studies	7/1/2011-6/30/2018 \$40,000 Annual DC
Chen K (Co-I) 1R01AG055444-01 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/17-03/31/22 \$1,654,577 Annual DC
Chen K (CoI) 1U01AG046150-01 (Reiman/Tariot) NIH/NIA Alzheimer's Prevention Initiative APOE4 Trial	09/20/13-08/31/18 \$22,280,073
Chen K (Co-I) 4UH3TR000967-02 (Strittmatter/Van Dyck) NIH/Yale University Fyn Inhibition by AZD0530 for Alzheimer's Disease	06/18/13-05/31/17 \$92,943 Annual DC
Chen K (Co-PI) 5U01AG051406-02 (Handen) NIH via University of Pittsburgh Neurodegeneration in Aging Down Syndrome (NiAD): A Longitudinal Study of Cognition and Biomarkers of Alzheimer's Disease	09/30/16-04/30/2018 \$263,470 Annual DC
Chen K (Site-PI) U19AG024904 (Weiner) NIA/Northern California Institute Res & Educ. Alzheimer's Disease Neuroimaging Initiative	09/30/17-7.31/2021 \$53,798 Annual DC
Chen K (Site-PI) W81XWH-13-1-0259 (Weiner) DOD/Northern California Institute Res & Educ. Effects of Traumatic Brain Injury and Post Traumatic Stress Disorder on Alzheimer's Disease (AD) in Veterans with Mild Cognitive Impairment (MC) using the Alzheimer's disease Neuroimaging Initiative (ADNI)	9/30/13-9/29/18 \$1,411 Annual DC

Chen K (Co-PI) 1R01AG054671-01A1 (Quiroz) NIA/NIA via Harvard University Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease	09/01/17-5/31/22 \$33,040 Annual DC
Chen K (PI) 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 \$473,520 Annual DC
Goradia D (Project Co-PI) Arizona Alzheimer's Research Consortium State of Arizona Resting State fMRI Fluctuations Modulated by Sleepiness in Individuals at Different Genetic Risk for Alzheimer's Disease	7/1/2011-6/30/2018 \$75,000 Annual DC
Langbaum JB (Co-I) 2 R01 AG031581 (Reiman, Caselli) NIH/NIA Brain Imaging, APOE, & the Preclinical Course of Alzheimer's disease	05/01/08-03/31/19 \$1,110,690 Annual DC
Langbaum JB (Co-I) 1R01AG055444-01 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/17-03/31/22 \$1,654,577 Annual DC
Langbaum JB (CoI) 1UF1AG046150-01 (Reiman/Tariot) NIH/NIA Alzheimer's Prevention Initiative APOE4 Trial	09/20/13-08/31/18 \$22,280,073 Total Project DC
Langbaum JB (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
Langbaum JB (Co-PI) Flinn Foundation (Reiman/Tariot/Langbaum) Alzheimer's Prevention Initiative	01/01/14-12/31/18 \$357,473 Annual DC
Langbaum JB (PI) Arizona Alzheimer's Research Consortium (Langbaum) State of Arizona Arizona Alzheimer's Registry	7/1/11-6/30/18 \$35,000 Annual DC

Savage C (Co-I) P01 AG052350 (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 Annual DC
Savage C (Co-I) 2 R01 AG031581 (Reiman, Caselli) NIH/NIA Brain Imaging, APOE, & the Preclinical Course of Alzheimer's disease	05/01/08-03/31/19 \$1,110,690 Annual DC
Savage C (Co-I) Flinn Foundation (Reiman/Tariot/Langbaum) Alzheimer's Prevention Initiative	01/01/14-12/31/18 \$357,473 Annual DC
Savage C (Co-I) 3R01AG031581-17S1(Reiman) NIH/NIA Administrative Supplement to Brain Imaging, APOE & the Preclinical Course of Alzheimer's Disease	06/15/16-03/31/19 \$352,478 Annual DC
Savage C (Co-I) 1R01AG055444-01 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/17-03/31/22 \$1,654,577 Annual DC
Savage C (Co-I) 5R01DK107390-02 (Leidy) NIH/NIDDK via Purdue University Increased Protein at Breakfast for Weight Management in Overweight Adolescents	7/1/17-6/30/18 \$9,747 Annual DC
Savage C (Project Co-PI) Arizona Alzheimer's Research Consortium (Reiman) State of Arizona Resting State fMRI Fluctuations Modulated by Sleepiness in Individuals at Different Genetic Risk for Alzheimer's disease	7/1/2011-6/30/2018 \$75,000 Annual DC
Saner D (Project PI) 5 P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center	09/30/01-06/30/18 \$1,628,650 Annual DC
Saner D (Co-I) 1UG3OD023171-01(Ojo, Reiman, Theodorou) NIH/ University of Arizona University of Arizona-Banner Health Precision Medicine Initiative Cohort Enrollment Center	07/01/16-06/30/21 \$674,750 Annual DC

Saner D (Project Co-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	7/1/2011-6/30/2018 \$40,000 Annual DC
Beach, Thomas (Core Leader) P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center	7/1/16 to 6/30/21 \$1,682,235 Annual DC
Beach, Thomas (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 Annual DC
Beach, Thomas (Co-I) 3UH3TR000891 (Jensen) NIH R21 via TGen This study proposes to compare enriched extracellular vesicles from two biofluids from subjects with confirmed diseases diagnosis. Dr. Beach will provide samples, analysis and assistance with publications.	9/15/17-7/31/18 \$5,596 Annual Direct Costs
Beach, Thomas (PI) MJFF (Beach) Michael J. Fox Foundation for Parkinson's Research Systemic Synuclein Sampling Study (S4)	4/30/16-3/31/18 \$149,798 Annual Direct Costs
Beach, Thomas (Co-PI) Mayo (Adler/Beach) Mayo Clinic via MJFF Feasibility of Repeat Submandibular Gland Biopsies as a Progression Marker in Parkinson's Disease	10/20/17-3/30/18 \$24,404 Annual Direct Costs
Beach, Thomas (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 The goal of this research is to accelerate promising research toward clinical testing and breakthroughs designed to improve the health of Arizonans. Dr. Beach will mentor Dr. Mehta in his research. Co-Investigator/Mentor	3/1/17-2/29/19 \$35,590 Annual DC

Beach, Thomas (Co-I)
Carl T. Hayden Medical Research Foundation 4/1/17-3/31/21
Phoenix VA \$4,500 Annual DC
Discovering novel mechanisms for aging-related dementia: probing medinand abeta vasculopathy

Beach, Thomas (PI)
Avid Radiopharmaceuticals, Inc. 9/1/15 to present
Dr. Beach is Leader of the Central Neuropathology Site for this imaging-to-autopsy Phase III clinical trial of a tau PET imaging agent for diagnostic usage.

Beach, Thomas (PI)
Navidea Biopharmaceuticals 4/01/2014 to present
Dr. Beach is Leader of the Central Neuropathology Site for this imaging-to-autopsy Phase III clinical trial of an amyloid imaging agent for diagnostic usage.

Beach, Thomas (Co-I)
ABRC ESI (Mastroeni) 10/23/14-10/22/17
Arizona Biomedical Research Commission \$68,167 Annual DC
A Novel Compound to Protect Mitochondria against Oligomeric Abeta Toxicity, Implications for the Synapse

Beach, Thomas
AARC (Reiman, Project PI: Beach) 7/1/17– 6/30/18
AZ DHS via AARC \$215,879 Annual DC
Developing a Shared Resource of CSF, Plasma, Serum, PBMC samples from Arizona’s Longitudinal Brain and Body Donation and APOE4 Gene Dose Program

Beach, Thomas
AARC (Reiman, Project PI: Beach) 7/1/17– 6/30/18
AZ DHS via AARC \$160,000 Annual DC
A Dissociated Cell Resource for Human Brain Neurodegenerative Disease Research

Beach, Thomas
AARC (Reiman, Project PI: Shprecher) 7/1/16 – 6/30/18
AZ DHS via AARC \$36,000 Annual DC
Clinicopathological Study Initiation for Incidental REM Sleep Behavior Disorder in Sun City, Arizona

Belden, Christine (Co-I)
P30 AG019610 (Reiman) 7/1/16 to 6/30/21
NIH/NIA \$1,682,235 Annual DC
Arizona Alzheimer’s Disease Core Center – Clinical Core

Serrano, Geidy (PI)
New Investigator Grant (Serrano) 11/1/14-10/31/17
ABRC \$68,030 Annual DC
The effects of APOE genotype on APP/A β levels in human liver and brain

Shprecher, David (PI) Grant (Shprecher) Sun Health Foundation Feasibility study of an early wellness program in Parkinson's disease and impact on quality of life	7/2013-present \$97,300 Annual Direct Costs
Shprecher, David (PI) AARC (Reiman, Project PI: Shprecher) 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 Annual DC
Shprecher, David (PI) AARC (Reiman, Project PI: Shprecher) AZ DHS via AARC Pilot Award: Autopsy-based Feasibility: Clinically Separating AD Subjects Based on Underlying Lewy Body Disease	7/1/17 – 6/30/18 \$30,000 Annual DC
Zamrini, Edward (Co-I) P30 AG019610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center – Clinical Core	7/1/16 to 6/30/21 \$1,682,235 Annual DC
Zamrini, Edward (Co-I) AARC (Reiman, Project PI: Beach) AZ DHS via AARC Developing a Shared Resource of CSF, Plasma, Serum, PBMC samples from Arizona's Longitudinal Brain and Body Donation and APOE4 Gene Dose Program	7/1/17 – 6/30/18 \$215,879 Annual DC
Zamrini, Edward (Co-I) R21AG055852-01 NIH via UA (Toosizadeh) MCI and Alzheimer's Disease Screening Using Upper-Extremity Dual-Task	5/31/18-4/30/20 \$39,225 Annual DC
Baxter, Leslie Department of Defense W81XWH-14-ARP-IDA Cognitive and Neural Correlates of Aging in Autism Spectrum Disorder	6/01/15- /30/18 \$358,757
Baxter, Leslie (PI) Institute for Mental Health Research Depression and anxiety in the aging autism spectrum disorders cohort	7/1/15-present \$20,000 (DC)
Liu (PI) Valley Research Partner Grant Microglia in synaptic pruning	09/01/2018 – 08/31/2019

Sattler (Co-PI), Zarnescu (PI) 07/01/2018 – 06/30/2020
Department of Defense
Small Molecules Targeting TDP-43-RNA interactions in ALS

Sattler (PI) 3/01/18 – 02/28/19
The Robert Packard Center for ALS Research
Role of microglial cells in C9orf72-mediated synaptic dysfunction

Dracheva (PI) 07/01/17 – 06/30/2021
Department of Veteran's Affairs
The role of ADAR2-associated RNA editing in pathogenesis of ALS

Sattler (PI) 07/01/17 – 06/30/18
Arizona Alzheimer's Disease Core Center
The role of microglial cells in C9orf72-mediated synaptic dysfunction

Mufson (PI) 2014-2019
W81XWH-12-PHRBI
Department of Defense
Tau phosphorylation in TBI CENC

Mufson (PI) 2013- 2019
NIA R01 AG043375
Cellular and molecular medial temporal lobe pathology in elderly pre MCI subjects

Mufson (PI) 2013- 2018
PO1AG014449
Neurobiology of Mild Cognitive Impairment in the Elderly

Mufson (PI) 2015-present
Barrow and Beyond Alzheimer's Research Award, Genetic of NFT cortical neurons in FAD and sporadic AD

Shi (PI) 2017-2018
Arizona Alzheimer's Research Consortium and Arizona Department of Health Services:
Effects of aging on brain pituitary adenylate cyclase activating polypeptide, pathology and cognition

Shi (PI) 2017-2019
Protocol Number: BN29553
Roche / Genentech
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Crenezumab in Patients with Mild Alzheimer's Disease

Shi (PI)	2017-2019
Protocol Number: BIIB037, ENGAGE	
Biogen Idec	
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BIIB037 in Subjects with Early Symptomatic Alzheimer's Disease (AD)	
Shi (PI)	2015-2017
Eli Lilly and Company	
A 24-month, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy, Safety, Tolerability, Biomarker, and Pharmacokinetic Study of AZD3293 in Early Alzheimer's Disease (The AMARANTH Study).	
Shi (PI)	2015-2017
Protocol Number: MK8931-019, APECS	
Merck	
A Phase III, Randomized, Placebo-Controlled, Parallel-Group, Double Blind Clinical Trial to Study the Efficacy and Safety of MK-8931 (SCH900931) in Subjects with Amnesic Mild Cognitive Impairment due to Alzheimer's Disease (prodromal AD).	
Shi (PI)	2015-2017
Protocol Number: Lundbeck 148621, STARBEAM	
Lundbeck	
Phase II, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Fixed Dose Study of Lu AE58054 in Patients with Mild Moderate Alzheimer's Disease Treated with Donepezil	
Stokes (PI)	7/1/17-6/30/18
Barrow Neurological Foundation Award	
Multiscale MR Perfusion Imaging of Multiple Sclerosis	
Stokes (PI)	7/1/17-6/30/18
Longitudinal assessment of advanced multi-parametric MRI biomarkers of Alzheimer's disease; Arizona Alzheimer's Research Consortium / Barrow Neurological Institute Pilot grant	
Stokes (PI)	3/1/17-2/29/20
Multiparametric MR imaging signatures of brain tumor burden (ADHS16-00005488)	
Arizona Biomedical Research Commission New Investigator Award	
Stokes (PI)	7/1/16-6/30/17
Multi-parametric MR imaging signatures of Alzheimer's disease	
Arizona Alzheimer's Research Consortium / Barrow Neurological Institute Pilot grant	
Sabbagh MN (PI)	10/23/14-10/22/17
ADHS14-00003606	\$223,816 Annual DC
Arizona Biomedical Research Commission	
Longitudinal Assessment of Flortetapir FET, FDG PET, and MRI in Down Syndrome	

Sabbagh, MN
Alzheimer's Association
Understanding the Development and Devising Treatment for Alzheimer's Disease in Individuals with Down's Syndrome

4/1/16—3/31/19
\$250,000

5U18 FD005320
Critical Path Public Private Partnerships

Zlokovic, Toga (Subaward PI)
P01AG052350
NIH/NIA
Vascular contributions to dementia and genetic risk factors for Alzheimer's disease
Program project to study imaging and molecular biomarkers of neurovascular dysfunction in individuals at genetic risk for AD both familial and sporadic.

9/1/16-8/31/21
\$1,793,519

Caselli (PI)
ADHS12-010553 State of Arizona, DHS
Arizona Alzheimer's Research Center (Consortium)
Normal and Pathological Aging (Preclinical Alzheimer's Disease)

7/1/11-6/30/21
\$360,000

Reiman (PI)
P30 AG019610
National Institute on Aging
Arizona Disease Admin and Clinical Core Center
Role: Associate Director and Clinical Core Director

8/15/11-6/30/21
\$131,530

Caselli (PI)
P30 AG019610
National Institute of Health
Arizona Alzheimer's Disease Center Plasma/Serum Storage at MCA Bio-repository

7/1/13-6/30/21
\$19,584

Caselli (PI)
MK-8931-017
Merck & Co., Inc.
13-000419/Protocol No. MK-8931-017-02 A Randomized, Placebo Controlled, Parallel-Group, Double Blind Efficacy and Safety Trial of MK-8931 in Subjects with Mild to Moderate Alzheimer's Disease

11/1/13-10/31/20
\$69,428

Caselli (PI)
MK-8931-019
Merck & Co., Inc.
IRB 13-006525/Protocol No. MK-8931-019 A Phase III, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Clinical Trial

11/1/13-10/31/20
\$81,781

Sierks (Co-I)
R01 AG054048
National Institute on Aging
Protein Variants as Blood Based Biomarkers for Diagnosing and Staging AD

9/01/16-8/31/21
\$24,092

Caselli (PI) 288A Novartis 16-005127/Randomized, doubleblind, placebo-controlled, two cohort parallel GRP study to evaluate the efficacy of CAD106&CNP520 in participants at risk for the onset of clinical symptoms of Alzheimer's	10/25/16-10/24/25 \$163,746
Reiman and Caselli R01 AG031581 National Institute of Neurological Disorders and Stroke PET, APOE & the Preclinical Course of Alzheimer Disease Role: Co-Investigator	5/1/14 – 4/30/19 \$73,956
Al-Nakkash, Layla (PI) Arizona Alzheimer's Consortium 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 Direct Costs
Al-Nakkash, Layla (PI) Diabetes Action and Research Foundation Genistein: Understanding its ability to ameliorate intestinal dysfunction in diabetes.	01/01/17-12/31/19 \$20,000 Direct Costs
Al-Nakkash, Layla (Consultant) NIH-R15 Physical activity as a therapeutic intervention in endometriosis.	04/01/18-03/31/21 \$470,124
Jentarra, Garilyn (PI) Arizona Alzheimer's Consortium Midwestern University Alzheimer's Advisory Committee (MAAC) The role of infection in Alzheimer's disease.	07/01/17-06/30/18 \$33,000 Direct Costs
Bae, Nancy and Swanson, Mark (PI) Arizona Alzheimer's Consortium 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 Direct Costs
Eckman, Delrae (PI) Arizona Alzheimer's Consortium Midwestern University Alzheimer's Advisory Committee (MAAC) Cerebrovascular Function in APOE3 and APOE4 Targeted-Replacement Mice	07/01/17-06/30/18 \$9,078 Direct Costs
Eckman, Delrae (PI) College of Health Sciences Research Facilitation Grant Midwestern University Cardiovascular and Cerebrovascular Function in APOE3 and APOE4 Targeted-Replacement Mice.	10/25/17-06/30/18 \$7,000

Eckman, Delrae (Co-PI) Multidisciplinary Stimulus Research Award Midwestern University Can laser therapy in the dental office heal cold sores better than anything else?	07/01/17-06/30/18 \$20,000
Jones, Carleton (PI) College of Health Sciences Research Facilitation Grant Midwestern University Effects of Losartan and Exercise on Aortic Inflammation in Marfan Syndrome Mice.	10/25/17-06/30/18 \$6,000
Veltri, Charles (Co-PI) Academic Research Enhancement Awards College of Veterinary Medicine Midwestern University Establishing pharmacokinetics of fluoxetine in horses	07/01/17-06/30/18 \$7,480 Direct Costs
Veltri, Charles (Collaborator) Grants for Laboratory Animal Sciences Title: Alternative Delivery Methods for Post-Operative Analgesia Using Meloxicam in Mice	07/01/17-06/30/18 \$7500 Direct Costs
Huentelman (MPI) R01 AG041232 NIH/NIA APOEomic: Searching for APOE interacting risk factors using omics data	07/01/2013 - 04/30/2018 \$125,000/year Direct Costs
Huentelman (MPI) UH2/UH3TR0000891 NIH/Trans-NIH Research exRNA signatures predict outcomes after brain injury	08/01/2013 - 07/31/2018 \$242,183/year Direct Costs
Huentelman and Barnes (MPI) R0AG048907 NIH/NIA CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox	09/15/2014 – 09/14/2018 \$245,145/year Direct Costs
Huentelman (Co-I) RO1 AG049465 (Barnes) NIH/NIA Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging	08/01/2014 – 03/31/2019 \$162,203/year Direct Costs
Huentelman (Co-I) 1 RO1 AG049464 (Coleman/Barnes/Alexander) NIH/NIA Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain	08/01/2014 – 05/31/2019 \$178,013/year Direct Costs

Huentelman (PI) R21NS093222 (NCE) NIH Identification of pathogenic mechanisms important in multiple system atrophy	09/01/2015 – 08/30/2018 \$119,500/year Direct Costs
Huentelman (Co-I) Grant#1994 (Trent) Flinn Foundation Grant	12/23/2014 – 03/31/2018 \$171,275/year Direct Costs
Huentelman (Co-I) Grant (Sabbagh) 03/31/2019Alzheimer’s Association Treatment for AD in individuals with Down’s Syndrome	04/01/2016 – \$37,829/year Direct Costs
Huentelman (Co-I) P30 AG019610 (Reiman) Competitive renewal NIH/NIA Arizona Alzheimer's Disease Core Center	07/01/2016 - 06/30/2021 \$12,190/year Direct Costs
Huentelman (Co-I) UG30D023313 (Deoni) NIH The Developing Brain: Influences and Outcomes	09/21/2016 – 08/31/2018 \$70,000/year Direct Costs
Huentelman (Co-I) R01AG054180 (Kaczorowski) NIH Systems Genetics of Cognitive Aging and Alzheimer's Disease	05/01/2017 – 04/30/2022 \$10,028
Huentelman (Co-PI) Grant #20170715 Aging Mind Foundation Ealry Onset Alzheimer’s Disease Genomic Study	11/08/2017 – 11/07/2019 \$32,441
Van Keuren-Jensen R03NS09001301A1 (Lifshitz) NIH/NINDS Gene Expression of Foci of TBI Neuropathology and Rod Microglia Interactions	06/01/2015 – 05/31/2018 \$11,000
Van Keuren-Jensen (MPI) UH2/4UH3TR000891 03 (Van Keuren-Jensen/Huentelman/Adelson/Kalani) NIH/Trans-NIH Research exRNA signatures predict outcomes after brain injury	08/01/2013 - 07/31/2018 \$118,835

Van Keuren-Jensen (PI)	
Grant 16-IIP-255	08/01/2015 – 07/31/2018
ALS Association Grant	\$80,000
Assessment of extracellular vesicle contents in patients with ALS	
Van Keuren-Jensen (MPI)	
Grant 12401 (Van Keuren-Jensen/El-Agnaf)	05/01/2016 – 9/31/2018
Michael J Fox Foundation for Parkinson’s Research	\$142,676
Pre-analytical extracellular vesicle enrichment for increased reliability for alpha-synuclein detection in plasma and CSF	
Van Keuren-Jensen (PI)	
Grant ID: 12749.01	04/01/2017 – 03/31/2019
Michael J Fox Foundation for Parkinson’s Research	\$96,183
RNAseq and miRNAseq in PPMI whole blood samples (Full study with USC)	
Van Keuren-Jensen (PI)	07/01/2017 - 06/30/2019
Siddell Kagan Foundation	\$135,000
Extracellular RNAs as candidates for monitoring Alzheimer’s patients	
Van Keuren-Jensen (PI)	
Michael J Fox Foundation for Parkinson’s Research	08/31/2017 – 08/30/2019
Grant ID: 14696:	\$91,362
RNAseq and miRNAseq in PPMI whole blood samples-Phase 2	Continuation of project with
the generation of RNAseq and miRNA seq data.	
Van Keuren-Jensen (Co-I)	
1U19CA179513-05 Supplement (Manus)	09/01/2017 – 08/31/2018
Genetic Models for exRNA Communication	\$50,000
Van Keuren-Jensen (MPI)	
3UH3TR000891-05S1	09/15/2017 - 07/31/2018
NIH/Trans-NIH Research	\$38,672
Supplement: exRNA signatures predict outcomes after brain injury: A comprehensive atlas of human small RNAs to enhance exRNA analytics	
Liang (Co-I)	
Contract (Jonathan Keats)	09/01/2011-08/31/2019
MMRF	\$1,364,526
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)	
Liang (Co-I)	
R01 (Trent/Weissman/)	04/01/2015–03/31/2020
NIH	\$223,475
The tumor suppressor role of SMARCA4 in SCCOHT	

Liang (Co-I) R01GM121698 (Brafman) NIH	02/01/2017–01/31/2018 \$11,144
Investigating the mechanisms of a multi-state model of Wnt signaling	
Liang (Co-I) R01 (Mufson) NIH	5/27/2017–5/26/2018 \$29,463
Liang (Co-I) W81XWH-16-TSCRP-IDA (Vinodh Narayanan) DoD	12/01/2016–11/30/19 \$150,000
TS160074:Phenotypic Variability in Tuberous Sclerosis Complex (TSC)	
Liang (Co-I) Grant (Daniel Von Hoff/Evans/Evan) AACR/Stand Up 2 Cancer	12/01/2015-11/30/2018 \$2,741,535
Reprogramming of Transcriptional Circuitry to Control Pancreatic Cancer	
Liang (Co-I) Grant (Reiman) NOMIS Foundation	07/01/2017–06/30/2021 \$1,133,608
Liang (Co-I) Contract (Jonathan Keats) Quantum Leap Health Care Collaborative	02/01/2017 – 01/31/2018 \$420,000
Ahern, Geoff (co-I; PI: Reiman) NIH/NIA P30 AG019610 Arizona Alzheimer's Disease Core Center (UA Clinical Core)	07/01/17 – 06/30/18 \$43,084 Annual DC
Ahern, Geoff (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium - Patient Recruitment and Outreach for Alzheimer's Disease and Related-Disorders	07/01/17 – 06/30/18 \$7,500 Annual DC
Ahern, Geoff (PI) Eisai	2013 – present \$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) Lilly Pharmaceuticals	2013 – present \$32,863/patient
Effect of Passive Immunization on the Progression of Mild Alzheimer's Disease: Solanezumab (LY2062430) versus Placebo. Protocol # H8A-MC-LZAX.	

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 – 05/31/19 \$439,857 Annual DC
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 Annual DC
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 \$310,587 Annual DC
Alexander, Gene (PI, co-I's: Glisky, Ryan) McKnight Brain Research Foundation McKnight Inter-institutional Cognitive Aging Assessment Core	09/01/15 – 08/31/17 \$266,667 Annual DC
Alexander, Gene (PI) State of Arizona, DHS Grant Influence of Health & Lifestyle Factors on Brain Aging and the Risk for Alzheimer's Disease	07/01/17 – 06/30/18 \$59,868 Annual DC
Alexander, Gene (PI, multi-PI) TLA Wheelhouse UA15-011 Evaluation of the aerobic and cognitive training system for enhancing cognitive performance in older adults	2/5/15-12/1/17 \$106,769 Total DC
Alexander, Gene (Co-I, PI: Reiman) NIH/NIA P30 AG019610 Arizona Alzheimer's Disease Core Center	7/1/16-6/30/21 \$12,345 Annual DC
Andrews-Hanna, Jessica (PI; co-I's: Grilli, O'Connor) State of Arizona, DHS Grant Arizona Alzheimer's Consortium - Daily thinking patterns in healthy and pathological aging	07/01/17 – 06/30/18 \$15,000 Annual DC
Andrews-Hanna, Jessica (UA PI; Bryan PI) NIH/NIA RO1 AG043452 Enhancing Function in Later Life: Exercise and Function Network Connectivity	06/15/14 – 02/28/19 \$25,533 Annual DC
Barnes, Carol (PI) NIH/NIA 1 R01 AG050548 Cell Assemblies, Brain Adaptation and Cognitive Brain	09/1/15 – 05/31/20 \$324,194 Annual DC
Barnes, Carol (PI) NIH/NIA 1 RO1 AG003376 Neurobehavioral Relations in Senescent Hippocampus	01/01/16 – 11/30/20 \$574,731 Annual DC

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 – 05/31/18 \$251,270 Annual DC
Barnes, Carol (PI) (co-I's: Alexander, Billheimer, Huentleman, Trouard) NIH/NIA RO1 AG049465 Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging	08/01/14 – 3/31/19 \$537,820 Annual DC
Barnes, Carol (PI) NIA/NIA T32 AG044402 Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease	05/15/16 – 04/30/21 \$223,800 Annual DC
Barnes, Carol (Co-I; PI: Reiman) NIH/NIA 5 P30 AG019610 Arizona Alzheimer's Disease Core Center Ad Hoc Review Program	08/15/16 – 06/30/21 \$15,945 Annual DC
Barnes, Carol (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Exploring the Microbiome-Gut-Brain Axis: Impact of Microbial Communities and their Genes on Cognition in Aging	07/01/18 – 06/30/18 \$29,439 Annual DC
Barnes, Carol (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Primate Models of Age-Related Memory Impairment: Tests of Agents Approved for Other Indications that are Safe and might be Successful Cognitive Enhancers	07/01/18 – 06/30/18 \$10,561 Annual DC
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 – 12/31/19 \$35,014 Annual DC
Brinton, Robbie D. (PI) NIH/NIA1 PO1 AG026572 Perimenopause in Brain Aging and Alzheimer's Disease	09/01/16 – 08/31/21 \$1,617,953 Annual DC
Brinton, Robbie D. (PI) NIH/NIA R37 AG053589 Aging and Estrogenic Control of the Bioenergetic System in the Brain	03/15/17 – 02/28/22 \$205,000 Annual DC
Brinton, Robbie D. (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 \$464,220 Total DC
Brinton, Robbie D. (PI; co-I: Rodgers) NIH/NIA UF1 AG046148 Allopregnanolone Regenerative Therapeutic and MCI/AD: Dose Finding Phase I	09/20/13 – 06/30/18 \$1,759,937 Total DC

Brinton, Robbie D. (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium - ApoE4: Accelerator of Bioenergetic Aging in Female Brain and Risk of Alzheimer's Disease	07/01/17 – 06/30/18 \$40,000 Annual DC
Brinton, Robbie D. (PI; co-I's: Rodgers, Mansour) Alzheimer's Drug Discovery Foundation Manufacturing of Allopregnanolone for Phase 2 Clinical Trial	01/01/17 – 12/31/17 \$450,000 Total DC
Brinton, Robbie D. (PI) Alzheimer's Drug Discovery Foundation Allopregnanolone Novel Patentable Formulations to Advance Commercialization	11/01/17 – 10/31/18 \$150,000 Total DC
Brinton, Robbie D. (PI) Alzheimer's Association Allopregnanolone Novel Patentable Formulations to Advance Commercialization	11/01/17 – 10/31/18 \$226,618 Total DC
Brinton, Robbie D. (PI) The Woman's Alzheimer's Movement Bioinformatics Analysis to Find Current Drug Therapies that can Prevent of Delay Alzheimer's Disease	11/14/16 – 11/14/17 \$60,000 Annual DC
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 – 06/30/18 \$30,000 Annual DC
Edgin, Jamie (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium - Validating a New Measure of Cognitive Aging and Decline in Down Syndrome	07/01/17 – 06/30/18 \$12,000 Annual DC
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 \$193,500 Annual DC
Edgin, Jamie O. (UA PI) NIH/NICHD 1 RO1 HD074346 Express Language Sampling as an Outcome Measure	04/01/13 – 02/28/18 \$75,427 Annual DC
Edgin, Jamie O. (PI) NIH/NICHD 1 RO1 HD088409 Memory Measure for Clinical Trials in Down Syndrome and Fragile X Syndrome	09/22/16 – 06/30/21 \$512,284 Annual DC

Fernandez, Fabian (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium - Calibrating the Function of the Aged Circadian Clock with High-Precision Light	07/01/17 – 06/30/18 \$12,000 Annual DC
Fernandez, Fabian (PI) National Science Foundation 2016 Bisgrove Scholar Program	08/01/16 – 07/31/18 \$200,000 Total DC
Glisky, Elizabeth (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Memory and Executive Function in Normally-Aging Older Adults	07/01/17 – 06/30/18 \$16,000 Annual DC
Grilli, Matt (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Forgetting One's Past: Episodic Autobiographical Memory in e4 Carriers	07/01/17 – 06/30/18 \$20,000 Annual DC
Mehl, Matthias (co-I; Lockhead Martin PI: Ziegler) Intelligence Advanced Research Projects Activity Multimodal Objective Sensing to Assess Individuals in Context (MOSAIC)	07/01/17 – 10/31/20 \$705,592 Total Costs
Mehl, Matthias (UA PI: PI: Nugent) NIH/NIMH RO1 MH108641 Understanding the interplay of social context and physiology on psychological outcomes in trauma-exposed adolescents	07/01/16 – 06/01/21 \$287,040 Total Costs
Mehl, Matthias (co-I; PI: Stone) NIH RO1 MD008940 Reducing implicit verbal and nonverbal bias towards Hispanic patients	09/01/14– 05/31/19 \$1,406,056 Total DC
Mehl, Matthias (UA PI: PI: Nugent) NIH/NIMH RO1 MH105379 Biomarkers, social, and affective predictors of suicidal thoughts and behaviors in adolescents	03/01/15 – 02/28/20 \$345,218 Total DC
Rapcsak, Steve (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium - Patient Recruitment and Outreach for Alzheimer's Disease and Related-Disorders	07/01/17 – 06/30/20 \$7,500 Annual DC
Rapcsak, Steve (co-I; PI: Reiman) NIH/NIA 5 P30 AG019610 Arizona Alzheimer's Disease Core Center (UA Clinical Core)	07/01/17 – 06/30/18 \$43,073 Annual DC

Rapcsak, Stephen (PI) Masaryk University Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioral Neurology	2017 - 2021 \$40,000 Total DC
Rodgers, Kathleen (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Amelioration of Neurodegenerative Changes in spSHR by Mas Agonists	07/01/17 – 06/30/18 \$30,000 Annual DC
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 \$44,787 Total DC
Rodgers, Kathleen (PI) Department of Defense MH060102 Evaluation of MMX1902 as an Oral Treatment of Duchenne Muscular Dystrophy	07/01/15 – 06/30/18 \$846,279 TC
Rodgers, Kathleen (PI) Department of Defense MH140084 Small Molecular Mas Agonists for the Amelioration of DMD-Associated Cardiomyopathy	09/01/17 – 08/30/19
Ryan, Lee; Hay, Meredith; Switzer, Nancy (multi-PI) 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 Annual DC
Ryan, Lee (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Memory Functioning in Heart Failure Patients with Risk for Alzheimer's Disease	07/01/17-06/30/18 \$60,000 Annual DC
Su, Judith (co-I) NIH/NIMH R21 MH111109 Label-Free, Highly-Specific, Small Molecule Detection Using Microtoroid Optical Resonators	08/01/16 – 05/31/19 \$150,000 Annual DC
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 \$109,177 Total DC
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 \$99,204 Annual DC
Ryan, Lee (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Ultra-Sensitive and Label-Free Detection of Alzheimer's Disease Biomarkers Using Microtoroid Optical Resonators	07/01/17-06/30/18 \$11,500 Annual DC

Trouard, Ted (PI) NIH Bruker Biospec 7T Small Animal MRI Upgrade	03/01/18 – 02/28/19 \$600,000 Annual DC
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	04/01/17 – 03/31/20 \$125,000 Annual DC
Trouard, Ted (co-I) NIH/NICHHD R01 HD079498 Intense Physiotherapies to Improve Function in Young Children with Cerebral Palsy	05/01/14 – 04/31/19 \$451,781 Annual DC
Trouard, Ted (co-I) Department of Defense W81XWH-12-1-0386 Model for Predicting Cognitive and Emotional Health from Functional Neurocircuitry	07/01/14 – 07/31/18 \$553,327
Trouard, Ted (PI) State of Arizona, DHS Grant Arizona Alzheimer’s Consortium – Advanced Diffusion and Perfusion MRI Methodology	07/01/17 – 06/30/18 \$45,000 Annual DC
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 – 06/30/18 \$30,000 Annual DC
Wilson, Robert C (PI) UA Faculty Seed Grant The Neural Substrates of Exploration and Exploitation	07/01/17 – 06/30/18 \$10,000 Annual DC
Wilson, Robert C (PI) UA Dean’s Innovation and Education Fund The High-Throughput Psychophysiology Lab - A Cognitive Neuroscience Resource for Research, Education and Outreach	07/01/17 – 06/30/18 \$10,000 Annual DC
Wilson, Robert C (co-I; PI: Barnard) UA Improving Health TRIF Building Capacity for Inferring Facial Communication from Video Data	07/01/17 – 06/30/18 \$80,000 Annual DC
Wilson, Robert C (co-I; PI’s: Imad, Kikuchi) UA CIS Seed Grant Integrative Education Mentoring in Higher Education	07/01/17 – 06/30/18 \$10,000 Annual DC
Yin, Fei (PI) State of Arizona, DHS Grant Arizona Alzheimer’s Consortium – Sex Differences in Translational Animal Models of Human LOAD Risk Factors	07/01/17 – 06/30/18 \$30,000 Annual DC

Lifshitz Diane & Bruce Halle Foundation Translational Neurotrauma Research Program	11/15/2013-11/14/2018 \$100,000
Lifshitz NS090013 R03 NIH/NINDS Gene expression at foci of TBI neuropathology & rod microglia	6/01/2015-5/31/2018 \$50,000
Lifshitz NIH R21 NS096515 Remote ischemic conditioning mitigates diffuse traumatic brain injury via specialized pro-resolving mediators	8/15/2016-7/31/2019 \$150,000
Lifshitz NIH R21 Supplement NS096515-Supp Remote ischemic conditioning mitigates diffuse traumatic brain injury via specialized pro-resolving mediators	12/01/2017-7/31/2019 \$26,058
Lifshitz Arizona Alzheimer's Consortium Modulation of the peripheral immune response using RIC improves chronic pathology and cognitive outcomes of TBI	7/1/2017-6/30/2018 \$38,484
Lifshitz VA Merit 101 RX002472 Brain injury rehabilitation modality, regulation, & structural plasticity	4/1/2018-3/31/2022 \$275,000
Lifshitz DOD CDMRP AZ160056 Probing the mechanistic role of vascular dysfunction and vascular inflammation in TBI-mediated cognitive dysfunction	8/1/2017-7/31/2019 \$191,000

Pending Grants

Caccamo, Antonella (PI) Project #: Pending Alzheimer's Drug Discovery Foundation Targeting Neuronal Death in Alzheimer's Disease	3/1/2018 - 2/29/2020 \$188,576.00 Annual
Caccamo, Antonella (PI) 1 R01AG059627-01 NIH Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome	7/2018 - 6/2023 \$3,595,608.00 Annual

Decourt (co-PI)	7/1/18 - 6/30/23
Diehnelt (co-PI)	\$3,837,250
R01	
National Institute of Neurological Disorders and Stroke	
Testing novel strategies to lower the incidence of Alzheimer's disease post-TBI	
Decourt (co-PI)	7/1/18 - 6/30/19
Diehnelt (co-PI)	\$100,000
Pilot Grant	
Coins for Alzheimer's Research Trust.	
Synthesis and testing of mouse brain penetration of synbodies.	
Wynne, Clive (PI)	1/17-7/2018
Maddies Fund	\$125,643
Mastreoni, Diego (PI)	
NIH R01	\$1,500,000
Can 3D Organoids Derived from Human Neurogenic Niches Recapitulate Pathological Features of Late Onset Alzheimer's Disease?	
Mastreoni, Diego (PI)	
NIH R01	\$1,250,000
The Efficacy of a Novel Blood Test to Detect Alzheimer's Disease in Longitudinal Samples from Hundreds of Presymptomatic Patient	
Mastreoni, Diego (PI)	
Department of Defense	\$500,000
The utility of peripheral blood test and neuroimaging to asses Alzheimer's disease risk in veterans with traumatic brain injury	
Mastreoni, Diego (Co-PI)	
NIH R01	
Necroptosis as a novel mechanism of neurodegeneration in Alzheimer's disease.	
Oddo, Salvatore	9/1/2018-8/31/2023
R01AG061134	\$505,421.00
HHS-NIH	
RIPK1 as a novel kinase involved in the pathogenesis of Alzheimer's disease	
Velazquez, Ramon	7/1/2018-6/30/2023
K99NS107633	\$79,754.00
Dissecting novel therapeutic strategies for Alzheimer's disease	
HHS-NIH	
Labaer, Joshua	5/1/2018-10/31/2019
FP00014732	\$51,357.00
IMMUNE RESPONSE PROFILING FOR BLOOD BASED BIOMARKERS IN PD	
INanoBio, Inc	

Oddo, Salvatore R01AG057596-01A1 Necroptosis as a novel mechanism of neurodegeneration in Alzheimer's disease	7/1/2018-6/30/2023 \$403,863.00
Caccamo, Antonella R01AG059627 HHS-NIH Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome	7/1/2018-6/30/2023 \$346,948.00
Coleman, Paul David FP00012119 The Effect of Novel Synthesized Multifunctional Radical Quenchers On Mitochondrial Function in Alzheimer's Models	10/1/2018-9/30/2020 \$447,490.00
Labaer, Joshua FP00014429 Advanced Label-Free Assays for Alzheimer's Target ID and HTP Drug Screening INanoBio, Inc	7/1/2018-6/30/2020 \$73,802.00
Oddo, Salvatore R01AG057596-01A1 Necroptosis as a novel mechanism of neurodegeneration in Alzheimer's disease	7/1/2018-6/30/2023 \$403,863.00
Caccamo, Antonella R01AG059627 Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome	7/1/2018-6/30/2023 \$346,948.00
Coleman, Paul David FP00012119 The Effect of Novel Synthesized Multifunctional Radical Quenchers On Mitochondrial Function in Alzheimer's Models Alzheimer's Drug Discovery Foundation	10/1/2018-9/30/2020 \$447,490.00
Co-PI: Coleman, Paul NIH R01 The Efficacy of a Novel Blood Test to Detect Alzheimer's Disease in Longitudinal Samples from Hundreds of Presymptomatic Patient	\$1,250,000
Co-PI: Coleman, Paul Department of Defense The utility of peripheral blood test and neuroimaging to asses Alzheimer's disease risk in veterans with traumatic brain injury	\$500,000

Smith, Brian H (PI) NSF-CRCNS US-German Research Proposal: Collaborative Research: Dynamics of Active Sensing of Odors	10/1/2018 - 9/30/2021 \$339,560
Smith, Brian (co-PI) NSF IGE: A Multiple Mentor Model of Graduate Training for Resilient Infrastructure Systems	7/1/2018 - 6/30/2021 \$500,000
Sanabria, Federico (PI) R01DA045840 NIH Dissociating the components of motivated behavior.	10/1/2018-9/30/2021 \$1,000,000
Sanabria, Federico (PI) R03MH115245 NIH Sustained threat and interval timing	\$100,000
Langbaum JB (PI) 1R01AG056333-01 NIH/NIA Alzheimer's Prevention Registry: The Science of Recruitment and Enrollment	7/1/17-6/30/22 \$499,606 Annual DC
Reiman EM 2U54MD000507-15 (Manson) NIH via University of Colorado, Denver American Indian and Alaska Native Health Disparities	9/01/2017-8/31/2022 \$50,000 Annual DC
Reiman EM (PI) P30 AG19610-19S1 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center – Brain Imaging and Fluid Biomarker Core	9/30/2018 -6/30/2021
Reiman EM (PI) 1R01AG058468-01 (Reiman, Tariot, Langbaum,S perling, Johnson,K, Aisen) The Aducanumab Alzheimer's Prevention Trial	4/1/2018-3/31/2019 \$3,602,043 Annual DC
Beach, Thomas NIH NIH R21 via ASU (Tsow) Novel biomarkers monitored with a non-destructive continuous volatile chemical sniffer for biospecimen quality control and workflow optimization	9/1/18-8/31/21 \$20,161
Beach, Thomas (Co-I) NIH NIH R21 via ASU (Tsow) Novel biomarkers monitoredwith a non-destructive continuous volatile chemical sniffer for biospecimen quality control and workflow optimization	12/1/18- 11/30/20 \$6,609 Annual DC

Zamrini, Edward (PI) R21 NIH R21 Adjusted Score Development for the Cognitive Reserve Index Questionnaire	9/1/18 – 8/31/19 \$25,000 Annual DC
Jentarra, Garilyn and Jones, T. Bucky (PIs) NIH R15 (AREA) Microbial Intrusion into the Brain: Is this the Cause of Alzheimer's disease?	09/01/18-08/31/21 \$444,000
Revill, Ann (PI) American Heart Association. Career Development Award. Cholinergic Modulation of XII Motoneurons and XII Premotoneurons	07/01/18-06/30/21 \$231,000
Eckman, Delrae (PI) New Investigator Award AZ NIA, Arizona RFGA ADHS17-00007401, Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4 Targeted-Replacement Mice	03/01/18-02/28/21 \$225,000
Griffin, Michael (PI) NIH NIDDK Transcriptional Regulation of Adipocyte Inflammation by Early B-Cell Factor-1 (Ebf1)	9/1/2018-8/31/2021 \$250,000 direct costs
Al-Nakkash, Layla (PI) CFF- Research Grant Understanding the link between growth and survival in genistein-fed mice.	07/01/18-06/30/20 \$216,000
Al-Nakkash, Layla (PI) NIH-R15 Understanding the link between growth and survival in genistein-fed mice.	07/01/18-06/30/21 \$375,000
Hernandez, Jose (PI) Morris Foundation Finding new strategies to combat bacterial Urinary Tract Infections (UTIs) in canines and felines.	08/01/18-08/31/19 \$10,800
Hernandez, Jose (PI) Morris Foundation Determining the feasibility of vaccination as a strategy to curtail the spread of RMSF in canines.	08/01/18-08/31/19 \$10,800
Veltri, Charles (PI) Dry Bean Health Research Program The Northarvest Bean Growers Association Identification and Characterization of Immunomodulatory Phytochemicals from Vigna angularis Able to Influence Cytokine Signaling.	07/01/18-06/30/19 \$20,000

Huentelman (Co-I) R01AG031581 (Reiman) NIH Brain Imaging, APOE & Preclinical Course of Alzheimer's Disease	04/01/2017 – 05/31/19 \$72,000 direct costs
Huentelman (Co-I) R01 (Oddo) NIH Necroptosis as a novel mechanism of neurodegeneraton in Alzheimer's disease	09/01/2019 – 08/31/2020 \$56,774
Huentelman (Co-I) R01 (Oddo) NIH RIPK1 as a trigger of neurodegeneration in Alzheimer's disease	09/01/2019 – 08/31/2020 \$38,497
Huentelman (Co-I) R01 (Hale) NIH Identifying a Pathogenic Fibroblast Subpopulation to Target for Protection Against Cardiac Fibrosis	09/01/2018 - 08/31/2023 \$53,356
Huentelman (Co-I) DoD (Schwedt) A Multidisciplinary Transnational Approach to Investigate the Mechanisms, Predictors and Prevention of Persistent post-traumatic headache	04/01/2018 – 03/31/2022 \$228,298
Van Keuren-Jensen (Co-I) Michael J Fox Foundation for Parkinson's Research Grant 14539: Program	01/01/2018–12/31/2019 LRRK2 Biology Consortium \$80,000
Van Keuren-Jensen (Co-I) Michael J Fox Foundation for Parkinson's Research Grant 15065 (Singleton, PI) The Foundational Data Initiative	01/01/2018 – 12/31/2019 \$158,723
Van Keuren-Jensen (MPI) R21/R23 (Van Keuren-Jensen , Carter-MasGen) NIH Selective extracellular vesicle enrichment for monitoring the central nervous system	09/01/2018 -08/31/2023 \$27,000
Liang (Co-I) W81XWH-16-PRARP-TRPA (Mastroeni) DoD Predicting Alzheimer's disease in at risk populations using novel blood test	05/01/2018–04/30/2020 \$149,512

Liang (Co-I) Grant (Mastroeni) Alzheimer's Association Gender Effects on identified cell population in Alzheimer's Disease	09/01/2018 – 08/31/2020 \$24,641
Alexander, Gene (Subcontract PI) NIA 2P30AG019610-17 Supplement ADCC Brain Imaging and Fluid Biomarkers Core Supplement	7/1/18-6/30/21 \$742,764 Annual DC
Alexander, Gene (Co-Investigator, PI: Su) NIH DP2 Label-Free Single Molecule Detection for Basic Science and Translational Medicine	9/30/18-6/30/23 \$331,065 Annual DC
Andrews-Hanna, Jessica (PI) NIH – Arizona Alzheimer's Disease Core Center Uncovering Neurocognitive Links between Alzheimer's Disease and Depression in Mid-Life to Early Aging	07/01/18 – 06/30/19 \$30,000 Annual DC
Andrews-Hanna, Jessica; Grilli, Matthew D. (co-I's; PI Ekstrom) NIH Precision and Binding as Two Dimensions of Medial Temporal Lobe Amnesia	10/01/18 – 09/30/23 \$2,463,125 Total DC
Barnes, Carol A. (PIs: Barnes/Ekstrom) NIH/ NIMH 1 R01 MH117050 Hippocampal Low-Frequency Oscillations across Different Scale and Species	09/01/18 – 08/31/23 \$3,041,558 Total DC
Barnes, Carol A. (co-I; PI: Liang) NIH Mapping of Behavioral Circuits: A Scalable Acquisition and Data Management System	09/01/18 – 08/31/23 \$41,496 Annual DC
Barnes, Carol A. (co-I; PI: LaComb) NIH Portable Fiber Optic Magnetoencephalography Imaging System for Use in Unshielded Environments	09/01/18 – 08/31/23 \$10,561 Annual DC
Barnes, Carol A. (UA PI; PI: Stern) NIH /Columbia University Collaboratory on Research Definitions for Cognitive Reserve and Resilience	09/01/18 – 08/31/23 \$12,342 Annual DC
Brinton, Robbie D. (UA-PI) NIH / Duke University Metabolic Networks and Pathways Predictive of Sex Differences in AD risk and Responsiveness to Treatment	04/01/18 – 03/31/23 \$540,000 Total DC

Brinton, Robbie D. (PI; co-I: Yin, Fei) NIH Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype	07/01/18 – 06/30/23 \$5,932,472 Total DC
Chou, Ying-Hui (co-I; PI: Chou) NIH RO1 Development of High-Speed and Quantitative Neuro MRI Technologies for Challenging Patient Populations	07/01/17 – 06/30/18 \$1,000,000 Total DC
Chou, Ying-Hui (Trouard: co-I's; PI: Chou) NIH R21 Turning MRI from a Pure Imaging System to an Integrated Imaging and Neuro-Modulation Machine	09/01/18 – 08/31/20 \$250,000 Total DC
Chou, Ying-Hui (co-I; PI: Sundman) Dannon Company, Inc. Exploring Gut Microbiota Influences on Mild Cognitive Impairment with Non-Invasive Brain Stimulation	06/01/18 – 05/31/20 \$20,000 Total DC
Fernandez, Fabian (PI) Arnold and Mabel Beckman Foundation Circadian Programming with High Precision Light	08/01/18 – 07/31/22 \$597,412 Total DC
Grilli, Matt (co-I; PI: Walker) NIH Multidimensional Evaluation of Cognitive Performance (MECP)	09/01/18 – 08/31/22 \$1,501,604 Total DC
Hay, Meredith (Multi-PI: Brinton, Rodgers) NIA/NIA UO1 AG060945 IND Enabling Studies for PNA6, a Novel Mas Receptor Agonist, for Treatment Cognitive Impairment in Patients at Risk for Alzheimer's Disease	09/01/18 – 08/31/23 \$3,919,091 Total DC
Rodgers, Kathleen (PI) RASRx Small Molecular Mas Agonist for Treatment of Cutaneous Lupus Erythematosus	04/01/18 – 09/30/18 \$51,126 Annual DC
Rodgers, Kathleen (PI) RASRx Small Molecular Mas Agonist for Treatment of Duchenne Muscular Dystrophy	04/01/18 – 09/30/18 \$52,670 Annual DC
Rodgers, Kathleen (PI) NIH Deciphering the Mechanisms by which Mas Agonists Improve SLE Associated Pathologies in MRL-lpr Mice to Develop Novel Therapeutics	04/01/18 – 03/31/21 \$56,694 Annual DC

Rodgers, Kathleen (PI) (co-I: Brinton) NIH Undergraduate Readying for Burgeoning Research for American Indian Neuroscientists	07/01/18 – 06/30/23 \$248,196 Annual DC
Rodgers, Kathleen (UA PI) USC Subcontract – DoD Prime NorLeu3-A (1-7) Stimulates Corneal Repair after PRK	07/01/18 – 06/30/21 \$80,007 Annual DC
Rodgers, Kathleen (PI) NIH Exploring the Mechanisms by which Mas Agonists Act as Therapeutic Treatment of SLE Associated Pathologies in MRL-lpr Mice	07/01/18 – 06/30/20 \$150,000 Annual DC
Rodgers, Kathleen (co-I; PI: Gaffney) DoD Small Molecular Mas Agonists for Treatment of Acquired Aplastic Anemia	09/01/18 – 08/31/20 \$152,877 Annual DC
Rodgers, Kathleen (co-I; PI: Gaffney) NIH BM170049 - Small Molecular Mas Agonists for Treatment of DMD-Associated Cardiomyopathy and Muscle Pathology	09/01/18 – 08/31/21 \$176,190 Annual DC
Rodgers, Kathleen (PI) DoD The Use of RAS-Modifying Drugs for the Prevention of Kidney Damage in SLE: A Step Towards Personalized Medicine	09/01/18 – 08/31/20 \$342,018 Total DC
Ryan, Lee (PI's: Hay, Rodgers, Switzer; co-I's: Bedrick, Glisky, Konhilas, Trouard) NIH Safety and Efficacy of Angiotensin-(1-7) on Cognitive Impairment in Heart Failure Patients At-Risk for Alzheimer's Disease	07/01/18 – 06/30/23 \$497,762 Annual DC
Su, Judith (PI) Defense Threat Reduction Agency #12326236 Sensitive, Selective, and Affordable Chemical Threat Sensing Using Frequency Locked Microtoroid Optical Resonator	09/01/18 – 08/31/21 \$1,487,598 Total DC
Su, Judith (PI) Pew Biomedical Scholars Label-free Single Biomolecular Detection & Spectroscopy	09/01/18 – 08/31/22 \$300,000 TC
Su, Judith (PI) NSF 1803800 Label-free, Sensitive, Robust Detection and Identification of Cyanobacteria in Water Using Microtoroid Optical Resonators	09/01/198- 8/31/21 \$208,593 Total DC

Lifshitz 7/1/2018-6/30/2020
NIH R21 \$150,000
Effectiveness of brain injury rehabilitation depends on hippocampal neuronal activation

Lifshitz (MPI) 4/1/2018-3/31/2023
NIH UG3 NS106947 (Stabenfeldt, MPI) \$250,000
Interplay between rod microglia neuroinflammation and post-traumatic sleep to track acute to post-acute trajectory after TBI



**Arizona Alzheimer's Consortium
20th Annual Scientific Conference
Thursday, May 17, 2018**

**Barrow Neurological Institute (Host Institution)
Goldman Auditorium
Phoenix, Arizona**

Poster Abstracts

Poster 1

NETWORK COVARIANCE OF HIPPOCAMPAL SUBFIELD VOLUMES ASSOCIATED WITH HEALTHY AGING AND THE RISK FOR ALZHEIMER'S DISEASE. Alexander GE, Bharadwaj PK, Raichlen DA, Klimentidis YC, Fitzhugh MC, Nguyen LA, Haws KA, Hishaw GA, Moeller JR, Habeck CG, Trouard TP. University of Arizona; Columbia University; Arizona Alzheimer's Consortium.

Background: Healthy aging is associated with regional brain atrophy, which be exacerbated by an increased risk for Alzheimer's disease (AD) with the apolipoprotein E (APOE) ϵ -4 allele. We have previously reported regionally distributed network patterns of gray matter volume throughout the brain associated with healthy aging and APOE risk for AD (Alexander et al., 2006, 2012; Bergfield et al., 2010) using magnetic resonance imaging (MRI) and a multivariate model of regional covariance, the Scaled Subprofile Model (SSM; Alexander and Moeller, 1994). Here, we sought to evaluate the effect of aging on the SSM network pattern of hippocampal subfield volumes in a cohort of healthy, community-dwelling middle-aged to older adults, who were screened to exclude common medical conditions of aging, including hypertension and diabetes.

Methods: T1-weighted 3T volumetric MRIs were obtained in 81 healthy adults (45F/36M, Age = 66.2 ± 10.1 , Mini-Mental State Exam = 29.2 ± 0.9 , APOE ϵ -4 status = 22 carriers/59 non-carriers), 50 to 89 years of age. Image processing was performed using Freesurfer (v6.0) software to obtain bilateral hippocampal sub-region volumes of CA1, CA3, CA4, dentate gyrus granule cells (DG), molecular layer, subiculum, presubiculum, and hippocampal tail. Regional network analysis was performed with SSM bootstrap re-sampling and 10,000 iterations on the TIV-adjusted hippocampal subfield volumes using the Akaike information criterion (AIC).

Results: A linear combination of the first eight SSM components was associated with increasing age in the sample ($R^2 = 0.27$, $p \leq 2.49E-3$). This regional pattern was characterized by volume reductions in bilateral DG and molecular layer sub-regions with relative increases in bilateral CA3. Univariate regional analyses showed that each of the bilateral DG and molecular layer sub-regions were inversely correlated with age (p -values $\leq 2.86E-5$), whereas CA3 regions did not reach significance (p -values = 0.07). After we controlled for age and gender, expression of the SSM pattern was greater in the APOE ϵ -4 carriers than non-carriers ($p \leq 0.004$).

Conclusions: The results indicate a regionally specific pattern of hippocampal subfield volumes with reductions in the vicinity of the dentate gyrus and relative preservation in the region of CA3 that is associated with healthy aging and is further expressed to a greater extent in APOE ϵ -4 carriers. Together, these findings support selective regional vulnerability of the dentate gyrus in the context of healthy aging and in relation to genetic risk for late onset AD.

Poster 2

DEMENTIA AWARENESS IN HOSPITAL SETTINGS (DAHS). Allen A, Snyder N, Long C, Johnson K, Nisson L, Dougherty J, Corley D, Rivas C. Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Patients with dementia admitted into the hospital have poorer outcome as it relates to their length of stay, increased mortality and further institutionalization. Furthermore, this group of patients require more nursing hours of care, and are more likely to have delayed discharge, which result in decline in health and increase in hospital cost. One reason related to the poor outcomes is the lack of awareness and understanding from healthcare professionals and other staff in providing appropriate care. The primary objective of this study was to assess the healthcare professionals' and staff's knowledge and attitude of dementia. Secondary objective was to address the available dementia resources offered within a large health care system.

Methods: A pretest and posttest design was used using convenience sampling methods and a 2-part questionnaire measuring the knowledge and attitude of dementia of a multidisciplinary team of acute care staff in 13 hospitals within a large health care system. Two hundred and forty-six acute care workers (nurses, social workers, therapist, dieticians, housekeepers and other hospital staff) completed a session that included pre-assessment, a 60-minute presentation on dementia care in the inpatient setting, and post-assessment.

Results: The participants demonstrated a significant in percentage of increase in the overall correct answers related to knowledge (78% to 86.4%) and attitude (56% to 63%) toward dementia care in an inpatient setting. After adjusting for disciplines, the therapists showed a significant increase in knowledge and attitude of care. The overall results demonstrated a need for a required dementia educational intervention and utilizing the resources available within the setting.

Conclusions: Recognizing this need provide a better understanding on how to communicate and manage the care of patients with dementia, decrease hospitalization and ultimately the cost of care.

Poster 3

SOCIOEMOTIONAL AND NEURAL CORRELATES OF OFF-TASK THINKING IN YOUNG AND OLD ADULTS. Andrews-Hanna JR, Gardiner CK, Helmuth T, Davis AE, Giordano GR, Bennett G, Banich MT, Bryan AD. University of Arizona; University of Colorado; Arizona Alzheimer's Consortium.

Background: Recent years have brought a growing appreciation that the human mind has a propensity to wander away from the task at hand. Adults spend upwards of half their waking day cognitively disengaged from the task at hand, yet despite this high frequency, the correlates and consequences of off-task thought are poorly understood. Off-task thought facilitate problem solving and contribute to one's sense of self-identity, but it can also fuel unhappiness and associate with psychiatric disorders. Further, little is known about how on- and off-task thoughts change in aging. Despite the well-established cognitive "positivity effect" in old age, the elderly are particularly vulnerable to social isolation and depression. These gaps call for a deeper understanding of the role of off-task thinking and their neural correlates in socioemotional well-being across the lifespan.

Methods: Toward this end, we explored the frequency, content, and correlates of on- and off-task thought in young (N = 42, ages 25-35, mean = 28.5) and older adults (N= 115, ages 60 - 88, mean = 70) across two contexts. First, we developed a trait questionnaire to estimate typical patterns of daily thinking. Second, we developed a retrospective self-report questionnaire to assess thought content during a 5-minute resting state paradigm while acquiring fMRI data to explore neural correlates of cognitive changes.

Results: Results reveal numerous differences between young and older adults, with broad consistency across the two contexts outlined above. Older adults reported less frequent internally-focused off-task thoughts (i.e., mind-wandering), and greater focus on the fixation crosshair. They also displayed greater present-focused and reduced past-focused content, and biases toward more positive and other-focused thoughts. Socioemotional well-being increased with age, and the relationship between age and wellbeing was mediated by age-related reductions frequency of off-task thinking and unconstructive thought content. Resting state connectivity analyses reveal that age-related changes in daily thoughts and increases in well-being stem from connectivity decreases in posterior- to-anterior DMN and increases in DMN-to-frontoparietal control network.

Conclusions: These findings raise the possibility that neural and cognitive changes associated with normal aging partially underpin increases in socioemotional wellbeing. However, important individual differences emerge in aging, marking an important area for future research, with relevance to geriatric depression and dementia.

Poster 4

CELL-SPECIFIC CHARACTERIZATION OF ALZHEIMER'S DISEASE USING SINGLE CELL RNASEQ. Antone JV, Geiger P, Enriquez D, 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. In previous work, we performed transcriptomic characterization of non-tangle bearing neurons in differentially impacted brain regions in AD using expression profiling. With the evolution of genomic technology, we are now expanding our analyses to perform cell-specific transcriptomic characterization using sequencing. One approach that has gained increased adoption is single cell RNA sequencing (scRNAseq) which enables classification of sub-populations of cells. To evaluate this approach, we designed a pilot study to test and optimize scRNAseq sample preparation using the 10x Genomics' platform, which enables high throughput analysis of single cells or nuclei from dissociated tissue, to identify the approach that allows us to capture measurements on the highest number of transcripts per cell or nuclei.

Methods: We received whole cell suspensions and fresh frozen tissue from 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. Whole cell suspensions provided by BSHRI were filtered and resuspended to remove cellular debris for loading onto the 10x Chromium Single Cell A chip. Fresh frozen tissues were dissociated using an in-house tissue dissociation protocol with modification of 10x's whole cell and nuclei isolation protocols. The dissociated tissue was: (a) treated as a whole cell suspension; or (b) prepared in lysis buffer for nuclei isolation. 3500 whole cells or nuclei were loaded for a targeted cell recovery of 2000 cells. Libraries were constructed and sequenced on the Illumina NextSeq500 and data were analyzed using 10x's Cell Ranger software.

Results: Overall, samples prepared using our in-house tissue dissociation protocol and prepared as nuclei preps demonstrated the most optimal performance with the highest number of genes detected (18,325 [ND] and 19,244 [AD]), and an estimated number of 436 (ND) and 1,222 (AD) cells. Across all ND and AD libraries, we generated 161,262,198 and 162,939,653 reads, respectively. While our analyses are preliminary, analysis demonstrated more defined separation of clusters in nuclei data compared to whole cell data. Interestingly, whole cell clusters did not overlap with nuclei clusters, suggesting that the data be complementary.

Conclusions: Our pilot study analysis evaluated the performance of: (a) fresh frozen cell suspensions from BSHRI; (b) whole cell suspensions dissociated from fresh frozen tissue; and (c) whole cell versus nuclei scRNAseq. Further analysis is needed to enable assignment of clusters to specific cell types. With our optimized protocol, next steps include scRNAseq of fresh frozen SFG from 50 ND and 50 AD subjects. We plan to perform laser capture microdissection (LCM) of microglia, astrocytes, tangle-bearing neurons, and non-tangle bearing neurons across SFG, and other brain areas differentially impacted in AD (entorhinal cortex, hippocampus, posterior cingulate, primary visual cortex) in the same ND and AD subjects. This complementary dataset will provide high-resolution characterization of brain cell types in healthy aging and AD.

Poster 5

THE INFLUENCE OF AGE AND ASD ON VERBAL FLUENCY NETWORK DIFFERENCES. Baxter LC, Braden BB, Nespodzany A, Wood EG, Smith CK. Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona State University; Arizona Alzheimer's Consortium.

Background: Language functioning is variable in autism, ranging from nonverbalism in more severely affected individuals to problems with pragmatic aspects of language comprehension as well as other aspects of language processing in high functioning individuals. Aging also influences word production, in part due to decline in processing speed and changes in executive functioning. Objective: To investigate the influence of age and autism on fluency and its underlying brain networks.

Methods: Participants were recruited through the community and underwent screening for ASD prior to cognitive and MRI assessments. Inclusion/exclusion criteria included IQ > 80, male, and general good health. Participants included older (n =21; M=53; SD=8; 40-70) and younger (n = 18, M=21; SD=3; 18-25) individuals with ASD and age- and IQ-matched Typically Developing (TD) participants (older: n = 20, M=50; SD=7; 40-64; younger: n = 13, M=21, SD=3; 18-25). Outside the scanner, participants performed the Controlled Oral Word Association Test (COWAT) and participants also performed a fluency task modified for functional MRI (fMRI) task on a Philips 3 Tesla scanner. Group ICA was first used to visualize any network differences across groups, and nodes from significant networks were extracted from group data for further analysis using SPSS (v19).

Results: The young adult ASD group had a lower mean COWAT score; therefore, the COWAT covariate was used for fMRI analyses. There were no significant group differences for fMRI task performance measured by mean number of words produced. All groups produced a network involving left inferior frontal cortex (LIFC), in the general area often termed "Broca's area" that is critical for expressive language. Other networks reflecting increased activity during word generation included the right cerebellum, anterior cingulate, left hippocampus. Precuneus/posterior cingulate regions showed greater engagement during the baseline condition. Not all groups utilized these regions to the same extent when performing the fluency task, despite all groups having very similar task performance. Some regions contributing to this fluency task showed clear aging effects, while others showed group differences. The left hippocampus was far less engaged in the fluency task for both older ASD and TD individuals; in contrast, both older and younger adult ASD groups showed less cerebellar activation compared to the TD groups. No significant age by ASD interactions were observed, but among older individuals only, significant increased engagement of Broca's area was observed in the ASDs compared to the TD group, possibly reflecting compensation for other weaknesses.

Conclusions: We found that both age and the presence of ASD influenced brain networks engaged during a fluency task. With our current sample, we did not find any significant age-by-group interactions, but a trend that older individuals with ASD utilize Broca's area to a greater degree to compensate for other network weaknesses. Interestingly older adults use less memory-related regions than their younger counterparts, while individuals with ASD generally tend to engage the cerebellum less than TDs.

Poster 6

FASTER COGNITIVE DECLINE IN ALZHEIMER'S DISEASE DEMENTIA WITH CLINICALLY-UNSUSPECTED LEWY BODY DISEASE. Beach TG, Malek-Ahmadi M, Zamrini E, Sabbagh MN, Shill HA, Adler CH, Jacobson SA, Belden CM, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta S, Burke AD, Shprecher D, Spann B, Tariot PN, Davis KJ, Long KE, Nicholson LR, Intorcchia A, Glass M, Walker J, Callan M, Curry J, Cutler B, Oliver J, Arce R, Serrano GE, Sue LI, Reiman EM. Banner Sun Health Research Institute; Banner Alzheimer Institute; Barrow Neurological Institute; Mayo Clinic Arizona; University of Arizona; Arizona Alzheimer's Consortium.

Background: Clinical trials for Alzheimer's disease dementia (ADD) over the last two decades have so far failed to identify disease-modifying treatments. Although biomarkers are expected to improve clinical trial success rates, the ultimate proof of an effective agent remains a clinical improvement in cognition, and establishment of this be critically hampered by subject response variability. Neuropathology has demonstrated a high rate of comorbid pathology in ADD. The most common major comorbidity is Lewy body (LB) disease, either as dementia with Lewy bodies (DLB) or Alzheimer's disease with Lewy bodies (AD-LB), the latter representing subjects with LB pathology that does not meet distribution and density thresholds for DLB. Although together these represent 50% of those with AD, it is well recognized that only a fraction of those with concurrent DLB, and virtually none of those with ADLB, are clinically recognized during life and hence are likely to be included with "pure" AD subjects in clinical trials. Although it has been established that AD subjects with concurrent DLB have a more rapid cognitive decline than those with AD alone, it is still unknown whether ADLB subjects, who represent approximately one-third of all those with AD, have a different clinical course.

Methods: Subjects with pure AD (n = 137), AD-DLB (n = 64) and AD-LB (n = 114) were selected by a database search of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP) and National Alzheimer's Coordinating Center (NACC) data for the National Institute on Aging Arizona Alzheimer's Disease Core Center. Search criteria specified that subjects had two or more complete Mini Mental State Examinations (MMSE) and a full neuropathological examination after death.

Results: An unadjusted linear model of annualized MMSE change showed that both the AD-DLB and the AD-LB groups had significantly faster rates of decline relative to the pure AD group ($p = 0.04$, $p = 0.002$, respectively). This difference remained significant in a second model that included age and neuropathology interactions ($p = 0.02$, $p = 0.002$, respectively). In both models, the AD-DLB and the AD-LB groups had relatively similar rates of decline. Lewy body disease diagnosed at autopsy was often unrecognized during life. Of those with dementia and meeting neuropathological criteria for DLB, only 66% had been diagnosed with DLB during life.

Conclusions: Clinically undetected LBD significantly affects the rate of cognitive deterioration in ADD. The probable cause of clinical detection failure is the lack, for many DLB subjects and the great majority of AD-LB subjects, of a sufficient set of characteristic core clinical features. Compared with clinically-diagnosed DLB subjects, those that were clinically undetected had significantly lower prevalences of parkinsonism, visual hallucinations and dream enactment behavior. Clinical identification of ADD with LBD would allow stratified analyses of ADD clinical trials, potentially improving the probability of trial success.

Poster 7

UPDATE OF A REGULATORY-ENDORSED CLINICAL TRIAL SIMULATOR FOR ALZHEIMER DISEASE (AD): NEW DATA INCORPORATION, STATISTICAL MODIFICATIONS, AND USER-FRIENDLY GRAPHICAL USER INTERFACE DEVELOPMENT. Burton JK, Conrado DJ, Corrigan B, Nicholas T, Chen D, Stone J, Sinha V, Willis B, Wang W, Kern VD, Arnerić SP, Romero K. Critical Path Institute; Pfizer; Merck & Co.; Eli Lilly and Company; Novartis Pharmaceutical Corporation; Arizona Alzheimer's Consortium.

Background: A publicly-available clinical trial simulator (CTS) for mild-to-moderate AD using ADAScog11 as the endpoint was previously endorsed by the FDA and EMA based on the integrated patient-level control arm data within the CPAD database. Since the development of the original CTS, the number of individuals in the CPAD database has increased 40%, warranting a statistical update of the tool. Data for the number of APOE- ϵ 4 alleles and concomitant medication use are additionally available and were not accounted for in the previous CTS warranting their incorporation. To increase accessibility to the updated tool, the development of a user-friendly graphical user interface (GUI) is planned which will allow members of clinical development teams to easily conduct clinical trial simulations.

Methods: A logistic function was chosen to model disease progression, including placebo effects. Covariates of interest included baseline age, sex, number of APOE- ϵ 4 alleles and concomitant medication use. Placebo effects were accounted for by using a subset of the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset for individuals with mild-to-moderate AD to describe natural disease progression. To develop the GUI, the RShiny package, part of the R language, was chosen.

Results: Parameters of disease progression, placebo effects, and covariate effects were estimated using the Hamiltonian Monte Carlo algorithm within the Rstan package, part of the R language. Population estimates for baseline severity and initial rate of progression were 22.2 points and 5.29 points/year, respectively. Covariate estimates indicate heterozygous/ homozygous carriers of APOE- ϵ 4 progress at 5 % to 25 % faster than non-carriers, and concomitant medication use is associated with 63% faster progression than non-concomitant medication use. The magnitude of the placebo effect was 1.7 points with duration of approximately 3 months. In parallel with this analysis, a GUI is currently in strategic development using RShiny.

Conclusions: The updated tool provides additional data driven insights not considered by the original CTS 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

DISSOCIATION OF PERFORMANCE IN HIPPOCAMPUS- AND PREFRONTAL CORTICAL-DEPENDENT TASKS IN AGING FISHER 344 RATS. Carey NJ, Zempare MA, Nguyen CJ, Bohne KM, Chawla MK, Sinari S, Huentelman MJ, Billheimer D, Barnes CA. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: It is well established that cognition and cognitive performance declines with age-related diseases, but it also declines during normative aging. Even within normal aging, there is a spectrum of performance levels at any given chronological age, where people show differing levels of behavior within a specific age, as well as across ages. This spectrum of decline is also observed in animal models.

Methods: In this study, we use Fisher 344 (F344) rats of three different ages (young 6mo, middle-aged 15mo, and aged 23mo) in attempt to identify behavioral and molecular markers that reveal clues to successful cognitive aging. All animals are tested on a thorough cognitive assessment battery to identify their level of performance on multiple domains of behavior that rely on the functional integrity of different brain regions. The first tests are the spatial and cued versions of the Morris water maze, the former relying on the function of the hippocampus, the latter is a test of visual and motor competence. These tests are followed by a spontaneous object recognition task, which relies on the function of the perirhinal cortex. A delayed-match-to-place version of the Morris water maze is then given, to test working memory that is dependent on the prefrontal cortex. Additionally, hippocampus subregion functionality is then assessed using a spatial and temporal ordering task with differing levels of interference. We used the performance level on the spatial version of the Morris water maze task to categorize each animal into a cognitive performance level of low, average, or high, within the young, middle-aged and old age groups.

Results: When we used this categorization scheme to group performance on the working memory task, this grouping did not correspond to low, average, and high performance for working memory in the middle aged and older animals, but did correspond to low, average, and high performance for working memory in the young animals.

Conclusions: Taken together, these data suggest that beginning in middle-age, the relationship between spatial and working memory performance begins to change: different animals can exhibit a high hippocampal and low frontal cortex performance, low hippocampal and high frontal cortex performance, high performance in both, or low performance in both tasks. This is reminiscent of other data in rats (Bizon et al., 2009) and human studies (Glisky & Kong, 2008) where correlations between hippocampus- and prefrontal cortical-dependent performance is often only weakly related within individuals (Alexander et al., 2012). This suggests that more work is needed to elucidate intervention targets that will be effective for personalized optimization of cognitive aging.

Poster 9

RELATIONSHIPS BETWEEN MEAN CORTICAL AMYLOID BURDEN AND REGIONAL GRAY MATTER REDUCTIONS IN ALZHEIMER'S DEMENTIA, MILD COGNITIVE IMPAIRMENT AND UNIMPAIRED OLDER ADULTS. Chen K, Lee W, Jagust WJ, Weiner M, Reiman EM, the Alzheimer's Disease Neuroimaging Initiative. Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; University of California Berkeley; University of California San Francisco; Arizona Alzheimer's Consortium.

Background: In this study, we used voxel-based morphometry (VBM) to characterize relationships between florbetapir PET measurements of mean cortical amyloid- β ($A\beta$) burden and MRI measurements of regional gray matter volume in over a thousand persons from the AD Neuroimaging Initiative (ADNI), including those who met clinical criteria for dementia or mild cognitive impairment (MCI) due to AD and in cognitively unimpaired APOE4 carriers and non-carriers.

Methods: The VBM (CAT12) routine in SPM12 and a linear regression model were used to characterize relationships between mean cortical-to-cerebellar florbetapir standard uptake value ratios (SUVRs) and regional gray matter in 1,067 ADNI participants, including 188 participants with the clinical diagnosis of Alzheimer's dementia, 519 participants with the clinical diagnosis of MCI, 101 cognitively unimpaired APOE4 carriers, and 259 cognitively unimpaired APOE4 non-carriers. Amyloid positivity was assessed using mean-cortical SUVR and a threshold of 1.18 (Fleisher, et al., 2013). Relationships were characterized in the overall group and each of the four sub-groups after adjusting for age, intracranial volumes, and, for AD and MCI groups, also the presence or absence of the APOE4 allele ($P < 0.001$, uncorrected for multiple comparisons).

Results: Amyloid positivity was 81%, 47%, 39% and 18% for AD, MCI, CU APOE4 carrier and CU APOE4 non-carrier groups separately. In the overall, Alzheimer's dementia and MCI analyses, mean cortical florbetapir SUVRs were associated with less gray matter bilaterally in posterior cingulate, precuneus, and temporal, parietal, frontal, and occipital regions, consistent with prior findings in persons with AD dementia and MCI. In the cognitive unimpaired APOE4 carrier analysis, mean cortical florbetapir SUVRs were associated with less gray matter bilaterally in medial frontal regions.

Conclusions: Fibrillar $A\beta$ burden is associated with reduced gray matter in brain regions known to be preferentially affected by AD-and it is preferentially associated with reduced gray matter in frontal regions in cognitively unimpaired persons at risk for AD.

Poster 10

TWELVE-MONTH GLUCOSE METABOLISM DECLINES IN AN EMPIRICALLY PRE-DEFINED STATISTICAL REGION-OF-INTEREST IN AMYLOID-POSITIVE PERSONS WITH ALZHEIMER'S DEMENTIA AND MILD COGNITIVE IMPAIRMENT: UPDATED ADNI FINDINGS. Chen K, Lee W, Kuang X, Luo J, Devadas V, Thiyyagura P, Chen R, Bauer R, Weiner M, Jagust W, van Dyck C, Reiman EM. Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; University of California Berkeley; University of California San Francisco; Yale University; Arizona Alzheimer's Consortium.

Background: We previously used data from the ADNI to track AD-related cerebral metabolic rate for glucose (CMRgl) declines and evaluate disease-modifying treatments in persons with mild-to-moderate AD and MCI with improved power and freedom from the inflated Type I error associated with multiple comparisons in an empirically prespecified statistical region of interest (sROI) (Chen, NeuroImage 2010). We now extend our sROI approach to those mild-to-moderate AD dementia and MCI patients who are amyloid-positive ($A\beta^+$).

Methods: Baseline and 12-month follow-up FDG PET scans from 31 persons with mild-to-moderate AD dementia and 44 $A\beta^+$ persons with mild cognitive impairment (MCI), all with florbetapir SUVRs ≥ 1.18 (Fleisher, JAMA Neurol 2011), served as a training set to establish AD-dementia and MCI-related SROIs as previously described. Baseline and 12-month follow-up scans from 23 other persons with AD dementia and 40 other persons with MCI, all with florbetapir SUVRs ≥ 1.18 , served as a test to estimate the respective number of persons with AD dementia or MCI per group needed to detect a 25% treatment effect on sROI CMRgl declines in a 12-month placebo-controlled randomized clinical trial (RCT) with 80% power and two-tailed $P=0.05$.

Results: Using the relevant $A\beta^+$ sROI, we estimate the need for 126 $A\beta^+$ persons with mild-to-moderate AD dementia or 320 $A\beta^+$ persons with MCI per group to detect a 25% treatment effect on sROI CMRgl declines in a 12-month placebo-controlled RCT with 80% power and two-tailed $P=0.05$. Power estimates were similar to the number of persons with AD dementia or MCI we had estimated to detect treatment effects prior to the availability of $A\beta$ PET scans.

Conclusions: This study provides sROIs and 12-month sample size estimates for the evaluation of AD-modifying treatments in $A\beta^+$ persons with mild-to-moderate AD dementia or MCI.

Poster 11

THERAPEUTIC PROGESTIN NESTORONE PROMOTES NEUROGENESIS: IMPLICATIONS FOR SUSTAINING REGENERATION IN FEMALE BRAIN. Chen S, Kumar N, Mao Z, Wang T, Sitruk-Ware R, Brinton RD. University of Arizona; Rockefeller University; Arizona Alzheimer's Consortium.

Background: Neurogenesis is the principal regenerative mechanism to sustain the plasticity potential in adult brains. Decreased neurogenesis parallels cognition decline with aging, and it has been suggested as a common hallmark in the progression of many neurodegenerative diseases, such as Alzheimer's, Parkinson's and depression. We previously reported that acute exposure to Nestorone® (NES), a synthetic progestin, alone or in combination with 17 β -estradiol (E2), increased human neural stem cells proliferation and survival both in vitro and in vivo. However, impact of clinically relevant chronic exposure in combination with E2 on the regenerative capacity of adult brain remained unresolved. In the present study, we expanded our previous findings to investigate the impact of clinic related chronic contraception exposure on neurogenesis in adult female mice.

Methods: Adult female mice were infused with NES or combination with E2 for 4 weeks followed by flow cytometry analysis to quantitatively determine BrdU positive or BrdU and NeuN double positive cells in hippocampus and cortex. To confirm the effect, we conducted immunoblot and immunofluorescence analysis.

Results: NES and E2 alone or in combination infusion for 4-weeks induced a significant increase of neurogenesis by a comparable magnitude, with minimum to no antagonistic or additive effects between NES and E2. In addition, chronic exposure of NES or NES+E2 stimulated oligodendrocyte generation, indicating potential elevated myelination. Further analysis shown Insulin-like growth factor 1 (IGF-1) and IGF-1 receptor (IGF-1R) were also upregulated, suggesting the involvement of IGF-1 signaling as the potential regulatory pathway transducing NES effect.

Conclusions: Our preclinical translational analysis indicate no adverse consequence of chronic exposure to NES on neurogenic regenerative potential of the brain. Further, NES did not antagonize estrogen-induced neurogenesis. Importantly, when administered alone NES promoted neurogenesis whereas in combination with estrogen NES neither increased nor decreased neurogenesis suggesting controlled cellular proliferation. These findings provide preclinical evidence and mechanistic insights for the development of NES as a neuroregenerative therapy to promote intrinsic regenerative capacity in female brains against aging and neurodegenerative disorders.

Poster 12

CORTICAL EXCITABILITY IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS OF TRANSCRANIAL MAGNETIC STIMULATION STUDIES. Chou Y-H, Rapcsak S, Chen N-K, Sundman M, Lim K, Ugonna C, Lindley M, Fuglevand A, Mohler J, Huang Y-Z. University of Arizona; Chang Gung University; Arizona Alzheimer's Consortium.

Background: Transcranial magnetic stimulation (TMS) is a safe and painless brain stimulation technique that has been used to measure in vivo cortical excitability in diverse disease states including Alzheimer's disease (AD) and mild cognitive impairment (MCI). The utility of TMS measures in characterizing excitatory and inhibitory properties of neurotransmitter systems and the integrity of corticospinal pathway has been substantially supported by numerous pharmacological TMS studies. Recently, neuropathological studies have suggested early-stage motor cortex involvement in AD, despite a lack of motor dysfunction. Thus, motor cortical excitability measures be sensitive enough to detect dementia in the incipient stage of disease. The purpose of this meta-analysis is to quantify alterations in cortical excitability associated with Alzheimer's disease and mild cognitive impairment.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods were utilized. Databases were searched using combinations of the following terms: (transcranial magnetic stimulation, theta burst stimulation, or TMS), and (Alzheimer's disease or mild cognitive impairment) and (cortical excitability).

Results: Ten studies (N = 418) were included in the meta-analysis. Patients with AD exhibited significantly (1) lower resting motor threshold (RMT), effect size $d = 1.61$, $z = 4$, $p < .0001$, (2) lower active motor threshold (AMT), effect size $d = 0.74$, $z = 1.98$, $p < .05$, (3) reduced short-latency afferent inhibition (SAI), $d = 1.14$, $z = 4.04$, $p < .0001$, and (4) reduced short-interval intracortical inhibition (SICI), $d = 6.91$, $z = 11.16$, $p < .0001$, compared to healthy controls. Patients with MCI also showed significantly lower RMT relative to healthy controls, $d = 0.63$, $z = 3.13$, $p < .002$. No significant group differences were observed in cortical silent period and central motor conduction time.

Conclusions: The pooled evidence suggests the existence of cortical hyper-excitability as documented by the reduced RMT and AMT in AD and MCI, as well as reduced inhibition as measured by the SAI and SICI in AD. First, hyper-excitability is associated with severity of dementia. For example, Sakura et al. (2007) reported that AD patients exhibited the lowest RMT, followed by the MCI, and then the healthy controls. Khedr et al. (2011) divided AD patients into mild, moderate and severe groups and found that dementia severity was significantly correlated with the reduction of RMT and AMT. Second, the level of SAI reflects the integrity of central acetylcholinergic pathways. The acetylcholine (ACh) is a neurotransmitter essential for processing memory and learning. Consistent with the cholinergic hypothesis, our meta-analysis also supports a reduction in levels of ACh in AD. Previous studies have shown that the reduced SAI in AD could be normalized by AChE inhibitors. Finally, intracortical inhibition as measured by SICI is decreased in AD and the reduced inhibition is related to cognitive deterioration. Future studies will be needed to examine whether these cortical excitability measures are reliable and accurate biomarkers that can be used to differentiate prodromal dementia from normal healthy aging prior to the disease progressing to a more clinically evident phase.

Poster 13

AN iPSC-BASED PLATFORM FOR INVESTIGATING IDIOPATHIC PARKINSON'S DISEASE. Corenblum MJ, Annadurai A, Shrestha K, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Human induced pluripotent stem cells (iPSCs) are proving to be a valuable source of patient cells for generating neural phenotypes relevant to Parkinson's disease. Here we characterize iPSCs, as well as iPSC-derived midbrain dopamine (DA) neurons derived from the skin fibroblasts of late-onset idiopathic Parkinson's disease (PD) subjects.

Methods: Specifically, we comparatively analyzed the survival, differentiation, morphology, and alpha-synuclein protein expression, in cells obtained from idiopathic PD and age-matched control (AMC) subjects.

Results: Our data indicate that the iPSCs from PD subjects had lower viability rates, and a reduced capacity to generate neurons when induced to differentiate via a floorplate dual SMAD inhibition method. At day 42 post-differentiation, although the efficiency of tyrosine hydroxylase positive (TH+) DA neuron generation did not differ between the PD and AMC DA cultures, the efficiency of production of GIRK2+ TH neurons (A9 DA neurons) was lower in the PD cultures. Furthermore, the morphology of DA neurons in the PD cultures appeared altered in that the cells displayed a smaller soma size, reduced number of neurites, lower neurite arborization, and shorter neurite lengths, compared to DA neurons in AMC cultures. In addition, it was found that the expression of the PD relevant protein, alpha-synuclein, was higher in the DA neurons obtained from PD subjects than AMC cells.

Conclusions: Our current studies are further extending these findings by examining the redox, mitochondrial, and electrophysiological profiles of the iPSC-derived PD and AMC DA neurons. In conclusion, our study develops an iPSC-based model that captures a phenotype relevant to the study of idiopathic PD, as well as biomarker and therapeutic testing.

Poster 14

MULTIVARIATE ANALYSES OF PERIPHERAL BLOOD LEUKOCYTE TRANSCRIPTS DISTINGUISH ALZHEIMER'S, PARKINSON'S, CONTROL AND THOSE AT RISK FOR DEVELOPING ALZHEIMER'S. Delvaux E, Mastroeni D, Nolz J, Chow N, Sabbagh M, Caselli RJ, Reiman EM, Marshall FJ, Coleman PD. Arizona State University; Banner Sun Health Research Institute; University of Rochester Medical Center; Barrow Neurological Institute; Mayo Clinic, Scottsdale; Arizona Alzheimer's Consortium.

Background: The need for a reliable, simple and inexpensive blood test for Alzheimer's disease (AD) suitable for use in a primary care setting is widely recognized. This has led to a large number of publications describing blood tests for AD, which have, for the most part, not been replicable.

Methods: We have chosen to examine transcripts expressed by the cellular, leukocyte compartment of blood. We have used hypothesis-based cDNA arrays and quantitative PCR to quantify expression of selected sets of genes followed by multivariate analyses in multiple independent samples. Rather than one study with no replicates we chose an experimental design in which there were multiple replicates using different platforms and different sample populations.

Results: We have divided 177 blood and 27 brain samples into multiple replicates to demonstrate the ability to distinguish early clinical AD (CDR 0.5), Parkinson's disease (PD), and cognitively unimpaired APOE4 homozygotes, as well as to determine persons at risk for future cognitive impairment with significant accuracy. We assess our methods in a training/test set and also show that the variables we use distinguish AD, PD and control brain. Importantly, we describe variability of the weights assigned to individual transcripts in multivariate analyses in repeated studies and suggest that the variability we describe be the cause of inability to repeat many prior studies.

Conclusions: Our data constitute a proof of principle that multivariate analysis of the transcriptome related to cell stress and inflammation of peripheral blood leukocytes has significant potential as a minimally invasive and inexpensive diagnostic tool for diagnosis and early detection of risk for AD.

Poster 15

STRATEGIC MEMORY ALZHEIMERS REHABILITATION TRAINING (SMART) MEMORY PROGRAM FOR AMNESTIC MILD COGNITIVE IMPAIRMENT (AMCI): REPORTING THE RESULTS OF A RANDOMIZED CLINICAL TRIAL. DenBoer, JW.
SMART Brain Aging, Inc.

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 16

ASSESSMENT OF DUAL-TASK MOTOR FUNCTION DETERIORATION FOR DETECTING COGNITIVE IMPAIRMENT. Fakhoury S, Gaytan-Jenkins D, Lopez A, Ehsani H, O'Connor K, Zamrini E, Mohler J, Toosizadeh N. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Simultaneous assessment of motor and cognitive "dual tasks" has been demonstrated as a promising method to identify the cognitive status of older adults. Our objective was to develop a novel dual-task cognitive function test incorporating a validated gait equivalent upper-extremity function (UEF) test simultaneously performed with counting backwards as a cognitive challenge.

Methods: Older adults (≤ 65 years) were recruited and stratified into three clinically confirmed groups: 1) cognitively healthy (CN), 2) mild cognitive impairment (MCI), and 3) early Alzheimer's disease (AD). Elbow angular velocity was measured using three-dimensional gyroscopes attached to the wrist and upper-arm. Participants completed six trials of single-task and dual-task UEF at two elbow flexion speeds (rapid and self-paced) and three cognitive counting tasks (no counting, backwards by ones, and backwards by threes). The outcome of interest was motor function performance (coefficient of variation between flexion time intervals to assess pauses/delays in motor task execution) per condition. Between group comparisons were made using ANCOVA models while controlling for age, sex, and body mass index. Subsequently, the UEF condition with the highest effect size was used in an ordinal logistic model for group discrimination.

Results: Thirty participants were recruited (10 CN: age= 86.3 ± 2.9 , 10 MCI: age= 87.2 ± 3.0 , and 10 AD: age= 86.5 ± 5.3). ANCOVA models showed significant associations between cognition groups and elbow flexion variability in all four dual-task conditions.

Conclusions: Accurate, objective, and rapid cognition screening strategies are needed for use in research and clinical settings. The reported method has high screening potential and could be likewise used to measure change over time. Our preliminary findings should be further explored in a larger study.

Poster 17

LONGITUDINAL DEPRESSIVE SYMPTOMS AND CORTICAL AMYLOID ARE ASSOCIATED WITH COGNITIVE DECLINE IN OLDER ADULTS. Gatchel JR, Rabin JS, Buckley RF, Locascio JJ, Quiroz YT, Vannini P, Amariglio RE, Rentz DM, Johnson KA, Blacker D, Donovan NJ, Sperling RA, Marshall GA. Harvard Medical School; Arizona Alzheimer's Consortium.

Background: Increasing evidence suggests that depressive symptoms in preclinical Alzheimer's Disease (AD) are associated with AD pathology, but it remains unclear how depressive symptoms together with amyloid relate to longitudinal cognitive decline. The current study was designed to determine how baseline and longitudinal depressive symptoms, in the setting of amyloid, relate to performance over time on a cognitive composite sensitive to detect decline in preclinical AD.

Methods: 276 older adults from the Harvard Aging Brain Study underwent annual assessment with the Geriatric Depression Scale (GDS) and the preclinical Alzheimer's Disease Cognitive Composite (PACC), as well as baseline amyloid (Pittsburgh Compound B) PET imaging. All were cognitively normal and non-depressed (or had at most mild depression) at baseline, with average 4.42 years of follow-up. A mixed model with backward elimination was used with dependent variable PACC, a random intercept and slope for each subject, and fixed predictors: baseline GDS and amyloid, baseline GDS X amyloid interaction, time (years in study), the interaction of predictors with time, and covariates sex, baseline age, and education. To determine the relationship between time-varying GDS, PACC, and baseline amyloid, GDS and PACC slopes were extracted, then entered into a linear model with dependent variable PACC-slope, and predictors: GDS-slope, amyloid, GDS-slope X amyloid, and the covariates above.

Results: In the model with baseline GDS, sex ($p=0.0005$; females with higher scores), higher age ($p<0.0001$), lower education ($p<0.0001$), and amyloid X time ($p=0.0088$; greater amyloid associated with greater PACC decline) were significant, but baseline GDS did not predict PACC decline. In the model with GDS-slope, higher age ($p<0.0001$), lower education ($p=0.03$) and GDS-slope X amyloid ($p=0.0002$) significantly predicted PACC decline, such that increasing GDS scores with baseline amyloid were associated with greater PACC decline. In secondary analyses holding time and all other predictors constant, longitudinally increasing GDS predicted decreasing PACC in those with amyloid levels above 1.10.

Conclusions: Results suggest that worsening depressive symptoms in the setting of elevated amyloid are associated with cognitive decline. While future work is needed to determine causality, findings support the potential prognostic utility of depressive symptoms in identifying older adults at risk for cognitive decline and AD.

Poster 18

THE SAFE AND EFFECTIVE APPLICATIONS OF ESSENTIAL OILS IN ALZHEIMER'S DEMENTIA. Geiger, JL. Banner Health; Arizona Alzheimer's Consortium.

Background: Alzheimer's dementia (AD) is characterized by impairment of memory and progressive neuro-degeneration resulting in profound cognitive dysfunction. The social, clinical and financial implications of AD are remarkable in view of the fact that the prevalence of AD is expected to double every five years. Dementia can be of mixed pathology, yet AD prevalence is about 60%, followed by vascular dementia (VD) 20% and dementia with Lewy bodies 10% (DLB). There are fronto-temporal dementias (FTD) and other sub-types perhaps related to stroke, decreased cerebral blood flow, concussion, traumatic brain injury or congestive heart failure. No prior mention has been made regarding the possible applications of the anticholinesterase inhibitions properties of essential oils from plants as treatment for AD.

Methods: The diagnosis and treatment of Alzheimer's dementia (AD) has gained much attention due to the current and predicted prevalence of the disease. A review of the biomarkers of neural inflammation, oxidative stress, epigenetics and the multiple medical etiologies of AD coupled with the poly-pharmacy of comorbid conditions and diseases associated with AD is complex. The medical diagnosis and treatments of AD need more reliability and integrative health regimens, such as supplementation with generally regarded as safe (GRAS) essential oils that could be implemented clinically to lessen the global economic impact to societies, and disruptions to families.

Results: The mainstay of initial treatment of memory loss is with anticholinesterase inhibitors (ACHEI) and can be coupled with non-pharmaceutical integrative health regimens such as music therapy, bright light therapy, ultrasound, massage and aromatherapy with generally regarded as safe essential oils (GRAS). The progressive nature of AD can lead to behavioral and psychological symptoms of dementia (BPSD) including neuroses such as agitation, anxiety, panic attacks, aggression, depression and psychoses requiring neuroleptic prescriptions. Treatment has focused on the management of AD based on the cholinergic theory attempting to prevent cognitive decline while preserving short-term memory with prescription medications. Certain essential oils exhibiting acetylcholinesterase inhibition (ACHEI) activity derived from natural phyto-preparations might also be utilized in the setting of the decreasing memory of AD. Prescription psychotropic medications might be therapeutically interchanged to certain essential oils to manage behavioral and psychiatric issues associated with AD. Advancing age and anesthesia increase the risk of post-operative cognitive decline (POCD) associated with common procedures and surgeries that AD patients commonly undergo. Globally, plant material preparations such as extracts and essential oils are analyzed for anti-inflammatory, anti-infectious and anti-anxiety, anti-depressive, analgesic and ACHEI activity.

Conclusions: The potential for use of GRAS essential oils as supplements for seniors in the prevention and treatment of the cognitive decline and behavioral disruptions of aging should be studied to determine the safe and effective methods of inhalational, topical and ingestion aromatherapy techniques. The landmark literature reviewed here explores the mechanisms and synergy of the aromatic sciences that can provide the basis for designing and implementing protocols for the integration of GRAS essential oils into the wide variety of clinical situations encountered in the aging population, with and without AD.

Poster 19

THE ROLE OF NICOTINIC ACETYLCHOLINE RECEPTOR (NACHRS) IN MEDIATING AMYLOID BETA-INDUCED ALTERATIONS IN BASAL FOREBRAIN CHOLINERGIC INTRINSIC EXCITABILITY. 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 AD with a loss of basal forebrain cholinergic neurons (BFCNs). Mechanisms underlying cholinergic neurodegeneration and subsequent memory impairments remain unknown. However, interactions between amyloid- β ($A\beta$), a suspected etiopathogenic agent in AD, with a nicotinic acetylcholine receptor subtype containing $\alpha 7$ subunits ($\alpha 7^*$ -nAChR) trigger hippocampal pyramidal neuronal homeostatic instability. Recently, a nAChR subtype containing $\alpha 7$ and $\beta 2$ subunits has been identified on BFCNs. These heteromeric $\alpha 7\beta 2$ -nAChRs have different pharmacological properties from those of homomeric $\alpha 7$ -nAChRs and are highly sensitive to functional modulation by $A\beta$ within the hippocampus.

Methods: To elucidate the precise interaction between $\alpha 7$ -containing nAChRs and $A\beta$, we used single-channel electrophysiology to investigate the functional interaction between $A\beta$ and $\alpha 7$ and $\alpha 7\beta 2$ -containing nAChRs. Toward understanding the roles played by $\alpha 7\beta 2$ -nAChRs in BFCN function, we used organotypic basal forebrain slice cultures and whole-cell patch clamp electrophysiology to investigate $A\beta$ -induced alterations in BFCN intrinsic excitability in the context of nAChR functional expression. Whole-cell current clamp recordings were taken from cholinergic neurons within the medial septal-diagonal band (MSDB), the horizontal diagonal band (HDB), and the nucleus basalis (NB).

Results: We demonstrate that oligomeric $A\beta 1-42$ activates both $\alpha 7$ and $\alpha 7\beta 2$ nAChRs and enhances $\alpha 7\beta 2$ nAChR single-channel open-dwell times when heterologously expressed in a mammalian cell line (mean change: 0.4 ± 0.08 ms to 3.2 ± 0.5 ms). Single-channel activation of both nAChR subtypes can be inhibited with the known $\alpha 7$ antagonists mecamylamine and methyllycaconitine. Furthermore, we demonstrate that chronic incubation (9 days) with oligomeric or fibrillar forms of $A\beta 1-42$ increases MSDB and HDB cholinergic action potential firing rates (mean increase of $64 \pm 8\%$ and $25 \pm 3.5\%$, respectively). Additionally, the magnitude of the medium after hyperpolarization (mAHP) phase following spike generation (mean reduction of $44 \pm 6.5\%$ and $15 \pm 2.5\%$, respectively) was lower when compared to control conditions (scrambled version of $A\beta 1-42$). No significant changes in action potential firing rates or mAHP magnitudes were observed in cholinergic neurons within the NB following chronic $A\beta$ administration. Using nAChR $\beta 2$ subunit knockout mice, we demonstrate normalization of $A\beta$ -induced alterations in firing rate and mAHP of BFCNs within the MSDB.

Conclusions: These preliminary findings suggest that specific forms of $A\beta 1-42$ alter cholinergic intrinsic excitability by interacting with $\beta 2$ -containing nAChR subtypes. These interactions be uniquely 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.

Poster 20

IMPROVED DIAGNOSIS OF PARKINSON'S DISEASE FROM A DETAILED OLFACTORY PHENOTYPE. Gerkin RG, Adler CH, Hentz JG, Shill HA, Driver-Dunkley E, Mehta SH, Sabbagh MN, Caviness JN, Dugger BN, Serrano G, Belden C, Smith BH, Sue L, Davis KJ, Zamrini E, Beach TG. Arizona State University; Mayo Clinic College of Medicine; Barrow Neurological Institute; Banner Sun Health Research Institute; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: Olfactory decline is a hallmark of both normal aging and of neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). In PD in particular, olfactory dysfunction precede the motor symptoms of the disease by up to seven years. Indeed, during the earliest, pre-motor stages of PD, there is associated pathology in olfactory-related areas. Previous studies have shown that clinically-diagnosed PD is associated with olfactory dysfunction, most using the now common University of Pennsylvania Smell Identification Test (UPSIT) multiple choice test. However, the only information typically retained from an UPSIT test – the total score – might be a crude measure for guiding diagnosis; while the mean total score of the PD subpopulation is lower than in healthy subjects, the sensitivity and specificity of the total score in distinguishing PD from non-PD-related olfactory deficits not be high enough, or early enough in disease progression, to be clinically valuable. But what if the pattern of olfactory decline due to PD differs from that due to other age-related pathologies or to normal aging?

Methods: We analyzed a large dataset from the Arizona Study of Aging and Neurodegenerative Disorders, a longitudinal clinicopathological study of health and disease in elderly volunteers. Using the complete pattern of responses to all 40 items in each subject's UPSIT test, we built predictive models of neurodegenerative disease, and we validated these models out-of-sample by comparing model predictions against post-mortem pathological diagnosis.

Results: Consistent with anatomical considerations, we found that the specific test response pattern had additional predictive power compared with a conventional measure--total test score--in Parkinson's disease but not Alzheimer's disease. We also identified specific test questions that carry the greatest predictive power for disease diagnosis.

Conclusions: Olfactory ability has typically been assessed with either self-report or total score on a multiple choice test. We showed that a more accurate clinical diagnosis can be made using the pattern of responses to all the test questions and validated this against the "gold standard" of pathological diagnosis. Information in the response pattern also suggests specific modifications to the standard test that optimize predictive power under the typical clinical constraint of limited time. We recommend that future studies retain the individual item responses for each subject, and not just the total score, both to enable more accurate diagnosis and to enable additional future insights.

Poster 21

COMPARING CEREBRAL WHITE MATTER, CEREBELLAR, AND PONTINE REFERENCE REGIONS TO CHARACTERIZE FLORBETAPIR PET MEASUREMENTS OF FIBRILLAR AMYLOID-B BURDEN IN PSEN1 E280A MUTATION CARRIERS AND NONCARRIERS FROM THE COLOMBIAN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE KINDRED. Ghisays V, Protas H, Yinghua C, DeMarco E, Tariot PN, Langbaum JB, Quiroz YT, Lopera F, Reiman EM, Chen K. Banner Alzheimer's Institute; University of Arizona, Tucson; Translational Genomics Research Institute; Arizona State University; Universidad de Antioquia; Massachusetts General Hospital, Harvard Medical School; Arizona Alzheimer's Consortium.

Background: We previously demonstrated that a cerebral white matter reference region could improve the ability of longitudinal florbetapir standard uptake value (SUV) ratios (SUVR) to track changes in amyloid- β ($A\beta$) levels (Chen et al., 2015). Here we sought to compare white matter to two candidate reference regions to test the ability to detect $A\beta$ elevations and associations with age and memory decline with cross-sectional florbetapir SUVRs in Presenilin (PSEN1) E280A mutation carriers from the Colombian Autosomal Dominant Alzheimer's Disease (ADAD) kindred.

Methods: Cerebral white matter (corpus callosum[CC], centrum semi-ovale[CSO], and combined[WM]), cerebellar, and pontine reference regions were used to compute cerebral-to-reference region SUVRs using florbetapir PET scans acquired as reported (Fleisher et al., 2012). Nineteen cognitively unimpaired mutation carriers (mean age=32), 11 impaired mutation carriers (mean age=47), and 20 age-matched non-carriers of the PSEN1 mutation were included in the analyses. We compared the ability of different reference regions to detect elevated SUVRs and characterize associations with age and memory performance in the carrier group. Finally, since deceased mutation carriers with cognitive impairment are known to have neuropathological evidence of $A\beta$ burden in the cerebellum, we compared reference region SUVs between our three groups.

Results: There were significant between-group SUVR differences (impaired carriers>unimpaired carriers>non-carriers) using each of the five reference regions. All reference regions similarly detected elevated levels of $A\beta$ and showed significant associations of SUVRs with age and worse memory performance in mutation carriers. However, associations with memory performance were stronger when using CC ($p=0.02$), CSO ($p=.002$), and WM reference regions ($p=.06$) compared to pontine. In comparison with impaired mutation carriers and non-carriers, SUVs were significantly greater in impaired mutation carriers in the cerebellar region, but not in white matter or pontine regions.

Conclusions: Use of a white matter reference region increase the ability to characterize cross-sectional florbetapir PET measurements of $A\beta$ burden in ADAD mutation carriers, aid in identifying individuals at preclinical stages, and better inform future clinical trials. While our previously used pontine reference region might be an acceptable alternative, a cerebellar reference region be confounded by $A\beta$ burden in the clinical stages of ADAD.

Poster 22

THE ALZHEIMER'S PREVENTION REGISTRY'S GENEMATCH PROGRAM: UPDATE ON PROGRESS AND LESSONS LEARNED IN HELPING TO ACCELERATE ENROLLMENT INTO ALZHEIMER'S PREVENTION STUDIES. Gordon D, Graf H, Walsh T, High N, Nichols J, Reiman EM, Tariot PM, Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Institute.

Background: Background: Considerable effort has been focused on creating programs to accelerate enrollment into Alzheimer's disease (AD) studies, with a need for efficient strategies to recruit participants for prevention trials. The Alzheimer's Prevention Initiative (API) is a collaborative program conducting preclinical AD trials in people who are at elevated risk of developing AD symptoms. In 2015, we launched GeneMatch to support and accelerate recruitment into API trials as well as other studies, by matching people to studies based in part on their APOE genotype.

Methods: Methods: GeneMatch is a US-based, trial-independent program performing APOE testing in cognitively unimpaired individuals ages 55-75 to enrich referrals to prevention studies. Buccal swabs are mailed to participants or distributed at study sites after enrollment. GeneMatch does not disclose APOE results to participants directly or inadvertently through invitations to studies. However, disclosure occur in the context of enrollment into a study that requires persons to know their genotype. Participants receive emails for engagement/retention purposes and are notified when they are matched to a study. When matched, participants are asked to opt into sharing their contact information with a study site of their choice. Participants are presented a list of enrolling sites in order of proximity to their home address from which to select. In addition, participants are notified by email when a new study site is added in their state, allowing them the opportunity to select a site if they had not already done so. The ability for GeneMatch to send referrals relies on consistent enrollment into the program. A variety of recruitment tactics are used, including community talks, earned media, and online advertising targeting potential participants based on their proximity to an API Generation Program study site.

Results: Results: As of February 2018, ~55,000 have joined GeneMatch; 70% returned their swab within 90 days, with return rate varying by enrollment source. 23 institutions are study sites. Online advertising has been the most successful enrollment tactic. Approximately 3% are APOE4 homozygotes, 30% heterozygotes. In July 2016, GeneMatch began inviting participants to API Generation Study 1; in November 2017 this expanded to include API Generation Study 2; together the trials are referred to as the "API Generation Program." To date, 2,077 have been invited to participate in the API Generation Program. 41% have their invitation. Proximity to a study site is a significant factor to participants accepting their invitation. 51% of participants who live < 50 miles from a study site accepted their invitation. In contrast, 38% of participants who live between 50-100 miles from a study site accepted their invitation, and 31% of participants who live > 100 miles from a study site accepted their invitation. Thus far, GeneMatch has been the most successful recruitment mechanism for the API Generation Program in the US.

Conclusions: Conclusion: GeneMatch is a key component of the API, facilitating enrollment into the API Generation Program. GeneMatch will begin recruiting for other studies in 2018 and we anticipate expanding the enrollment age range to accommodate new studies. New approaches are being explored to increase enrollment and engagement of enrollees.

Poster 23

MEASURING PRE-CLINICAL COGNITIVE AND FUNCTIONAL DECLINE OVER TIME: SEPARATING AND COMBINING ALZHEIMER'S SPECIFIC DECLINE AND COGNITIVE AND FUNCTIONAL DECLINE RELATED TO AGING IN COGNITIVE COMPOSITE SCORES. Hendrix S, Ellison N, Langbaum JB, Chen K, Bennett DA. Pentara Corporation; Banner Alzheimer's Institute; University of Arizona; Rush University; Arizona Alzheimer's Consortium.

Background: Measuring progression in pre-clinical Alzheimer's disease presents unique challenges due to ceiling effects, subject heterogeneity, and within patient variability. Cognitive aging effects are particularly relevant in this stage since disease-related changes are of the same magnitude as cognitive aging effects. In addition, some clinical trial interventions be hypothesized to affect only disease related changes, only cognitive aging, or both, requiring different approaches for each of these measurement goals. The Alzheimer's Prevention Cognitive Composite (APCC) was empirically derived to measure very early AD related change by maximizing the signal to noise ratio of the change over time in those later diagnosed with AD corrected for cognitive aging.

Methods: A principal components analysis (PCA) was graphed on all Neuropsychological Test Battery (NTB) items, with and without Activities of Daily Living (ADLs) (Lawton Brody scale), using data from older participants in 3 cohorts from the Rush AD Center who started out with normal cognition. The analysis was performed for both absolute and change from baseline scores at year 4. Baseline age was also included as an outcome. Means were compared between genders and future MCI and AD patients and those who remained normal.

Results: The most prominent graphical feature of the absolute scores including cognition and ADLs at each visit was the gender difference on ADL scores with females worsening more on PCA factor 2, ADLs, especially cleaning and walking, than males. This was more related to aging than disease and involved less than 10% of females. Factor 1 included NTB items including APCC, and factor 3 had MMSE items. The figure showing changes at 4 years in cognition and ADLs had one factor of MMSE items, one of NTB items and one functional items. Females tended to decline more on NTB items and males tended to decline on MMSE items, with both groups declining on function with AD diagnosis.

Conclusions: A graphical display of factor loadings clearly separates ADLs and cognitive items, and shows age, gender and diagnosis group differences associated with each factor. Complex relationships between subgroups across multiple related outcome measures are easier to understand graphically.

Poster 24

PHARMACOKINETICS AND SAFETY PROFILE OF INTRAVENOUS ADMINISTRATION OF ALLOPREGNANOLONE IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE. Hernandez GD, Lopez CM, Desai M, Kono N, Irwin R, Rodgers KE, Mack WJ, Schneider LS, Brinton RD. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: To date, no interventions have demonstrated substantial therapeutic efficacy to prevent, delay or treat Alzheimer's disease (AD). The neurosteroid Allopregnanolone (Allo) is a novel therapeutic approach to reducing the burden of AD pathology by targeting the regenerative system of the brain. In this phase 1 trial we assess the safety, tolerability and pharmacokinetics of intravenous administration of Allo.

Methods: A randomized double-blind, placebo-controlled, multiple ascending dose, phase 1 clinical trial was conducted in patients with mild cognitive impairment due to AD or mild AD. Men and women age ≤ 55 years, with a MMSE score ≤ 20 and clinical dementia rating of 0.5-1 were recruited to the study. Participants were randomly assigned to receive weekly intravenous treatment of 2, 4 and 6mg of Allo or placebo. Primary outcome was to assess safety, tolerability and maximally tolerated dose (MTD) of Allo at the three doses administered intravenously once per week over 12 weeks. In addition we sought to establish the maximally tolerate dose (MTD) of Allo in a subset of the study population at doses > 6 mg.

Results: A total of 24 patients were enrolled into the trial and participated in the pharmacokinetic assessment. Blood was collected at 15, 30, 45 minutes, and 1, 2, 4, 6 and 24 hours post the 30-minute infusion. Mean T_{max} was 30 minutes across all cohorts. Mean C_{max} at 2, 4 and 6mg was 14.5 ± 7.3 ng/ml, 42.1 ± 14.6 ng/ml and 60.1 ± 12.8 ng/ml, respectively. The C_{max} closely correlated (R=0.77) with Allo delivered in mg/kg dose. Mean area under the curve (AUC) total exposure also showed a near linear dose dependent response. MTD was established by onset of sedation at doses ≤ 10 mg, and a gender difference in the dose inducing sedation was observed (males 10mg; females 14mg). Twelve-week exposure to multiple doses of Allo once per week resulted in no reportable adverse effects, serious adverse events or ARIA.

Conclusions: Allopregnanolone administered intravenously once a week was well tolerated, appeared without adverse effects, and exhibited a favorable pharmacokinetic profile in our study population.

Poster 25

PHARMACOKINETICS AND SAFETY PROFILE OF SINGLE-DOSE ADMINISTRATION OF AN ESTROGEN RECEPTOR β -SELECTIVE PHYTOESTROGENIC (PHYTOSERM) FORMULATION IN WOMEN WITH COGNITIVE DEFICITS AND MENOPAUSAL SYMPTOMS. Hernandez GD, Zhao L, Chen YL, Franke A, Mack WJ, Schneider LS, Brinton RD. University of Arizona; University of Kansas; University of Southern California; University of Hawaii; Arizona Alzheimer's Consortium.

Background: Women account for 68% of all cases of Alzheimer's disease (AD). Estrogen and hormone replacement therapies (HRT) begun at the time of menopause transition have been associated with reduced risk and delayed onset of AD. However, adverse outcomes of HRT have led to increasing number of women declining its use but seeking non-pharmaceutical alternatives. The search for a safe approach to promote estrogenic signaling in the brain, without eliciting adverse effects, has focused on the development of tissue-selective estrogen receptor modulators (SERMs). Selective estrogen receptor- β (ER- β) targeting has been attempted in the development of therapies for a range of conditions including cognitive impairment and menopausal symptoms. PhytoSERM, a preparation of genistein, daidzein, and S-equol, has an 83-fold selective affinity for (ER- β) and promote neuronal survival and estrogenic mechanisms in the brain without having feminizing activity in the periphery. The objective of this study was to assess the safety, tolerability and single-dose pharmacokinetics of the phytoSERM formulation in peri- and postmenopausal women.

Methods: Eighteen women aged 45-60 years from a 12-week clinical trial evaluating cognitive performance and vasomotor symptoms were randomly assigned to placebo, 50 mg, or 100 mg phytoSERM treatment groups. Plasma levels of the 3 parent phytoestrogens and their metabolites were measured before and at 2, 4, 6, 8 and 24 hours after ingestion by isotope dilution HPLC electrospray ionization tandem mass spectrometry.

Results: Plasma concentrations of genistein, daidzein and S-equol peaked at 9, 6 and 4 h, respectively for the 50mg dose, and at 6, 6 and 5 h, respectively for the 100 mg dose. The maximum concentration (C_{max}) and area under the curve (AUC) for the 3 parent compounds were greater in the 100 mg dose group indicating a dose-dependent change in concentration with the phytoSERM treatment. No adverse events were elicited.

Conclusions: The phytoSERM combination was well tolerated, appeared without adverse effects, and exhibited a favorable pharmacokinetic profile. After single oral administration of 50 and 100mg tablets of the phytoSERM formulation, the phytoestrogens genistein, daidzein and S-equol were rapidly absorbed, reached high plasma concentrations, and showed a dose proportional increase in concentration exposures in its pharmacokinetics. The formulation prove to be advantageous for several peri- and post-menopausal conditions.

Poster 26

EVALUATION OF CARDIOVASCULAR STRUCTURE AND FUNCTION IN YOUNG AND AGED FEMALE APOE3 AND APOE4 MICE. Hoxha B, Jones C, Vallejo-Elias J, Powell J, Virden T, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common form of dementia in the United States with age and sex being the biggest risk factors. In addition, individuals with cardiovascular disease (CVD) have an increased risk for development of AD. A link between AD and CVD is apolipoprotein E (APOE), a protein that primarily functions to traffic lipids in the body and brain. Individuals with a particular allele of APOE, APOE4, are at increased risk for developing both CVD and AD/dementia. To study the mechanisms of APOE4-mediated pathogenesis, mouse models were developed that express the normal human APOE3 (hAPOE3) or APOE4 (hAPOE4) in place of the murine APOE. To the best of our knowledge there have been no studies assessing the relationship between carotid artery (CA) function, thoracic aorta (TA) function, and cardiac (C) function in these mice. We hypothesize that female mice expressing hAPOE4 will exhibit augmented age-related decline in C, TA and CA function than aged matched hAPOE3 mice.

Methods: In vivo investigation of C, TA and CA structure/function was assessed in young (4 \pm 1 months) and aged (18 \pm 2 months) female hAPOE3 and hAPOE4 mice using high-resolution ultrasound (U/S). In addition, blood pressure (BP) was determined using the tail-cuff method. All U/S and BP values were collected under isoflurane anesthesia. Results were considered significant at $p < 0.05$.

Results: hAPOE3 mice exhibited an age-related increase in bodyweight ($p < 0.05$) and hAPOE3 mice weighed significantly more than hAPOE4 mice at 18-20 months ($p < 0.05$). There was no age-associated increase in bodyweight in the hAPOE4 mice. CA structure and function was assessed by wall thickness (WT) and pulse wave velocity (PWV) respectively. Both hAPOE3 and hAPOE4 mice displayed an age-related increase in WT ($p < 0.05$). CA PWV was significantly greater in aged hAPOE4 vs young APOE4 mice ($p < 0.05$), however there was no age-related CA PWV increase in hAPOE3 mice. Both hAPOE3 and hAPOE4 mice exhibited an age-related increase in TA PWV ($P < 0.05$), but measurements of aortic structures: aortic annulus, sinus of valsalva, and sinotubular junction, showed no significant age-related changes. Cardiac output (CO) and stroke volume (SV) was higher in young- and aged- hAPOE3 mice compared to age matched hAPOE4 mice (CO: $p < 0.05$ and SV: $p < 0.05$). All other cardiac indices (e.g., stroke volume, ejection fraction, E/A ratio, etc.) were similar between groups. Finally, the systolic and diastolic BP values showed no significant difference between groups.

Conclusions: These preliminary data suggest that female hAPOE3 and APOE4 mice exhibit age-related changes in C, TA and CA structure and function. Additional studies will be needed to determine whether hAPOE mice exhibit structural and/or functional changes similar to that seen in women. Funding Information: Midwestern University/Arizona Alzheimer's Consortium (MAAC: DME, CJ, JVE, JP, TV, BJ), Biomedical Sciences start-up funds (DME).

Poster 27

CARDIOVASCULAR CHARACTERIZATION OF YOUNG AND AGED, FEMALE AND MALE APOE4 MICE. Hoxha B, Vallejo-Elias J, Jones C, Powell J, Virden T, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common form of dementia in the United States with age and sex being the biggest risk factors. In addition, individuals with cardiovascular disease (CVD) have an increased risk for development of AD. A link between AD and CVD is apolipoprotein E (APOE), a protein that primarily functions to traffic lipids in the body and brain. Individuals with a particular allele of APOE, APOE4, are at increased risk for developing both CVD and AD/dementia. CVD remains the leading killer of both women and men in the United States. By the age of 65, women have 1 in 6 chance of developing AD compared to a 1 in 11 chance for men. Therefore, out of the 5 million people living with Alzheimer's in the U.S., 3.2 million are women. Because of these differences, this study was designed to assess the effect of the hAPOE4 genotype on carotid artery (CA) function, thoracic aorta (TA) function, and cardiac (C) function in young and aged hAPOE4. We hypothesize that female mice expressing hAPOE4 will exhibit augmented age-related decline in C, TA and CA function than aged matched male hAPOE4 mice.

Methods: In vivo investigation of C, TA and CA structure/function was assessed in young (4 \pm 1 months) and aged (18 \pm 2 months), female and male, hAPOE4 mice using high - resolution ultrasound (U/S) system. In addition, blood pressure (BP) was determined using the tail-cuff method. All U/S and BP values were collected under isoflurane anesthesia. Results were considered significant at $p < 0.05$.

Results: In this study, young and old, female and male hAPOE4 mice exhibited similar bodyweights. CA structure and function was assessed by wall thickness (WT) and pulse wave velocity (PWV) respectively. Both female and male hAPOE4 mice displayed an age-related increase in PWV ($p < 0.05$), but only the female APOE4 mice displayed an age related increase in CA wall thickness (WT) ($p < 0.05$). Female and male hAPOE4 mice exhibited an age-related increase in TA PWV ($P < 0.05$), but measurements of aortic structures: aortic annulus, sinus of valsalva, and sinotubular junction showed no significant sex or age related change. Interestingly, except for a modest increase in mitral valve deceleration time with age in male hAPOE4 mice, there was no effect of age or sex on cardiac parameters assessed by U/S (e.g., cardiac output, ejection fraction, stroke volume, etc.). Finally, blood pressures were similar in female and male, young and old hAPOE4 mice with the only exception being an elevated pulse pressure in young male hAPOE4 mice vs young female APOE4 mice ($p < 0.05$).

Conclusions: These preliminary data suggest that female and male, hAPOE4 mice, exhibit age-related changes in TA and CA structure and function. Additional studies will be needed to determine whether hAPOE4 mice exhibit structural and/or functional changes similar to that seen in women and men. Funding Information: Midwestern University/Arizona Alzheimer's Consortium (MAAC: DME, JVE, CJ, JP, TV, BJ), Biomedical Sciences start-up funds (DME).

Poster 28

AMELIORATION OF NEURODEGENERATIVE CHANGES IN MICE UNDERGOING TRANSVERSE AORTIC CONSTRICTION BY MAS AGONISTS. Jadhav SS, Gaffney KG, Rodgers KE. 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, have also been shown to be involved in AD and cognition along with being cardioprotective. Several studies from our lab have shown that treatment with MAS agonists in different disease models results in increase in MSC's, which we believe contribute to part of the beneficial effects of these therapeutics. MSC's have also been shown to have benefit in treating AD. Thus, we hypothesized that MAS agonists could help ameliorate hypertension-induced AD-like pathology in mice.

Methods: In order to test this, we are using a mouse model of hypertension, where C57BL/6J mice receive a transverse aortic constriction (TAC) which leads to AD-related brain pathology. One week after induction of TAC, mice are divided into 4 treatment groups (saline, A(1-7) , RASRx1902 and RASRx1911) and treated daily via subcutaneous injection for 2 months. RASRx1902 and RASRx1911 are small molecule MAS agonists developed in our lab. A sham surgery group, treated with saline, is used as a control. Towards the end of the treatment period, the cardiac health of the mice will be analyzed using echocardiography followed by assessment of their cognitive abilities using novel object recognition. Upon necropsy, brains are collected to study ACE \leq , tau, neuro-inflammation and microglial activation using histology. Hearts are collected and assessed using histology. Blood and bone marrow are collected and analyzed for mesenchymal stem cells (MSC's) using flow cytometry and cultures

Results: Results are being collected for this pilot study. To date, we have shown that the Mas agonists have no effect on blood pressure in this model.

Conclusions: Results from this study could help identify novel therapeutics for treating hypertension related AD.

Poster 29

IDENTIFICATION OF A WIDE VARIETY OF BACTERIA IN THE BRAIN TISSUE OF INDIVIDUALS WITH EITHER MILD COGNITIVE IMPAIRMENT (MCI) OR ALZHEIMER'S DISEASE. Jentarra G, Chu P, Jones TB, Kaufman J, Vallejo J, Jones D, Tullot T, Potter P. Midwestern University; Arizona Alzheimer's Consortium.

Background: Previous reports identified a wide range of microorganisms in brain tissue in association with Alzheimer's disease (AD), including various bacteria, HSV-1, and fungi/yeast. The chronic presence of any of these microorganisms in the brain be sufficient to induce the inflammation and microglial activation commonly seen in AD. As a number of disparate microorganisms have been associated with AD, we hypothesized that the identity of the microorganisms is not as important as their chronic presence, which would be expected to drive a long-term inflammatory response. To determine if microbes could potentially play a role in the pathogenesis of AD, we tested post-mortem brain tissue for the presence of bacterial DNA using an unbiased analysis method.

Methods: Tissues were acquired from the Brain and Body Donation Program at Banner Sun Health Research Institute in Sun City, Arizona. DNA was extracted from superior frontal gyrus and inferior temporal gyrus, from four subject groups (n=12 per group). Extracted DNA was enriched for microbial DNA and subsequently subjected to 16S rRNA sequencing (Arizona State University Genomic Core Facility) to identify the presence of bacterial DNA.

Results: Patients with either mild (MCI) or severe cognitive impairment (AD) had a large variety of bacterial DNA present in their brain tissue. Individuals with high AD-associated pathology in their brains, but no cognitive impairment (HPC) had a moderate variety of bacterial DNA. Normal control individuals with minimal pathology and no cognitive impairment had only a low burden of bacterial DNA. We identified bacteria that were present only in either AD or MCI subjects, or AD, MCI, and HPC subjects but not in normal control individuals.

Conclusions: Our data are consistent with the potential involvement of bacteria in the pathogenesis of AD, perhaps beginning when the individual first develops cognitive impairment. Individuals with characteristic pathology but no cognitive impairment display more moderate levels of bacterial involvement that be sufficient to induce brain pathology but not cognitive impairment. The presence of a small variety of bacteria even in brain tissue from normal non-demented control individuals indicates that some baseline level of microbial intrusion into the brain is not unusual.

Poster 30

EFFECTS OF CANDIDA ALBICANS INFECTION IN 3X-TG-AD MICE. Jones TB, Vallejo J, Gonzalez F, Kaufman J, Jentarra G, Kerry-Gnazzo A, Potter P, Tullo T, Jones D. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by the presence of amyloid plaques and neurofibrillary tau tangles in the brain. Many reports have identified the presence of a wide range of microorganisms in brain tissue in association with AD, including spirochete-type bacteria, herpes simplex virus 1 (HSV-1), and fungal organisms, including various species of *Candida albicans*. The chronic presence of any of these microorganisms in the brain be sufficient to produce inflammation in AD patients. The presence of fungal organisms in the brain activate resident microglia which would promote the recruitment of inflammatory cells from the periphery; many of the cytokines produced in response to fungal infections have been identified in AD brains. The goal of this project was to assess the ability of an animal model of AD, the 3xTg mouse, to clear *C. albicans* from the brain and various peripheral tissues. We hypothesized that 3xTg mice would exhibit impaired clearance of the candida and as a consequence, would exhibit a greater fungal load compared to age-matched controls (C57/BL6). **Methods:** *C. albicans* was cultured on Sabouraud dextrose agar at 30°C. Prior to inoculation of mice, the concentration of yeast cells was adjusted to 1.0×10^6 /mL. Female and male mice (6-7 and 12-13 months old) were inoculated with 0.1 mL (1.0×10^5) of the fungal suspension via the lateral tail vein. This protocol has been shown to produce widespread dissemination of *Candida*. Infected mice were sacrificed at 1, 3, 7, and 14 days post-inoculation and the spleen, kidney, liver, and brain were aseptically removed, weighed, and then bisected for analyses. To test fungal burden and clearance, tissue was homogenized, plated on agar and fungal growth was determined.

Results: At 6 months of age, C57BL/6 mice had 100% survival compared with 3xTg mice who had 75% survival. Interestingly, the rate of survival of control mice at 12 months of age decreased to 67% while the rate of survival of 3xTg mice at 12 months of age did not change from that observed at 6 months of age. These preliminary data suggest strain- and age-dependent effects on the response to fungal infection. It is also of interest to note that 100% of the control mice that succumbed to infection were males, whereas in the 3xTg mice 50% were males, suggesting that sex also influences response to fungal infection. In addition, marked splenomegaly and hepatomegaly was identified in 3xTg mice inoculated at 6 and 12 months of age compared with inoculated C57BL/6 mice. Spleen and liver weights continued to increase in 3xTg mice as the mice aged in contrast to C57BL/6 mice and predominated in males. Finally, viable *Candida* organisms were isolated from all of the tissues surveyed, including the brain, confirming that our infection protocol produced widespread distribution of the fungus.

Conclusions: Organomegaly observed in the 3xTg mice compared to C57 controls suggest that the transgenic mice exhibit chronic inflammation following *C. albicans* inoculation. These results are consistent with an impaired ability of the 3xTg mice to clear the infection. This response be due to 1) the inability to clear the fungal infection and 2) an exaggerated immune/inflammatory response. Preliminary observations on fungal load suggest that at 6 months of age, C57BL/6 mice have a decreased ability to clear the fungus as indicated by the greater number of organisms being recovered from the tissues.

Poster 31

TEMPORAL CONTIGUITY PREDICTS REWARD ASSOCIATION LEARNING IN BONNET MACAQUES. Kyle C, Smith AC, Gray DT, Burke SN, Barnes CA. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.

Background: When human subjects freely recall items from a list, they are more likely to name a neighbor of the item they last recalled. This finding, known as the temporal contiguity effect, has led to the development of the "temporal context model" of memory which theorizes that temporally neighboring events share similarity in the underlying neural representations (Howard and Kahana, 2002). While this model is supported by studies examining brain activity using local field potential or functional MRI measurements in humans (Hsieh et al., 2014, Kyle et al., 2015, Manning et al., 2011), because only humans can perform free recall, the scope of research on this topic has remained limited.

Methods: However, state-space models, which through Bayesian statistics can uncover the precise timing of learning, make it possible to investigate temporal contiguity in tasks that do not rely on verbal responses. Here we utilize a state-space model and new methods to calculate the conditional probabilities in a fixed-sequence, forced-choice reward association task performed by 16 bonnet macaques.

Results: The results suggest that during multiple days of association-pair learning, newly-learned pairs tend to be more temporally contiguous to recently-learned pairs than to more distant pairs in both young (10 yrs, n=7) and old (23 yrs, n=9) monkeys.

Conclusions: To our knowledge, our data represent the first evidence that temporal contiguity can underlie reward association learning and extends the study of contiguity using conditional probabilities to non-verbal tasks.

Poster 32

EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE WITH VOXEL-BASED FEATURES: A DEEP LEARNING APPROACH. Lee D, Pan R, Chen K. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: An early diagnosis of Alzheimer's Disease (AD) plays an important role in delaying the progress of cognitive decline. In recent years, the application of machine learning techniques to AD diagnosis has been broadly investigated due to its potentials of accurate and object diagnosis. However, the direct application of the advanced machine learning techniques has been limited because MRI brain image data contains extensive number of attributes compared to the volume of available data.

Methods: The previous AD diagnosis through 3-dimensional MRI brain image data has been usually performed by two approaches: 1) the visual assessment by medical doctors or 2) the biomarker achieved from pixel-based information. However, the first diagnosis method lacks the objective and quantitative data analysis, and the second diagnosis approach generally requires complex data pre-processes and can lost critical information such as anatomical shape and location of brain structure. In this study, we propose to apply deep learning technique to AD diagnosis. The proposed methodology will provide objective and quantitative AD diagnosis results by analyzing MRI brain image data.

Results: This study proposes a novel deep learning approach for analyzing MRI brain image data, which diagnoses AD based on features from voxel-based information. Our approach will effectively eliminate noise in MRI data to leverage the utilization of available data.

Conclusions: The proposed methodology will not only minimize data pre-processing for feature extraction but also preserve essential and crucial information in MRI brain image data.

Poster 33

PROTECTING DNA: ARE INDIVIDUALS WITH AUTISM SPECTRUM DISORDER AT RISK FOR ACCELERATED COGNITIVE AGING? Lewis CR, Agrawal K, Walker N, Taguinod F, Smith C, Ringenbach S, Huentelman M, Braden BB. Translational Genomics Research Institute; Arizona State University; Southwest Autism Research and Resource Center; Arizona Alzheimer's Consortium.

Background: Many of the first children diagnosed with autism spectrum disorder (ASD) are now older adults who have outlived their caregivers; yet, the impact of aging on adults with ASD is poorly understood. In 12 years, there will be ~700,000 adults with ASD who are over the age of 65 in the U.S.; thus, there is a critical need to elucidate mechanisms of age-related cognitive changes in older adults with ASD to develop effective interventions and adequate care plans. Recently, our group and others reported preliminary cross-sectional findings that older adults with ASD have sharper age-related declines in cognitive and brain measures, but little is known about the biological mechanism(s) driving these differential aging trajectories. Telomeres are repetitive non-coding DNA nucleotides that protect genes by capping chromosome ends. They progressively shorten with each cell division, providing a biological measure of aging. Shortened telomeres have been associated with accelerated normal and pathological cognitive aging. Recently, studies reported preliminary evidence associating shortened telomere length with ASD or familial relation to a proband. Objective: We aimed to replicate this work in a larger sample of children with ASD who also have the potential to be followed longitudinally for a comprehensive understanding of differential aging trajectories of telomere length and cognition in ASD. We hypothesized children with ASD would have shorter RTL than age-matched typically developing (TD) controls.

Methods: Using blood leukocytes, we investigated the association between relative telomere length (RTL) and childhood ASD in males (ASD: $n = 186$; TD: $n = 107$). We used an established quantitative polymerase chain reaction method, and designed telomere and single-copy reference gene primers from an established protocol. We assessed RTL between groups using independent samples t-test ($p < 0.05$; one-tailed).

Results: With a subset of the entire sample (ASD: $n = 31$; TD: $n = 28$), who were well matched in age (ASD: 5.79 ± 2.12 years; TD: 5.93 ± 2.71 years), preliminary findings demonstrate that children with ASD group had shorter RTL length compared to TD children [$t(57) = 1.69$, $p = 0.04$]. Continued analysis of the entire sample and correlational analyses with cognitive measures are in progress.

Conclusions: Findings replicated other recent studies, providing additional evidence that ASD is associated with shortened telomere length. Further investigations aimed at understanding the relationship between telomere length and cognitive aging are planned and warranted. Telomere length be an important biological mechanism in understanding the aging trajectory of ASD and providing a novel treatment target for future interventions.

Poster 34

AGE STRATIFICATION CORRECTS BIAS IN ESTIMATED HAZARD OF APOE GENOTYPE FOR ALZHEIMER'S DISEASE. Liu L, Caselli RJ. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Age, sex, and APOE genotype each contribute to overall risk for Alzheimer's disease (AD), but studies examining how their interactions affect AD risk have shown conflicting results.

Methods: We performed Cox regression analysis on five independent cohorts including 6,814 subjects. We tested if hazards of APOE genotype violate the common assumption of proportionality and change during aging, and if incorporating time-dependent coefficients resolve discrepancies among cohorts.

Results: Hazards of APOE genotype are non-proportional. The effect of e4 allele takes a step-wise decline around age 75 in men and age 80 in women. The effect of e2 allele gradually decreases over time following a similar trajectory in men and women. We also found e4 allele is a significant risk factor of AD onset before age 65.

Conclusions: Discrepancy is due to different age compositions of study cohorts. We provide guidelines of age and sex stratification for experimental design and analysis.

Poster 35

NEUROPSYCHOLOGICAL COMPARISON OF INCIDENT MILD COGNITIVE IMPAIRMENT AND PREVALENT MILD COGNITIVE IMPAIRMENT. Locke DEC, Hansen A, Golafshar MA, Dueck AC, Woodruff BK, Stonnington CM, Geda YE, Caselli RJ. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Mild cognitive impairment (MCI) is the intermediate symptomatic stage between normal cognitive aging and dementia. The objective of this study is to assess whether patients seeking evaluation for memory complaints who were subsequently diagnosed with single-domain amnesic Mild Cognitive Impairment (aMCI; prevalent MCI cases) are diagnosed at a state of greater cognitive decline than participants diagnosed with aMCI in a longitudinal research setting (incident aMCI cases).

Methods: The sample included 53 incident cases of aMCI from our longitudinal research cohort (the Arizona APOE cohort) and 52 consecutive aMCI cases from one neuropsychologist's (DECL) practice.

Results: Prevalent MCI cases were older at the time of diagnosis (prevalent MCI 76.17 [5.62] vs. incident MCI 73.09 [6.60]; $p=0.01$) and performed worse even after controlling for age on a memory task (AVLT-TL $p=0.01$, AVLT-LTM $p<0.01$), but also performed worse on non-memory measures including a global indicator (DRS $p<0.01$), construction (CFT Copy $p<0.01$), phonemic verbal fluency (COWA $p<0.01$), semantic verbal fluency (Animals $p<0.01$), naming BNT ($p=0.02$) and attention and speed (TMT-A $p<0.01$).

Conclusions: This suggests that by the time patients seek evaluation for memory loss they have a more advanced stage of MCI than incident MCI cases identified with the benefit of longitudinal neuropsychological evaluation in a research setting. This demonstrates the value of longitudinal neuropsychological evaluation, especially in those who are asymptomatic but potentially at risk for development of cognitive decline. This is also important in treatment trials with the goal of treating people as early as possible.

Poster 36

PATIENT AND PARTNER PERCEPTION OF THE IMPACT OF THE MAYO CLINIC HABIT HEALTHY ACTION TO BENEFIT INDEPENDENCE & THINKING PROGRAM FOR MILD COGNITIVE IMPAIRMENT. Locke DEC, Cuc AV, Eilertsen J, Lucas P, Hurst D, Khayoun R, Morris M, Chandler M. Mayo Clinic Arizona; Mayo Clinic Florida; Arizona Alzheimer's Consortium.

Background: The HABIT program is a 5 component intervention for patients with MCI and a partner. Patients receive 50 hours of treatment across 5 components including: physical exercise, cognitive exercise, patient and family education, support group, and cognitive rehabilitation. We have previously demonstrated empirical support for the impact of HABIT using measures of activities of daily living, patient self-efficacy, and partner depression and burden. However, these data has not been proportionate to the qualitative feedback we have received from participants about the program's impact. Thus, this analysis examined patient and partner perception of the impact of the HABIT program.

Methods: We utilized an anonymous patient and partner satisfaction survey that asked about their perception of impact of HABIT on various outcomes, the relative importance of the five components of the program, how each component of the program might be of benefit (if at all), and an overall rating of the likelihood they would recommend HABIT to a friend or family member.

Results: Using Likert scales, patients agreed to strongly agreed they learned tools to cope with memory loss and that HABIT improved their ability to function despite memory loss, improved quality of life, and improved mood. Partners expressed similar satisfaction with the program for the patient's outcomes as well as their own quality of life and mood. Among the components, cognitive rehabilitation was ranked as most important and impactful on daily functioning.

Conclusions: These data expand upon the impact of the HABIT program from the viewpoint of the patient with MCI and partners, in addition to the quantitative measures published previously.

Poster 37

COMPARATIVE EFFECTIVENESS OF BEHAVIORAL INTERVENTIONS TO PREVENT OR DELAY DEMENTIA: PRELIMINARY OUTCOMES. Locke DEC, Chandler M, Cuc AV, Eilertsen J, Lucas P, Caselli M, Hoffman-Snyder C, Wethe J, Hurst D, Francone A, Smith GE. Mayo Clinic Arizona; Mayo Clinic Florida; University of Florida; Arizona Alzheimer's Consortium.

Background: Mayo Clinic offers a multi-component treatment program for patients with amnesic Mild Cognitive Impairment (MCI). The objective of this trial was compare the effectiveness of 5 behavioral interventions for MCI that compose the HABIT Healthy Action to Benefit Independence and Thinking® program

Methods: HABIT is a group-based non-pharmacological treatment program for patients diagnosed with amnesic MCI and a program partner. Couples receive 50 hours of treatment across 5 components including: physical exercise, cognitive exercise, patient and family education, support group, and cognitive rehabilitation. For this trial, 216 couples involved in the program had 1 component of the program suppressed while receiving the other 4 components. Block randomization was utilized to suppress 1 of the 5 components from groups of couples enrolled in each session.

Results: Survey data from former HABIT program completers indicated that MCI patients and their partners rate patient quality of life (QOL) as the most important outcome. Therefore, this is our primary outcome. Secondary outcomes include patient mood, self-efficacy, and memory activities of daily living (mADLs). All 5 treatment models resulted in significant improvement in patient QOL at treatment end. However, for secondary patient outcomes only a few combinations of treatment resulted in significant improvement.

Conclusions: Multiple combinations of behavioral interventions improve QOL in patients with MCI at treatment end. The loss of any one intervention did not significantly reduce QOL outcomes. However, for other secondary outcomes, the suppression of some interventions resulted in loss of improvement on that outcome. There was no one combination of treatments that provided the best results for all outcomes. In keeping with the patient-centered nature of our study, what outcome is most valued by an individual help dictate which combination of interventions would be most useful. Further, it is likely that the synergy of multiple behavioral interventions rather than the impact of one single intervention that is most beneficial across a range of outcomes in patients with MCI.

Poster 38

SYNAPTIC DEFICITS IN C9ORF72-ALS/FTD PATIENT-DERIVED HUMAN STEM CELL DIFFERENTIATED NEURONS AND IN VIVO MODELS OF C9ORF72. Lorenzini I, Ghaffari L, Levy J, Burciu C, Shenoy D, Twishime N, Bhatia D, Lall D, Baloh R, Sattler R. Barrow Neurological Institute; Cedars-Sinai Medical Center; Arizona Alzheimer's Consortium.

Background: The hexanucleotide repeat expansion GGGGCC (G4C2) found in the non-coding region of the C9orf72 (C9) gene represents the most common genetic abnormality in amyotrophic lateral sclerosis (ALS) (40-50%) and frontotemporal dementia (FTD) (10-30%). ALS and FTD patients have genetic, pathologic and symptomatic overlap. Therefore, understanding the molecular mechanisms of disease pathogenesis in this ALS/FTD disease spectrum could lead to the development of novel therapeutic strategies. Cognitive decline as seen in normal ageing or Alzheimer's disease (AD) is characterized by changes in neuronal morphology, spine density and progressive synapse loss. We hypothesize that similar mechanisms are responsible for the dementia symptoms caused by the C9 mutation and that these events arise early during disease progression before any neurodegeneration has occurred. Furthermore, based on recent findings in AD and FTD, we hypothesize that this synaptic dysfunction involve the neural-immune complement pathway.

Methods: Here we present preliminary data supporting this hypothesis using C9-ALS/FTD patient-derived human induced pluripotent stem cells differentiated into motor neurons (hiPSC-MNs) and cortical neurons (hiPSC-CNs), in addition to C9 mouse models.

Results: We found significant changes in dendritic branching, dendritic length, spine density and detected alterations in the expression pattern of synaptic proteins in hiPSC neurons. We also observed changes in neuronal excitability using longitudinal micro-electrode array analysis. Similar changes in dendritic arborization and dendritic length were observed in homozygous C9orf72 $-/-$ knockout mice. In addition, increased complement pathway activation and decreased gene expression of pre-synaptic markers were observed in this C9 mouse model.

Conclusions: Our data suggest that synaptic deficits are present in C9 ALS/FTD which are likely to be triggered by aberrant neural-immune interactions. These synaptic dysfunctions are hypothesized to contribute to cognitive impairment and neuronal cell death found in C9orf72 patients.

Poster 39

PERFORMANCE OF IMR-BASED ASSAYS IN MEASURING ALZHEIMER'S DISEASE CORE BIOMARKERS IN PLASMA AND POTENTIALS FOR CLINICAL USE. Lue LF, Guerra A, Sabbagh MN. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Accurate measurement of Alzheimer's core pathological markers such as amyloid beta, tau, and phosphorylated tau in plasma samples has been a challenge until recent development of new approaches and technologies that provide technical specificity and sensitivity. Among these promising technologies, we have first-hand experience in utilizing Immunomagnetic Reduction (IMR)-SQUID technology in last three years. Here we assess the performance of this technology from our own and others' published results for potential use of the technology clinically for Alzheimer's disease blood test.

Methods: The technology requires reagents containing specific antibody-conjugated magnetic nanoparticles and a superconducting quantum interference device (SQUID) to detect magnetic signal changes due to the amounts of antigen bound to the antibody (MagQu, Ltd, New Taipei City, Taiwan). The concentrations are expressed in pg/ml, calculated from the standard curve of each specific antigen detected in the same manner. The reagents are commercially available for assays of amyloid beta 40, amyloid beta 42, and total tau. New reagents for research purposes have been developed for detecting alpha-synuclein and phosphorylated tau. We assessed the performance of the IMR assays from the aspects of technique, data, findings, and ROC sensitivity/specificity for distinguishing Alzheimer's disease from normal controls.

Results: The IMR-SQUID technology involves simple sample preparation steps and less than 1 ml of plasma samples for assaying, in triplicate, total tau, phosphorylated tau, amyloid beta 40, and amyloid beta 42. The limiting factors are the availability and capacity of the equipment and duration for each run of the assay. However, the findings from several cohort studies are rather impressive. These studies reported increased levels of amyloid beta 42 and total tau, but reduced levels of amyloid beta 40 in Alzheimer's plasma samples. Some of these studies also reported increases in subjects with mild cognitive impairment due to Alzheimer's disease. The U.S. Sun City cohort study reported an almost significant increase in amyloid beta 42 level, significantly increased total tau level, and decreased amyloid beta 40 level in older-age Alzheimer's disease patients. It also has been consistently demonstrated that using calculated product of amyloid beta 42 and total tau levels, the high sensitivity and specificity for identifying Alzheimer's disease subjects could be achieved. In a recent report, IMR-assayed amyloid beta 42 levels in plasma had been shown to be negatively correlated with IMR-assayed amyloid beta 42 levels in the cerebrospinal fluid samples.

Conclusions: Considering all data published up to this date indicates that IMR-SQUID assay platform has a great potential to be used in a confirmatory blood test for diagnosis of Alzheimer's disease.

Poster 40

CEREBRAL AMYLOID ANGIOPATHY WITH NEURITIC PLAQUE PATHOLOGY CORRELATES WITH COGNITIVE DECLINE IN PRECLINICAL AD. Malek-Ahmadi M, Chen K, Perez SE, Mufson EJ. Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Cerebral amyloid angiopathy (CAA) is a vascular neuropathology commonly reported in non-cognitively impaired (NCI), mild cognitive impairment (MCI) and Alzheimer's disease (AD) brains. Although previous studies report that the presence of CAA affects cognition in MCI and AD subjects, an association between non-demented elderly subjects that display either limited or extensive AD pathology, remain unclear. This study determined the association between CAA and cognitive composite score among a cohort of elderly NCI subjects with a differing extent of AD lesions.

Methods: 182 autopsy cases from the Rush Religious Order Study were analyzed. All subjects were NCI at their first clinical assessment. At time of death, 98 subjects remained NCI while 84 progressed to either MCI (n = 40) or AD (n = 44). A cognitive composite score was used to measure cognitive change over time. CAA was dichotomized (present/absent) based upon a standard 0 to 3 severity scale used as a predictor variable along with dementia progression and other demographic covariates. Cases were also grouped according to neuritic plaque (NP) and neurofibrillary tangle (NFT) load. A mixed model-repeated measures analysis was used to assess change from baseline on the cognitive composite score.

Results: CAA individuals with high NP scores had significantly greater composite score change from baseline relative to the low NP group [-3.52 (95% CI: -5.85, -1.18), p = 0.003]. Those cases without CAA were not different between the low and high NP groups [-3.19 (95% CI: -9.15, -2.76), p = 0.29]. By contrast, change from baseline between the high and low NFT groups with [3.13 (95% CI: -3.42, 9.68), p = 0.35] or without [-0.69 (95% CI: -3.03, 1.65), p = 0.56] CAA were not significantly different.

Conclusions: CAA and high NP load, but not NFTs are associated with greater decline on a cognitive composite score. Accounting for the presence of CAA be important in assessing treatment efficacy in AD prevention trials.

Poster 41

A SEPARABLE STATE-SPACE MODEL OF LEARNING ACROSS TRIALS AND DAYS IN AN AGING STUDY IN MACAQUE MONKEYS. Malem-Shinitzki N, Zhang Y, Gray DT, Burke SN, Smith AC, Barnes CA. University of Berlin; Harvard University; University of Arizona; University of Florida; Arizona Alzheimer's Consortium.

Background: Understanding how learning and memory changes with normal aging is increasingly important as the aged population grows. Obtaining objective measures of behavioral changes associated with aging is challenging since learning is dynamic, varies considerably between individuals, and observations are frequently binary.

Methods: We introduce a method for analyzing binary response data from young and aged macaque monkeys performing tasks across multiple days that enables us to compare within-day and across-day performance. The data set comprises 14 female bonnet macaques-6 young and 8 old animals-performing a reversal learning task in the form of a modified Wisconsin Card Sort Task. Conventional methods to analyze these data are unable to capture their inherent two-dimensional nature, fail to distinguish groups, and cannot adequately assess inter-individual differences in performance. We propose a separable two-dimensional (2D) random field (RF) model of the binary data from these experiments, wherein the joint probability of a monkey's correct performance as a function of task and trial depends on two latent Markovian state sequences that evolve separately but in parallel. In this instantiation of the model, we use a Laplacian random walk prior for the monkey-dependent latent process that characterizes the dynamics of a monkey's learning across days. This captures abrupt transitions and allows the detection of change points in the observations across days due to reversal. A Monte Carlo Expectation-Maximization (EM) algorithm is used to maximize the marginal likelihood of the data from the separable 2D RF, followed by a Maximum a Posteriori estimation algorithm for change point detection.

Results: The method results in an estimate of performance within a day for each age group, and a learning rate across days for each monkey. We show that as a group the older monkeys find the tasks harder than the young monkeys, and that the cognitive flexibility of the younger group is higher. We further demonstrate the efficacy of the model by using the resulting estimates of performance as features for clustering the monkeys into two groups. The clustering results in two groups that, for the most part, coincide with those formed by the age groups.

Conclusions: Simulation studies suggest that clustering based on the model's results captures inter-individual differences in performance levels, which allows us to identify "high performing" old monkeys. These analyses, therefore provide a method to estimate an animal's behavioral/cognitive age independent of chronological age.

Poster 42

RESPONSE TO HORMONAL INTERVENTION IN AGING FEMALE BRAIN IS ENDOCRINE STATUS DEPENDENT: IMPLICATIONS FOR ALZHEIMER'S DISEASE.

Mao Z, Yin F, Yao J, Brinton R. University of Arizona; Arizona Alzheimer's Consortium.

Background: The perimenopause is an aging transition unique to females and is associated with multiple neurological symptoms. Our previous study in a rodent model of human perimenopause revealed the perimenopausal transition as a critical transition period characterized by a significant decline in bioenergetic and synaptic functions, that is reminiscent of early stage of Alzheimer's disease (AD). Combinations of 17β -estradiol (E2) and progestogens (P4) in varying regimens are widely used as hormone therapy for menopause-related climacteric symptoms. The present study was aimed to determine the efficacy and optimal intervention window of E2 in combination of cyclic P4 therapy on female rat brain at different stages of the perimenopausal transition, against bioenergetic deficits and AD risks.

Methods: Placebo or E2+CyP4 therapy was initiated on female rats at 9-10 months with either pre- or perimenopause stages at the same age, and for each stage, ovariectomy (OVX) or Sham OVX surgery was performed before the intervention. Hormone therapy consisted of two 30-day cycles of continuous E2 and cyclic P4 (10 days/cycle) delivered by silastic capsules. Upon completion of the regime, rats were subject to transcriptomic, biochemical, immunocytochemical and brain metabolic investigations.

Results: We previously reported that a two-month treatment of E2+CyP4 on (OVX) young rats induced a bioenergetic gene-expression profile comparable to the ovary intact females. Our data from this study indicate that the efficacy of E2+CyP4 therapy on brain bioenergetic functions in terms of glucose metabolism and mitochondrial respiratory capacity was differentially affected by the endocrine status of the rats when the intervention was initiated. Interestingly, our data also suggested that OVX initiated on pre- or perimenopausal stages elicited opposed effects on bioenergetic-, inflammatory- and AD-related gene expressions. Immunocytochemistry study for key metabolic and inflammatory markers in the brain, and bioinformatic analyses of the hippocampal transcriptome after intervention are under investigation.

Conclusions: Outcomes of this study determine the window of opportunity for preventing the at-AD-risk bioenergetic phenotype by hormone intervention and will provide mechanistic details for developing novel strategies to maintain neurological health and function throughout menopausal aging against AD vulnerability. This work was supported by P01AG026572 to RDB (Project 1 to RDB, Analytic Core to FY).

Poster 43

OLIGOMERIC AMYLOID β PREFERENTIALLY TARGETS NEURONAL AND NOT GLIAL MITOCHONDRIAL-ENCODED MRNAS. Mastroeni D, Nolz J, Khmour OM, Sekar S, Delvaux E, Cuyugan L, Liang WS, Hecht SM, Coleman PD. Arizona State University; Translational Genomics Institute; Arizona Alzheimer's Consortium.

Background: Our laboratories have demonstrated that accumulation of oligomeric amyloid β (OA β) in neurons is an essential step leading to OA β -mediated mitochondrial dysfunction.

Methods: Alzheimer's disease (AD) and matching control hippocampal neurons, astrocytes, and microglia were isolated by laser-captured microdissection from the same subjects, followed by whole-transcriptome sequencing. Complementary in vitro work was performed in OA β -treated differentiated SH-SY5Y, followed by the use of a novel CoQ10 analogue for protection. This compound is believed to be effective both in suppressing reactive oxygen species and also functioning in mitochondrial electron transport.

Results: We report decreases in the same mitochondrial-encoded mRNAs in Alzheimer's disease laser-captured CA1 neurons and in OA β -treated SH-SY5Y cells, but not in laser-captured microglia and astrocytes. Pretreatment with a novel CoQ10 analogue, protects neuronal mitochondria from OA β -induced mitochondrial changes.

Conclusions: Similarity of expression changes in neurons from Alzheimer's disease brain and neuronal cells treated with OA β , and the effect of a CoQ10 analogue on the latter, suggests a pretreatment option to prevent OA β toxicity, long before the damage is apparent.

Poster 44

INTERVENTION DEVELOPMENT FOR CAREGIVERS OF PEOPLE WITH ADRD AND DOWN SYNDROME/ID: AN UPDATE. Montague R, Carll P, Goldman J, Gomez Morales A, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: There are no evidence-based interventions for family caregivers of Down Syndrome or Intellectual Disability (DS/ID) populations affected by Alzheimer's Disease and related dementias (ADRD). Down syndrome (DS) populations can develop ADRD up to 20 years earlier than those without DS. Family caregivers, who have provided lifelong care for their loved ones with DS/ID, face the difficulty of "adding on" the caregiving responsibilities associated with the ADRD. Caregiver research is needed to help identify key stressors and develop interventions that decrease distress for these caregivers. Most research in this area has focused solely on non-Hispanic White samples and therefore it is important to obtain input from more diverse populations to help develop efficacious caregiver interventions.

Methods: This project extends prior data collection with family caregivers and providers helping people DS/ID in Arizona. It combines anonymous data (N=95) gathered at two different conferences focused on DS and ADRD. The data include descriptive information about family caregivers of those impacted by DS/ID and ADRD as well as family caregiver and provider opinions about the potential utility of a number of psychoeducational skill-building intervention strategies for alleviating distress and enhancing coping with these family caregivers. This information will help develop an intervention for caregivers of people with DS/ID and ADRD.

Results: Participants (N = 95) described themselves as non-Hispanic White (68.4%), Hispanic/Latino (15.8%), African American/Black (6.3%), Native American (5.3%), Asian American (3.2%), no primary group or another ethnic/racial minority (10.5%). Respondents varied in their roles with regard to caregiving: 1) family or friend caregivers (40%); 2) professionals helping develop or manage programs to serve these individuals (14.7%); 3) professionals working directly with people with DS/ID and/or their families (9.5%); or 4) people with multiple roles (35.8%). Respondents were asked to rate the usefulness of nine different strategies in helping reduce family caregiver distress. Strategies varied from 85 (89.5%) to 95 (100%) in their number of participant responses. The following list outlines the proportion of participants rating that strategy as useful: skills training to improve communication with care recipients (98.9%); skills training to improve communication with providers (97.9%); care values and care task clarification for future care planning (96.8%); strategies to help caregivers manage unhelpful thinking (97.9%); communication skills to improve interactions with family and friends (96.8%); stress relaxation techniques (97.6%); pleasant events scheduling for care recipients (98.9%); and pleasant event scheduling for caregivers (100%); techniques to manage behavior changes (96.8%). Informants raised other issues for consideration: the potential for a combination of in-person and telephone or online modes of delivery; the need for interventions for individuals in group home/group living situations; and the need for interventions for staff that recognize challenges in education and intervention delivery costs.

Conclusions: Feedback from family members and professionals provided overwhelming support for the use of psychoeducational skill-building strategies in an intervention for caregivers of people with ADRD and DS/ID. Focus groups are underway to provide additional insights into the intervention's development as well as its recruitment and retention strategies.

Poster 45

PLANNING AND EFFICIENCY ON THE TOWER OF LONDON TEST IN ASD.

Nespodzany A, Braden BB, Baxter LC, Smith CK. Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona State University; Arizona Alzheimer's Consortium.

Background: Planning is a critical component of executive functioning that facilitates the proper execution of goal-directed behavior. Deficits in executive functioning can underlie many of the challenges faced by individuals with autism spectrum disorder (ASD), and many studies show that individuals with ASD exhibit poor planning compared to Typically Developing (TD) individuals. Objective: To investigate the effect of ASD on planning ability in adults.

Methods: Participants were recruited through the community and underwent screening for ASD prior to cognitive assessments. Inclusion/exclusion criteria included IQ > 80, male, and general good health. TD participants (n = 38, age 18-64, M = 38, SD = 15.24) were age- and IQ-matched to individuals in the ASD group (n = 52, age 18-70, M = 38, SD = 17). Participants performed a Tower of London test, a commonly used neuropsychological test requiring planning. The test requires participants to arrange beads on pegs in specified patterns in as few moves as possible, where consecutive trials get progressively more difficult. Total moves, initiation time (time spent planning), execution time, and total number of correct trials (completed without making extra moves) was recorded. SPSS (v19) was used to test mean differences between ASD and TD groups, and linear regression modeling was conducted to test the relationship between initiation time and number of trials completed correctly for each group.

Results: TD subjects completed significantly more correct trials than did their ASD counterparts, and the ASD group made significantly more moves across all trials. The two groups did not show significant differences in the amount of time they used to plan moves. However, linear regression revealed that there was a significant and negative relationship between planning time and total move count for the ASD group, but not for the TD group. Thus, for individuals with ASD, more time spent planning moves resulted in the making of fewer unnecessary moves.

Conclusions: Compared to healthy controls, adults with Autism displayed deficits in planning on a Tower of London task. While both ASD and TD groups showed similar variability in time spent planning, planning time was an important determinant of correctly completing the task for only the ASD group. In summary the study indicates that though some individuals with ASD had difficulty in motor planning, those who utilized longer planning periods had the best performance. TD individuals completed the task with more ease than did the ASD individuals, with little to no benefit from longer planning periods. Since no instruction was given regarding using planning as a strategy, it is difficult to know whether the use of planning was incidental or deliberate. This study suggests that increased emphasis on planning improve some aspects of executive functioning in individuals with ASD.

Poster 46

ALZHEIMER'S PREVENTION REGISTRY: CAN EMAIL INTERACTION PREDICT STUDY INTEREST IN COGNITIVELY HEALTHY, PROSPECTIVE VOLUNTEERS?

Nichols JB, High NM, Gordon DJ, Graf HP, Malek-Ahmadi MH, Chen K, Reiman EM, Tariot PN, Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: As the field of Alzheimer's disease ("AD") prevention research grows, understanding the best way to recruit healthy volunteers for such trials has become increasingly important. In 2012, the web-based Alzheimer's Prevention Registry ("Registry") was launched to help accelerate enrollment into AD-related studies. Since this launch, the Registry has placed an emphasis on sending engagement emails - monthly newsletters, community event promotions and caregiver guidance - to its members ("Registrants") to help retain and grow their interest in AD-related research. The following retrospective analysis sought to better understand the efficacy of such emails by examining whether prospective volunteers who interacted with (opened or clicked a link within) engagement emails were more likely to consider participating in a prevention trial compared to those who did not interact with the emails.

Methods: In 2015, the Registry introduced GeneMatch ("GM"), a separate, web-based research program aimed at enriching referrals to AD prevention studies based in part on participants' genetic profiles. GM is open to adults ages 55-75 who live in the US and self-report not having a diagnosis of cognitive impairment. After signing an online consent, GM Registrants submit a cheek swab to be analyzed for the APOE gene. Results are securely stored in the GM database and used to help match GM Registrants to AD prevention trials, which could take months or years. GM Registrants ages 60-75 who were matched to a prevention trial ("invitees") between May and October 2017, received an email entitled 'You have a study match from GeneMatch!' To accept the invitation, an invitee had to log into his or her account, review a description of the trial, select a study site, agree to share his or her contact information, and click 'Accept.' Invitees could alternatively select 'Not now, remind me later', or 'Decline.' Invitees who did not respond to the first email were sent a reminder email, and lastly a paper invitation via the postal service. Invitees who received engagement emails within three months of being invited to the trial were included in this analysis. Engagement email interactions were recorded and analyzed alongside invitation responses via logistic regression analyses, both unadjusted and adjusted for distance to closest study site and source of recruitment into GM.

Results: 438 were invited to participate in the prevention trial: 211 accepted, 11 declined, 8 chose to be reminded of the trial at a later date and 208 did not respond. Mean invitee age was 66.4 years (SD 4.4 years); 76% were female; 43% reported having a family history of AD; 62% lived within 50 miles of the nearest study site. Regression analysis found that those who accepted the invitation were twice as likely to have opened at least one engagement email within three months of receiving the invitation as those who did not open any engagement emails [OR=2.03 (95% CI: 1.42, 2.90), p-value <0.001]. Those who accepted the study invitation were more likely to have clicked a link within an email [OR=1.89 (95% CI: 1.30, 2.73), p-value=0.003].

Conclusions: There is a strong relationship between engagement email interaction and study invitation acceptance. This relationship serve as a tool to predict who is more likely to accept future study invitations. More importantly, these results suggest that it is important to invest in activities such as engagement emails to retain prospective volunteer interest since it could be months or years between when they join and when a study opportunity becomes available. Future analyses will explore other potentially important covariates.

Poster 47

PREDICTIVE NETWORK MODELING IDENTIFIED NOVEL TARGETS IN AD. Petyuk VA, Chang RR, Ramirez-Restrepo M, Beckmann ND, Henrion MYR, Piehowski PD, Zhu K, Wang S, Clarke J, Huentelman MJ, Xie F, Andreev V, Engel A, Guettoche T, Navarro L, De Jager P, Schneider JA, Morris CM, McKeith IG, Perry RH, Lovestone S, Woltjer RL, Beach TG, Sue LI, Serrano GE, Lieberman AP, Albin RL, Ferrer I, Mash DC, Hulette CM, Ervin JF, Reiman EM, Hardy JA, Bennett DA, Schadt E, Smith RD, Myers AJ. Pacific Northwest National Laboratory; Icahn School of Medicine at Mount Sinai; University of Miami Miller School of Medicine; University of Nebraska-Lincoln; The Translational Genomics Research Institute; Arbor Research Collaborative for Health; Children's Hospital of Philadelphia; Brigham and Women's Hospital; Harvard Medical School; Broad Institute; Rush University Medical Center; Newcastle University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: We have proposed that systems approaches to finding novel genes involved in disease pathways can be more powerful than DNA-only approaches (Myers, 2012, 2013, 2014). We have previously examined genotype-transcript relationships via expression eQTL analysis and constructed regulatory networks (Myers et al., 2007a; Webster et al., 2009; Zhang et al., 2013). In this report, we extended the original work by using two independent datasets and by integrated mass spectrometry proteomics (Piehowski et al., 2013). In addition, by experimentally validating the top replicated key drivers using two independent cell-based models, we directly tested predictions from the network models regarding their impact on LOAD pathology.

Methods: In this report, we present the first two-series replicated screen that includes DNA variation, RNA expression, and MS/MS proteome profiles in two series of human brains, ~50% of which are pathologically confirmed LOAD tissues (see Supplemental Figure 1). These two sets were analyzed independently to determine relationships between DNA, RNA and protein. Network analyses were used to capture the causal structures within the data. This type of analysis is more comprehensive than testing single transcripts or proteins against SNPs, which is the common procedure in eQTL studies and is the procedure carried out in many prior reports including the human proteome (Garge et al., 2010; Stark et al., 2014). Additionally, the multiple layers of regulation that can occur between DNA and protein make the protein-SNP relationships more complex and multivariate network approaches are capable of capturing relationships among all targets. While it was important to identify targets in brain, the causal consequences of changing levels of targets are statistically inferred; therefore, validating the predictions is critical. We used several different cell lines to validate targets outside the context of human brain tissue, measuring levels of Abeta40, Abeta42, total Tau and Phospho-Tau to examine the downstream consequences of changing predicted target transcript and protein expression. Our hypothesis is that novel findings will be acting on a background of pathological expression of both Abeta and Tau, i.e. our effects would act as modifiers of known pathology.

Results: We present an integrated, multi-level analysis of how the integration of DNA, RNA, and protein data can facilitate the study of the relationships among genes and proteins and their impact on the human brain in the context of LOAD. These targets are vetted through a multi-pass validation procedure including multiple types of analysis, replication across multiple datasets, in silico predictions and in vitro validations.

Conclusions: We identified and validated some key drivers in LOAD.

Poster 48

CLASSIFICATION OF DIFFERENTIALLY EXPRESSED GENES FROM ALZHEIMER'S DISEASE BRAIN HOMOGENATES ACCORDING CELL SPECIFIC EXPRESSION. Piras IS, Coleman PD, Huentelman MJ. Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Here we proposed a cell enrichment approach leveraging a Laser Capture Microdissection (LCM) RNA expression database. This approach can be applied to RNA profiling from brain homogenates, to classify differentially expressed genes (DEGs) according their specific cell expression. We tested the approach using two large Alzheimer's Disease (AD) datasets, including patients and non-demented (ND) controls.

Methods: The Brain-RNAseq database (Zhang et al., J Neurosci 34, 11929-47) includes RNA profiling of 22,458 genes in 6 LCM cell types from mouse cortex: astrocytes (A), neurons (N), microglia (M), endothelial cells (EC), myelinating oligodendrocytes (MO), newly formed oligodendrocytes (NFO), and oligodendrocytes precursor cells (OPC). We excluded low expressed genes (< 0.01). Finally, we conducted pathways analysis for each cell type and the complete list of DEGs.

Results: A total of 2,560 genes were classified in DS1, and 32.5% of genes were assigned to a specific cell type. The most prevalent were: N (10.0%), M (6.4%), EC (6.1%) and A (4.6%), whereas oligodendrocytes types accounted for 5.3% of the total. In DS2 (n=4,046) we found similar proportions, but with higher prevalence of genes expressed in EC (7.4%, second most cell type detected), and lower for N (7.9%). When we considered the expression trend related to AD in different cell types, we detected a strong downregulation in N genes (>89.1% in both dataset), and a strong upregulation for A, EC and M (>72.9% in both datasets). MO showed 76.2% upregulation in DS1, but 55.6% in DS2; OPC showed a weak downregulation trend (>56.3% in both datasets). Finally, NFO showed discordant trends between DS1 and DS2. We detected 103 significant pathways in DS1. Interestingly, most of them were cell type specific. Only one pathway ('axon guidance') was detected in NFO and in the complete DEGs list (n=2,560), whereas 7 pathways were detected in N and in the complete list (e.g.: "Neuronal System", and "Synaptic vesicle cycle"). The specific pathways detected reflect exclusive functions related to the cells and to AD pathogenesis, not detected when using the complete list, as: EC: 'angiogenesis' M: 'innate immune system' N: 'GABAergic synapse'. In the DS2 we obtained similar results. 14 pathways (on a total of 149) were found in both the complete list and at least in another cell type, whereas 5 were shared between two cell types. We confirmed the cell/pathway specificity as in the DS1.

Conclusions: Our approach allowed us to identify enriched groups of genes functionally related and associated with AD, not detectable using the complete list of DEGs. We observed the highest prevalence of neuronal genes (downregulated) and endothelial genes (upregulated) associated with AD. Microglia genes are generally upregulated, and enriched for specific process related to neuroinflammation in AD. In absence of LCM, our approach can provide useful information for the investigation of RNA expression profiling using brain homogenates.

Poster 49

DECREASED LEVELS OF BETA-ARRESTIN 1 IN BRAINS OF PATIENTS WITH ALZHEIMER'S DISEASE. Potter PE, Choi S, Jones D, Beach T. Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Previous studies in our laboratory have shown that muscarinic receptors become uncoupled from G-proteins in brains of patients with Alzheimer's disease (AD). Interestingly, this process began prior to the development of dementia, in that there was some degree of uncoupling in patients without cognitive impairment but who had increased levels of beta-amyloid post-mortem. This suggested that these patients might have been on a pathway of progression to AD and might have represented a very early stage of the disease process. In order to further understand this process, we began to investigate levels of G protein receptor kinases and beta-arrestin in these brain samples. These proteins are involved in trafficking of G-protein coupled receptors, and we hypothesized that uncoupling of muscarinic receptors could be a result of altered levels of these proteins. We previously reported, using Western blot, that there was a decrease in beta-arrestin in the brains of patients with AD1, but we were not able to differentiate between beta-arrestin 1 and beta-arrestin 2. Using Western blotting, we also found a loss of membrane bound GRK-2, but no change in total GRK-2.

Methods: In this study, we used the more quantitative analysis provided by ELISA assays to investigate levels of beta-arrestin 1 and 2 in temporal cortex samples of patients with AD, or non-demented controls with either a very low to zero amount of amyloid plaques (low pathology; LP), or a high amount of amyloid (high pathology; HP). Levels of total GRK-2 and GRK-5 were also measured using Western Blot and ELISA.

Results: We found a decrease in levels of beta-arrestin 1 in the AD brains. There was some decrease in beta-arrestin-1 in the brains of high pathology controls, compared to those in low pathology controls. This contrasts with the increase in beta-arrestin 1 described using Western blot in AD patients². In contrast to the results reported by Thatiah et al.³, we did not find an increase in beta-arrestin 2 using ELISA. We previously found a trend towards an increase in beta-arrestin 2. It is possible that the temporal cortex is less likely to develop alterations in this protein than the entorhinal cortex and hippocampal regions, which are affected earlier in AD, and which were used in that study. In agreement with earlier results, total levels of GRK-2 and GRK-5 were unaffected.

Conclusions: In this study we describe a loss of beta-arrestin 1 in patients with AD, with no alteration in beta-arrestin 2 or GRK-2 and GRK-5. Increases in beta-arrestin 1 precede the development of dementia, as they begin to decrease in patients who are cognitively normal but have high levels of amyloid plaque pathology. Changes in beta-arrestin could affect receptor function and alter processing of beta-amyloid in AD. Our study also suggests the possibility that alterations in proteins involved in signal transduction vary in different regions of the brain as AD develops. References: 1. Potter, P.E, et al, FASEB Journal. 28 (1) Supplement: 153.4, 2014 2. Liu, X, et al, Cell Research 23: 351-365 (2013) 3. Thatiah, A, et al, Nature Medicine 19: 43-51.

Poster 50

FLORTAUCIPIR PAIRED HELICAL FILAMENT TAU BURDEN AND CORRELATION WITH COGNITIVE DECLINE IN MCI PATIENTS WITHOUT ANY AB. Protas HD, Ghisays V, Luo J, DeMarco EL, Thiyyagura P, Devadas V, Bauer III R, Landau SM, Weiner M, Jagust WJ, Reiman EM, Chen K. Banner Alzheimer's Institute; University of California Berkeley; University of California San Francisco; Arizona State University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: We previously investigated flortaucipir PET measurements paired helical filament (PHF) tau burden in MCI patients with and without florbetapir PET criteria of moderate to frequent amyloid plaques (SUVR>1.18), and we found tau burden even in those who did not meet this criteria for any amyloid positivity. We now extend this study to MCI patients who did or did not meet florbetapir PET criteria for any amyloid (Fleisher 2011) (SUVR>1.08) to investigate the relationship of cognitive decline and higher tau burden in MCI patients even in the absence of any amyloid.

Methods: Flortaucipir PET scans were acquired in 27 A β ⁺ and 32 A β ⁻ persons with MCI and in 50 A β ⁻ cognitively unimpaired adults from ADNI-3. A β positivity was defined using mean cerebral-to cerebellar florbetapir SUVRs>1.08 (Fleisher 2011). We compared regional flortaucipir SUVRs in a voxel-based approach and also in pre-specified regions, precuneus, parahippocampal and inferior temporal regions, among these groups. The same pre-specified regions were used to characterize relationships between regional flortaucipir SUVRs and cognitive impairment assessed with MMSE, ADAS-cog, CDR-SB and AVLT long-term memory (LTM) in the A β ⁺ and/or A β ⁻ MCI groups.

Results: In comparison with the A β ⁻ unimpaired controls, the A β ⁺ and A β ⁻ MCI groups had significantly higher flortaucipir SUVRs in a number of locations, including in the Braak ROIs that are preferentially affected by AD. In comparison with the A β ⁻ MCI group, the A β ⁺ MCI had significantly higher flortaucipir SUVRs in the same locations. In A β ⁻ MCI group, higher entorhinal, parahippocampal, and inferior temporal flortaucipir SUVRs were associated with CDR-SB measure. Correlation of MMSE with inferior temporal flortaucipir SUVR was also significant. With the more liberal A β ⁺ threshold, we found significant correlation of CDR-SB with entorhinal, parahippocampal, inferior temporal, and precuneus flortaucipir SUVRs and also between MMSE and precuneus and entorhinal flortaucipir SUVR in A β ⁺ MCI.

Conclusions: Even when we limited our analysis to people who did not have any plaques, we observed elevated tau burden and correlation with cognition raising the possibility that tau pathology in this population not depend on amyloid pathology in relationship to cognitive impairment.

Poster 51

AN ALTERNATIVE TO DYE-BASED APPROACHES TO REMOVE LIPOFUSCIN-INDUCED BACKGROUND AUTOFLUORESCENCE FROM PRIMATE BRAIN TISSUE. Pyon W, Gray DT, Chawla MK, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Lipofuscin results from the collection of lipid residues in lysosomes within cells throughout the body, including neurons. An accumulation of this pigment is one of the most consistent findings across age in the brains of primates with its appearance being correlated with chronological age. This process has generally been considered to be the result of normal cellular "wear-and-tear." Such age-related pigment accumulation, however, presents challenges for fluorescence-based cell quantification in the midbrain since these pigment molecules possess fluorescent emission spectra that invade the normal collection range of most fluorescent microscopes. The use of fluorescence microscopy for anatomical studies has multiple benefits including the ability to label multiple fluorophores, which necessitates a standardized procedure for reducing the background effects of neurolipofuscin-induced autofluorescence that can obscure relevant fluorescent signals. Current strategies to combat such autofluorescence include the use of lipophilic dyes to mask native fluorescent emission from brain tissue (Schnell et al., 1999; Romjin et al., 1999). While these dyes successfully remove autofluorescence, they also degrade the emission of fluorophores commonly used in immunofluorescent microscopy.

Methods: Here we present an alternative method for removing lipofuscin-induced autofluorescence. This strategy involves defining lipofuscin's emission spectrum given laser lines ranging from 405nm - 633nm on a Leica SP5-II spectral confocal microscope. These spectra are used to subtract lipofuscin-based autofluorescence from fluorescent channels commonly used in immunofluorescent studies.

Results: This collection protocol reliably diminishes native autofluorescence while preserving the fluorescence of tyrosine hydroxylase- and calbindin-immunolabelled cells in the ventral tegmental area of young and aged rhesus macaque brains.

Conclusions: Here the autofluorescence subtraction procedure is compared to the standard method (Sudan Black B protocol) to evaluate which technique most successfully reduces autofluorescence while maintaining the integrity of relevant fluorescent signals.

Poster 52

IN VIVO MEASUREMENTS OF CORTICAL THICKNESS, AMYLOID AND TAU PATHOLOGY, AND EPISODIC MEMORY IN PRECLINICAL AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE. Quiroz YT, Agüero C, Lopera F, Norton D, Aguirre-Acevedo D, Chen, K, Baena A, Guzman-Velez E, Pardilla-Delgado E, Alvarez S, Dickerson BC, Sperling RA, Reiman EM, Johnson KA. Universidad de Antioquia; Massachusetts General Hospital; Harvard Medical School; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Cortical thinning has been reported in individuals with autosomal dominant Alzheimer's disease (AD), several years before anticipated clinical onset. Here we compared brain imaging measurements of cortical thickness, amyloid and tau pathology, and characterized associations with memory performance in cognitively unimpaired mutation carriers and non-carriers from the Colombian Presenilin-1 (PSEN1) E280A kindred.

Methods: We used structural MRIs, PiB and flortaucipir PET images of amyloid and tau burden, and CERAD word list learning memory scores in the assessment of 12 cognitively unimpaired 37±3 year-old mutation carriers, approximately 7 years before the kindred's median age at mild cognitive impairment (MCI) onset. Automated brain mapping algorithms were used to compute mean cortical PiB DVRs, entorhinal cortex (EC) and inferior temporal (IT) flortaucipir SUVRs, and cortical thickness in 9 regions-of-interest (ROIs) known to be affected by AD. Spearman's correlations were used to characterize relationships among these brain imaging and memory measurements.

Results: Compared to non-carriers, cognitively unimpaired PSEN1 mutation carriers showed cortical thinning in the inferior temporal gyrus ($p < 0.001$), middle temporal gyrus ($p = 0.03$), superior temporal gyrus ($p < 0.001$), and temporal pole ($p < 0.001$). In the carrier group, amyloid burden was only associated with thinning in the superior parietal lobule ($r = -0.78$, $p < 0.001$). EC and IT tau burden were associated with thinning in the anterior cingulate ($r = -0.87$, $p < 0.001$ and $r = -0.76$, $p = 0.04$, respectively) and precuneus ($r = -0.96$, $p < 0.001$ and $r = -0.94$, $p < 0.001$, respectively). Poorer memory performance was associated with thinning in the supramarginal gyrus ($r = 0.57$, $p = 0.05$), thinning in posterior cingulate cortex ($r = 0.69$, $p = 0.013$), and EC tau burden ($r = -0.67$, $p = 0.01$).

Conclusions: This study provides preliminary information about the limited associations between amyloid burden and neurodegeneration, and the more extensive associations between tau burden, neurodegeneration and cognitive decline, several years before the estimated age of MCI onset in individuals at virtually certain risk for autosomal dominant AD.

Poster 53

SEX DIFFERENCES IN AGING WITH INJURY: THE USE OF REMOTE ISCHEMIC CONDITIONING AS AN ANTI-INFLAMMATORY TREATMENT FOR BRAIN INJURY INDUCED PERIPHERAL INFLAMMATION. Saber M, Rowe R, Lifshitz J. University of Arizona; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; Arizona Alzheimer's Consortium.

Background: Chronic effects of TBI increase the risk and accelerate the development of multiple neurodegenerative diseases, most famously, Alzheimer's disease (AD) by causing a robust inflammatory response. The status quo for TBI and AD is restricted to few treatment options that mask symptoms rather than pursuing a root cause analysis. Injury-induced neuroinflammation and concomitant peripheral immune system activation advance TBI as a disease process. As such, populations of peripheral monocytes migrate through the leaky blood brain barrier towards chemoattractants released by CNS immune cells. The acute infiltration of these peripheral cells has chronic detrimental effects, whereby inhibiting macrophage infiltration after TBI using genetically modified mice reduced functional deficits. Remote ischemic conditioning (RIC; transient restriction of blood flow to a limb) alters peripheral inflammatory populations, with the potential to disrupt inflammatory signaling and its impact on cognitive performance in murine models of both TBI and vascular dementia. Objectives: This study quantified the extent to which RIC modulated the peripheral and central immune response to experimental brain injury and sex differences. We hypothesized that RIC impedes the infiltration of peripheral monocytes into the brain and reduces chronic cognitive deficits after TBI by dampening the influence of the peripheral immune response.

Methods: Diffuse brain injury by midline fluid percussion was performed on adult (8-10 weeks of age) male and female C57BL/6 (B6) mice. After 1 hour, half of the mice in both the injured and uninjured sham group received 4x5 minute sessions of RIC (elastic band on one thigh) with 5-minute reperfusion between each session. To examine the acute effects of RIC on the immune response, blood, spleen, and brains were collected at 3 and 7 days post injury (DPI) and processed for flow cytometry to quantify inflammatory monocytes in the spleen and blood (Ly6chighCd115+) and peripheral macrophages in the brain (Cd11b+ CD45high). A separate group of mice were used to determine chronic cognitive and anxiety related outcomes of RIC treatment. Tests included rotarod to test motor function, open-field and elevated plus for anxiety-like behavior (30DPI), and Y-maze (45DPI and 90DPI) and Novel object recognition (14 and 120DPI) for spatial memory and cognition.

Results: Female mice showed a more robust change in both peripheral inflammatory monocyte populations in the blood and spleen after TBI at 3DPI, and an increased peripheral monocyte population in the brain compared to sham controls. RIC treatment reduced brain injury induced peripheral monocyte populations down to sham levels in these females. Males showed a similar trend but were not significantly different from each other. Peripheral inflammatory monocyte and macrophage population changes were resolved by 7DPI.

Conclusions: These data suggest that RIC can modulate the peripheral macrophage and monocytes response. Behavioral studies will be able to correlate whether this can be beneficial in reducing pathological age-related deficits of brain injury. Further studies are needed to refine the mechanism and determine the therapeutic efficacy of immune modulation by RIC.

Poster 54

SINGLE-CELL ANALYSIS IN HUMAN BRAIN NEURODEGENERATIVE DISEASE: A PILOT STUDY. Serrano G, Lue L-F, Brafman D, Huentelman M, Intorcica A, Guerra A, Walker J, Cutler B, Curry J, Callan M, Glass M, Arce R, Oliver J, Sue L, Beach TG. Banner Sun Health Research Institute; Arizona State University; 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 study we 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 with H & E and immunophenotyping with antibodies specific for neurons (MAP2 and/or NeuN), astrocytes (GFAP) and microglia (Iba-1), on slides of paraffin embedded suspensions, as well as by fluorescence-activated cell sorting (FACS). Additionally, we extracted RNA from the cell suspensions which was then probed using qPCR for cell-type-specific RNA for the same markers. The final optimized protocol, performed at 40C to minimize processing-related gene expression changes, uses enzymatic digestion with Accutase for 4 hours, mechanical disruption by repetitive pipetting, and removal of myelin, neuropil and other cellular debris using Percoll centrifugation.

Results: The resulting yield is roughly 2.5 million cells per gram of fresh human gray matter and the mean RNA integrity number is 6.2. Histological staining, FACS and qPCR demonstrated that neurons, astrocytes and microglia are all present in the single cell suspensions. The relative concentrations of cell-type markers suggest that roughly 50% of the cells are neurons, with microglia and astrocytes each making up 25% of the total.

Conclusions: These results show that currently we are capable of producing adequate yields of single cell suspensions with a good representation of different cell types together with RNA quality suitable for use in biochemical analysis targeting phenotypically-defined cell populations. Future goals include developing optimized cryopreservation methods and determining suitability for single-cell transcriptomic analysis.

Poster 55

PREVALENCE OF REM SLEEP BEHAVIOR DISORDER IN SUN CITY, ARIZONA.
Shprecher DR, Intorcia A, Glass M, Curry J, Walker J, Cutler B, Callan M, Serrano G, Zhang N, Sue LI, Davis KJ, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: RBD is the strongest known clinical risk factor for Parkinson disease (PD) and related disorders, however prevalence data necessary to guide design of PD prevention trials are limited.

Methods: In order to determine the prevalence of REM Sleep Behavior Disorder (RBD) in Sun City, Arizona; we designed a survey using the RBD single item question (RBD1Q) for probable RBD (pRBD), "have you ever been told, or suspected yourself, that you act out your dreams while asleep (for example, punching; flailing your arms; making running movements; shouting out loud; knocking things over; jumping out of bed)?" and the Innsbruck RBD Inventory for high-likelihood RBD (HL-RBD). Four out of 5 "yes" responses to these more specific questions have been shown to increase specificity of RBD1Q in a community-based sample.¹ Attempts by telephone and mail were made to administer it to 1000 individuals in the Sun City, Arizona zip code. Individuals answering "yes" to 4/5 Inventory questions were considered to have HL-RBD.

Results: 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.

Conclusions: Previous research suggests that 66% of HL-pRBD respondents will have polysomnogram confirmed RBD.¹ Recognizing potential limitation of respondent bias, prevalence of idiopathic cases was 8.5% pRBD and 2.7% HL-RBD in our retirement community with a mean age 78.

Poster 56

PREDICTING ALPHA-SYNUCLEIN PATHOLOGY BY REM SLEEP BEHAVIOR DISORDER DIAGNOSIS. Shprecher DR, Adler CH, Zhang N, Hentz JG, Serrano GE, Dugger BN, Shill HA, Savica R, Caviness JN, Sabbagh MN, Belden CM, Driver-Dunckley E, Mehta SH, Sue LI, Davis KJ, Zamrini E, Beach TD. Banner Sun Health Research Institute; Mayo Clinic Arizona; University of California Davis; Barrow Neurological Institute; University of Arizona; Mayo Clinic; Arizona Alzheimer's Consortium.

Background: Inability to accurately diagnose Lewy type alpha-synucleinopathy (LTS) pre-mortem has been a major obstacle to clinical care and research. Probable REM sleep behavior disorder (PRBD) diagnosed with support of instruments such as the Mayo Sleep Questionnaire (MSQ) provide a cost-effective means of predicting LTS.

Methods: Since 2007, 602 subjects in the Arizona Study of Aging and Neurodegenerative Disorders had clinician assessment for PRBD (298 with, 304 without support of the MSQ), completed cognitive and movement examinations, and had neuropathological assessment.

Results: Mean age at death was 84.8 years. Histological evidence of LTS was found in 80/101(79.2%) cases with PRBD and 198/501 (39.5%) without PRBD ($p < 0.001$). Overall sensitivity for predicting LTS by PRBD diagnosis was 28.8%, specificity 93.5%, positive predictive value (PPV) 79.2%, negative predictive value (NPV) 60.5%. Without MSQ supported diagnosis sensitivity was 7.3% and specificity 99.4%. With MSQ but no caregiver informant, sensitivity was 30.4% and specificity 95%. With MSQ and caregiver informant, sensitivity was 53.4% and specificity 84.6%. Diagnosis of PRBD was less frequently present in subjects without LTS [4/105 (3.8%) of healthy controls, 42/255 (16.5%) AD, 2/33 (6.1%) progressive supranuclear palsy (PSP) without LTS] than in subjects with LTS [11/46 (23.9%) DLB, 58/104 (55.8%) PD, and 4/16 (25.0%) PSP with LTS.] PRBD was not present in any of 46 subjects with incidental Lewy body disease (ILBD).

Conclusions: MSQ-supported diagnosis of PRBD appears useful for predicting LTS in manifest neurodegenerative disease, but not ILBD.

Poster 57

ARE LEWY BODIES ASSOCIATED WITH SYMPATHETIC PATHOLOGY IN DEMENTIA SUBJECTS? 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. Barrow Neurological Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Comorbid Lewy body (LB) pathology is very common in Alzheimer disease (AD) and confound clinical trial design- yet there is no in-vivo test to identify it. Tissue studies have shown cardiac sympathetic denervation in Parkinson disease and dementia with Lewy bodies, but have not been explored in mixed AD/LB cases.

Methods: In order to determine if Alzheimer subjects with Lewy bodies show sympathetic cardiac denervation, we analyzed 30 cases with autopsy-confirmed AD/DLB, 30 AD/LB not meeting DLB criteria, 30 AD-no LB, 22 controls- no LB, 30 control/LB (ILBD). Using tyrosine hydroxylase (TH) staining of epicardial and myocardial tissue, 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. Staining 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 ($p = 0.008$) between the groups, and subsequent pair-wise Mann-Whitney analysis showed that PD ($p = 0.014$) and DLB ($p = 0.008$) subjects have significantly reduced TH fiber density as compared to controls. The TH density in ILBD hearts was midway between the control and PD or DLB groups but the difference was too small for this to reach significance ($p = 0.16$).

Conclusions: The clear separation of DLB from controls based on cardiac TH fiber density is the first report of a statistical difference between these groups. Our data therefore strengthen the rationale for using cardiac nuclear imaging with a nor-adrenergic nuclear imaging ligand, meta-iodobenzylguanidine (MIBG) to separate DLB from AD with DLB, an important concept as most cases of AD/DLB are not recognized as such during life. Our results indicate that MIBG would not be likely to clinically separate the AD/LB from AD subjects without LB.

Poster 58

AN INTEGRATED BIOMANUFACTURING PLATFORM FOR THE LARGE-SCALE EXPANSION AND NEURONAL DIFFERENTIATION OF HUMAN PLURIPOTENT STEM CELL-DERIVED NEURAL PROGENITOR CELLS. Srinivasan G, Morgan D, Varun D, Brookhouser N, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Human pluripotent stem cell derived neural progenitor cells (hNPCs) have the unique properties of long-term in vitro expansion as well as differentiation into the various neurons and supporting cell types of the central nervous system (CNS). Because of these characteristics, hNPCs have the tremendous potential in the modelling and treatment of various CNS diseases and disorders. However, expansion and neuronal differentiation of hNPCs in quantities necessary for these applications is not possible with current 2-D approaches.

Methods: Previously, we developed a fully defined peptide-based substrate, referred to as vitronectin-derived peptide (VDP), that allowed for the long-term expansion and directed neuronal differentiation of multiple hNPC lines in completely defined medium conditions. In this work, we use this defined substrate as a basis for a microcarrier (MC)-based suspension system that enables the long-term growth and highly efficient neuronal differentiation of several hNPC lines. In turn, we were able to use this MC-based approach in a low-shear rotating wall vessel (RWV) bioreactor to enable the large-scale expansion and differentiation of hNPCs.

Results: In this study, we developed a microcarrier (MC)-based approach for the long-term expansion of hNPCs. This MC-based approach is compatible with our previously described defined substrate, vitronectin derived peptide (VDP), or conventional laminin (LN)-based coatings. In fact, the use of small scale MC cultures enabled almost a 10-fold increase in hNPC expansion (per passage) when compared with 2-D methods. In addition, expanded hNPCs, including those from patient-specific hiPSCs, could be differentiated with high efficiency to neuronal cultures. In fact, neurons generated on MCs expressed higher levels of genes associated with maturity, synapse formation, neurotransmitter synthesis, release, and transmission, and ion channels associated with action potential generation. Neurons generated on MCs could also be dissociated and replated onto 2-D surfaces with minimal cell death, which will be important for downstream high-content phenotypic drug screening assays where the culture of neurons in 2-D will be required. Importantly, these MC-based approaches were easily adaptable to large-scale rotating wall vessel (RWV) bioreactors. Specifically, using a 55 mL bioreactor vessel, we were able to reproducibly generate over 250 million hNPCs and 125 million hNPC-derived neurons.

Conclusions: We developed a MC-based system that uses a completely defined substrate for the long-term growth and directed neuronal differentiation of several independent hNPC lines. When combined with low shear RWV bioreactors, we were able to use this MC approach to facilitate large-scale hNPC expansion and neuronal differentiation. In the future, this fully defined and integrated biomanufacturing system will provide a platform for the generation of hNPCs and neuronal derivatives under GMP/GLP standards in numbers (>10⁹) necessary for many downstream drug screening and regenerative medicine applications.

Poster 59

SEX-DEPENDENT DIFFERENCES IN GENISTEIN- AND EXERCISE-INDUCED WEIGHT LOSS IN HIGH FAT-HIGH SUCROSE-FED MICE. St. Aubin C, Fisher A, Plochocki J, Broderick T, Al-Nakkash L. Midwestern University; Arizona Alzheimer's Consortium.

Background: Chronic consumption of a western diet is associated with metabolic syndrome, insulin resistance, type 2 diabetes, cardiovascular disease, loss of bone mass, inflammation, cognitive decline and neurodegenerative diseases like Alzheimer's (AD). Genistein, a naturally occurring isoflavonic phytoestrogen found in soy, improves insulin sensitivity, and exerts both anti-inflammatory and neuroprotective properties. Similar benefits have also been demonstrated with moderate exercise. The goal of this study was to determine whether dietary genistein (600 mg genistein/kg diet, Gen) or exercise (Ex), or both (Gen+Ex) would reduce the obese-diabetic phenotype and thus limit the likelihood of AD progression in C57BL/6J male and female mice.

Methods: Five to 6-week-old C57BL/6J mice were randomly assigned to one of the following groups (n=10/group): lean control, high fat diet (HFD), HFD+Gen, HFD+Ex, and HFD+Gen+Ex. The HFD consisted of 60% saturated fat, 20% carbohydrate, 20% protein including sucrose and fructose in the drinking water. Exercise consisted of daily moderate treadmill running for a total duration of 150 minutes per week for 12 weeks. Data presented here is at week 11 of the diet/exercise study.

Results: In males, body weight was 12-18% ($P<0.05$) lower in exercised or genistein-fed mice compared to those fed HFD. Body weight was 42% ($P<0.05$) lower in the HFD+Gen+Ex males compared to those fed HFD. Of note, the HFD+Gen+Ex group's average body weight was similar to that of lean controls and the benefits of genistein and exercise were noted from the start of the study. In females, body weight was unchanged by exercise and decreased only 8% with genistein supplementation compared to those fed HFD. Body weight was 16% ($P<0.05$) lower in the HFD+Gen+Ex females compared to those fed HFD, again, comparable to the leans. Weight loss was not attributed to reduced food intake. To determine whether Ex or Gen improved insulin sensitivity, glucose tolerance tests (GTT) were performed in subgroups of male mice (n=3-5/group). Overnight fasted mice were i.p. injected with 2 g glucose/kg body weight, and GTT curves were obtained using a glucometer at the following time points; baseline, 15, 30, 60 and 120 minutes. HFD+Ex had no effect on the GTT (compared to HFD). HFD+Gen and HFD+Gen+Ex had similar effects on the recovery of serum glucose to return to baseline levels. Rate of recovery was improved with HFD+Gen+Ex, which appeared more "lean-like".

Conclusions: We conclude that genistein and exercise have sex-dependent effects on HFD-fed mice: (1) Improvements in weight (i.e., less weight gain) were noted in males with either Gen or Ex treatments. (2) Genistein and exercise (HFD+Gen+Ex) together have synergistic effects on body weight, compared to each independently administered in both males and females. (3) Genistein and exercise (HFD+Gen+Ex) together have synergistic effects on GTT, compared to each individually administered in males. We aim to provide mechanistic evidence for these sex-dependent effects and ultimately to demonstrate an association between genistein- and exercise-mediated improvements in body weight to markers for AD. Support: Layla Al-Nakkash, Tom Broderick and Jeffrey Plochocki were supported by Midwestern-Arizona Alzheimer's Consortium.

Poster 60

LONGITUDINAL ASSESSMENT OF ADVANCED MULTI-PARAMETRIC MRI BIOMARKERS OF ALZHEIMER'S DISEASE. Stokes AM, Baxter LC, Nespodzany A, Caselli RJ, Sabbagh MN, Li Z, Pipe JG. Barrow Neurological Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: The goal of this project is to assess longitudinal changes in advanced MR imaging signatures of each stage of AD, including preclinical, mild cognitive impairment (MCI), and dementia stages. These advanced imaging methods allow us to non-invasively investigate the underlying neurobiological changes that precede the cognitive impairments characteristic of later stages of AD. We previously presented our results from a cross-sectional analysis of a single time-point. Here we have expanded our study to include a longitudinal assessment in the same subjects. We will present the biological trajectory of each imaging metric, which were specifically chosen for sensitivity to a known neuropathological change associated with AD. In particular, vascular, cellular, and molecular characteristics were probed using advanced MR imaging methods.

Methods: Three subject groups were recruited for the initial cross-sectional study: cognitively normal (CN) (n = 12), MCI (n = 11), and AD (n = 12). For the longitudinal expansion, each subject was scanned between 11 and 15 months after the first imaging time-point. At each visit, all subjects underwent cognitive testing using the Montreal Cognitive Assessment (MoCA) and functional assessment staging (FAST) immediately prior to MRI. MRI data were acquired at 3T (Ingenia, Philips). Structural MRI data were obtained using ADNI (Alzheimer's Disease Neuroimaging Initiative) protocols, and structural parcellation was performed using FreeSurfer software. Advanced MRI methods are used to measure cerebral blood flow (using arterial spin labeling (ASL)), microvascular perfusion fraction (using intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI)), and molecular species (using chemical exchange saturation transfer (CEST)). To reduce variability for longitudinal analysis, a base template was created using all time-points, and each individual time-point was subsequently resampled to this template within the longitudinal stream available in FreeSurfer. Regional metrics were compared both cross-sectionally and longitudinally.

Results: Across all subjects, cross-sectional analysis of structural MRI revealed significantly reduced cortical thickness and hippocampal volume, while lateral and inferior lateral ventricular volumes were elevated. Both cerebral cortex and cerebral WM showed lower perfusion for the AD subjects, though these results were not significant. The perfusion-insensitive 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 indicate altered microstructural characteristics. GluCEST was reduced in the AD subjects, while APT-CEST showed lower CEST signal in the AD subjects, suggesting altered protein content in these patients. Longitudinal analysis is ongoing and will be presented at the meeting.

Conclusions: This study lays the framework for the development of advanced multi-parametric MRI to characterize the neuropathological changes that occur in Alzheimer's disease. These advanced imaging signatures be early indicators of incipient AD-related MCI or dementia, when intervention would prove most beneficial.

Poster 61

BRAIN DERIVED NEUROTROPHIC FACTOR AND APOLIPOPROTEIN E4: THEIR ASSOCIATION WITH GLUCOSE METABOLISM, BETA-AMYLOID AND COGNITIVE DECLINE IN COGNITIVELY UNIMPAIRED ADULTS. Stonnington CM, Sharieff S, Thiyyagura P, DeMarco E, Caselli RJ, Locke DEC, Lu B, Reiman EM, Chen K. Mayo Clinic Arizona; Midwestern University; Banner Alzheimer's Institute; Tsinghua University; Arizona Alzheimer's Consortium.

Background: Brain derived neurotrophic factor (BDNF) Val66Met polymorphism Met-positivity has been linked to increased rates of cognitive decline among those with both higher beta-amyloid load and Apolipoprotein E (APOE) E4 carriage. It is not known how BDNF and its interaction with APOE4 carriage relate to cerebral metabolic rate for glucose (CMRgl) in preclinical Alzheimer's disease (AD).

Methods: 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 and change in CMRgl from 114 CU adults (59 with PiB PET) who had been both BDNF and APOE4 genotyped.

Results: As expected, APOE4 carriers had significantly higher frontal amyloid, decreased CMRgl in a pattern similar to AD, and greater rate of decline in memory than APOE4 noncarriers. Among APOE4 carriers, BDNF Met carriers had significantly greater frontal amyloid, higher CMRgl, slower decline of the increased CMRgl in frontal regions, and a trend for increased rate of memory decline than Val carriers. These BDNF effects were not found among APOE4 noncarriers. Increased amyloid deposition was positively correlated with areas of greater cerebral metabolism.

Conclusions: Our results confirm an interaction between BDNF met and APOE4 carriage suggesting that BDNF val/val carriage is protective for APOE4 carriers. The increased CMRgl in APOE4/BDNF met carriers reflect a compensatory response leading to amyloid metabolism and beta-amyloid deposition.

Poster 62

IMPROVED PREDICTION OF IMMINENT PROGRESSION TO CLINICALLY SIGNIFICANT MEMORY DECLINE USING MULTIVARIATE SURFACE MORPHOMETRY OF MRI BIOMARKERS AND PATCH-BASED SPARSE CODING.

Stonnington CM, Zhang J, Li Q, Shi J, Bauer RJ, Reiman EM, Caselli RJ, Chen K, Wang Y. Mayo Clinic Arizona; Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Intervening before the symptomatic onset of Alzheimer's disease (AD) will necessitate identifying the combination of sensitive biomarkers and diagnostic methods that precede and predict such clinical impairment. 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. Here, we aimed to improve prediction using hippocampal surface multivariate morphometry statistics combined with patch-based sparse coding algorithms.

Methods: 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.

Results: We achieved 100% prediction accuracy in the Arizona cohort and 90% accuracy in the ADNI cohort. Combining the two cohorts (36 progressors and 54 nonprogressors) achieved 93% prediction accuracy, 90% sensitivity, 100% specificity, 100% positive and 80% negative predictive values.

Conclusions: While our findings should be considered preliminary, sparse coding together with the surface multivariate morphometry be applied to individual volumetric MRIs to predict imminent progression to clinically significant memory decline with great accuracy.

Poster 63

WEB-BASED TESTING SHOWS EFFECT OF FAMILY HISTORY OF ALZHEIMER'S DISEASE ON LEARNING, MEMORY, AND REACTION TIME SPECIFICALLY MODIFIED BY DIABETES AND APOLIPOPROTEIN E GENOTYPE. Talboom JS, Håberg AK, DeBoth M, Siniard AL, Ryan L, Glisky E, Huentelman MJ. Translational Genomics Research Institute; University of Arizona; Norwegian University of Science and Technology; Arizona Alzheimer's Consortium.

Background: A family history of Alzheimer's disease (FH) can be a proxy for heritable and non-heritable risks of dementia. However, the exact influence of FH on cognition across the lifespan is poorly understood. Further, the presence of FH specific interactions with medical conditions and genetics on cognition remains unknown.

Methods: We developed a web-based verbal associative memory (PAL) and simple visual reaction time (svRT) tasks and tested of over 75,000 individuals between the ages of 18-85. Next, we developed a follow-up health and lifestyle factor survey. Over 3000 of the 75,000 original respondents completed this new survey. Lastly, we examined the well-known Alzheimer's disease genetic risk factor, apolipoprotein E (APOE). APOE genotype, from more than 300 FH individuals, was assayed via restriction fragment length polymorphism (RFLP). The DNA for RFLP was extracted from dried blood spots sent to us from consenting individuals via the United States Postal Service.

Results: FH was associated with decreased performance on PAL and svRT. This difference was larger in participants under the age of 60. Further, propensity score matching analysis revealed an effect size of approximately half a word pair deficit in FH individuals. Next, we identified factors modifying the FH effect, we found that diabetes significantly interacted with FH. Specifically, the magnitude of the FH PAL deficit was increased within diabetic individuals. Lastly, APOE genotype was associated with PAL and svRT performance in FH individuals. Specifically, carriers of the APOE2 allele had higher PAL and quicker svRT, while those carrying the APOE4 allele showed lower PAL and slower svRT.

Conclusions: This study suggests that FH, APOE genotype, and diabetes are important factors modifying the trajectory of an individual's cognitive performance across their lifespan.

Poster 64

COMPARISON OF COLLATERAL CIRCULATION (LEPTOMENINGEAL ARTERIOLE) FUNCTION IN COGNITIVELY NORMAL, MILD COGNITIVE IMPAIRMENT, ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA. Truran S, Karamanova N, Beach T, Serrano G, Madrigal C, Madine J, Davies H, Reaven P, Migrino RQ. Phoenix Veteran's Association; Banner Sun Health Research Institute; Banner University Medical Center; University of Liverpool; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Clinical/preclinical data show that vascular disease and cardiovascular risk factors are associated with Alzheimer's disease (AD) and AD-related dementia disorders. Impaired cerebrovascular hemodynamics found in early AD patients and pathologic vascular changes suggesting altered arteriolar vasoregulation and hemodynamic disturbances point to the critical role of vascular dysfunction in disease pathogenesis. Leptomeningeal collateral arterioles (LMA) link the 3 major arterial territories over the brain surface. Although it is known that LMAs play a significant role in cerebrovascular autoregulation, represent an important compensatory mechanism in cerebrovascular disease and affect prognosis following stroke, the role of LMA function in the pathophysiology of dementia disorders remains poorly understood despite pathologic observations that LMA are widely affected in AD. The study aims to test the hypothesis that LMA endothelium-dependent function and smooth muscle-dependent function are impaired in patients with AD and vascular dementia (VaD) when compared to patients with normal cognition (CN) or mild cognitive impairment (MCI).

Methods: Following rapid autopsy (post-mortem interval 2.9 ± 0.1 hour), LMA were isolated from CN (N=12), MCI (N=15) or dementia subjects (AD N=24 or VaD N=9) and endothelial and smooth muscle function were compared.

Results: There was no difference in endothelial function (maximum dilation: CN 72.8 ± 8.2 , MCI 68.4 ± 4.0 , AD 71.1 ± 3.5 , VaD $69.2 \pm 7.1\%$) and smooth muscle function (CN 93.1 ± 2.7 , MCI 84.8 ± 3.0 , AD 91.3 ± 2.2 , VaD $91.7 \pm 2.2\%$). There was no correlation between last cognitive function score and measures of endothelial or smooth muscle function.

Conclusions: Ex-vivo LMA function did not differ among CN, MCI, AD and VaD subjects. Results suggest that cognitive dysfunction in dementia disorders cannot be attributed to differences in baseline brain collateral circulation function. However, in-vivo metabolic milieu leading to vascular dysfunction still play a role and should be investigated.

Poster 65

INTERMITTENT FASTING RESCUES NECROPTOSIS-MEDIATED NEURONAL LOSS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE. Turner EC, Branca C, Ferreira E, Velazquez R, Belfiore R, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by severe neuronal loss, yet the mechanisms by which neurons die remain elusive. Recently, we have shown that necroptosis, a programmed form of necrosis, is activated in AD. Necroptosis is activated by formation of a necrosome, a multiprotein complex which consists of protein kinases RIPK1 and RIPK3 and pseudokinase MLKL. The mammalian target of rapamycin (mTOR) plays a role in AD pathogenesis and it has been linked to necroptosis-mediated cell loss. We hypothesize that mTOR hyperactivity contributes to necroptosis-mediated neuronal death in AD.

Methods: To test this hypothesis, we modulated mTOR signaling by regulating caloric intake.

Results: We show that necroptosis induced by TNF α and zVAD-fmk in vitro in HT-22 cells is decreased during starvation, while overfeeding results in a higher susceptibility to necroptosis-mediated neuronal loss. To validate these results in vivo, we show that bilateral stereotaxic injection of MLKL in the hippocampus causes neuronal loss in wild type and APP/PS1 mice, but not in 3xTg-AD mice. However, our preliminary data obtained through stereological assessment of neurons suggest that intermittent fasting rescues this neuronal loss.

Conclusions: Together, these data suggest a link between necroptosis and mTOR signaling that affects neurodegeneration in AD.

Poster 66

TAU INDUCES NEURODEGENERATION BY ACTIVATING NECROPTOSIS. Vartak RS, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Tau plays a crucial role in neuronal loss in AD and other tauopathies; however, the mechanisms underlying tau-induced neuronal loss remain elusive. Necroptosis is a caspase-independent cell death pathway activated by formation of the necrosome, which consists of kinases RIPK1 and RIPK3 and the pseudokinase MLKL. Recently, we have shown that necroptosis is activated and contributes to neuronal loss in Alzheimer's disease (AD). Our preliminary data in human AD brains suggest a possible interaction between tau and necroptosis activation.

Methods: We conducted stereotaxic injections of AAV-Tau(P301L) or AAV-GFP into the hippocampus of C57/129 mice. We did western blot analyses of brain homogenates with anti-RIPK1, anti-MLKL and anti-p-MLKL antibody as well as immunostaining of fixed brain sections of tau transgenic rTG4510 and PS19 mice using the above antibodies. We conducted DNA transfections in HT-22 cells using expression plasmids expressing tau (P301L) or GFP. This was followed by MTT assay in HT-22 cells to assess viability following treatments with DMSO or necrostatin or z-VAD.

Results: We show that stereotaxic injection of tau in the hippocampus of wild type mice causes neuronal loss. This neuronal loss is accompanied by increase in the levels of RIPK1 and p-MLKL, two hallmarks of necroptosis activation. We also observe an increase in necroptotic markers in two tau transgenic models that show neuronal loss. In vitro studies in HT-22 cells, a mouse hippocampal cell line, show that the tau induced neuronal loss is rescued by necrostatin-1s, a specific inhibitor of RIPK1 kinase, but not by z-VAD, a caspase inhibitor.

Conclusions: Together, our data indicate that necroptosis activation contributes to the tau-induced neurodegeneration.

Poster 67

ACUTE TAU KNOCKDOWN IN THE HIPPOCAMPUS OF ADULT MICE CAUSES LEARNING AND MEMORY DEFICITS. Velazquez R, Ferreira E, Tran A, Turner EC, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Misfolded and hyperphosphorylated tau accumulates in several neurodegenerative disorders including Alzheimer's disease, frontotemporal dementia with Parkinsonism, corticobasal degeneration, progressive supranuclear palsy, Down syndrome, and Pick's disease. Tau is a microtubule binding protein and its role in microtubule stabilization is well defined. In contrast, while growing evidence suggests that tau is also involved synaptic physiology, a complete assessment of tau function in the adult brain has been hampered by robust developmental compensation of other microtubule-binding proteins in tau knockout mice.

Methods: To circumvent these developmental compensations and assess the role of tau in the adult brain, we generated an adeno-associated virus (AAV) expressing a doxycycline-inducible short-hairpin (Sh) RNA targeted to tau, herein referred to as AAV-ShRNATau. We stereotaxically and bilaterally injected 7-month-old C57Bl6/SJL wild type mice with either the AAV-ShRNATau or a control AAV.

Results: We found that acute knockdown of tau in the adult hippocampus significantly impaired motor coordination and spatial memory. Blocking the expression of the AAV-ShRNATau, thereby allowing tau levels to return to control levels, restored motor coordination and spatial memory. Mechanistically, the reduced tau levels were associated with lower BDNF levels, as well as reduced levels of synaptic proteins associated with learning, and decreased spine density.

Conclusions: We provide compelling evidence that tau is necessary for motor and cognitive function in the adult brain, thereby firmly supporting that tau loss-of-function contribute to the clinical manifestations of many tauopathies. These findings have profound clinical implications given that anti-tau therapies are in clinical trials for Alzheimer's disease.

Poster 68

INTRACEREBROVENTRICULAR INJECTION OF STREPTOZOTOCIN PROMOTES INCREASE IN BODY TEMPERATURE: IMPLICATIONS FOR ALZHEIMER'S DISEASE. Vizin RCL, Harris G, Kunstetter AC, Almeida MC, Carrettiero DC, Romanovsky AA. St. Joseph's Hospital and Medical Center; Universidade Federal do ABC; University of Wisconsin-Madison; Universidade Federal de Minas Gerais; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease that promotes the decline of cognitive abilities and non-cognitive symptoms, which include alteration of body temperature (Tb). In fact, a growing number of studies have reported an association between AD and abnormalities in Tb regulation. Intracerebroventricular streptozotocin (icv-STZ) injection has been proposed as an important model to study late-onset sporadic AD (SAD), which corresponds to 99% of AD cases. However, there is no information about the effect of icv-STZ injection on the thermoregulatory system. In this sense, the understanding of the STZ effect on Tb is important to a better characterization of icv-STZ injection as an AD model and the relation between AD and thermoregulatory dysfunction. Thus, the aim of this study was to evaluate the effect of the icv-STZ injection in low-dose in Tb of rats.

Methods: Wistar rats were subject to implantation of Tb-measuring device into the peritoneal cavity and intracerebroventricular injection of streptozotocin (icv-STZ; 1mg/kg) or vehicle. The core Tb was recorded for 35 days after icv injection.

Results: Icv-STZ injected rats showed significant increased Tb response compared to vehicle-treated animals ($p > 0.001$). The thermoregulatory dysfunction of STZ-treated animals starts at an early stage and persists throughout the 35 days measured, with a pick in the second-week post-surgery.

Conclusions: Icv-STZ injection promotes an increase in core Tb. Moreover, the disruptions in thermoregulation might be an early event in the AD.

Poster 69

GENDER DIFFERENCES IN ALZHEIMER'S DISEASE: BRAIN ATROPHY, SYNAPTIC LOSS, HISTOPATHOLOGY BURDEN AND COGNITION. Walker J, Curry J, Oliver J, Intorcica AJ, Callan M, Glass M, Cutler B, Arce R, Sue LI, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Multiple studies have suggested that females are affected by Alzheimer's disease 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.

Methods: In this study we wanted to investigate if gender differences observed in ADD brain weight loss were due to presynaptic or axonal loss. 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 semi-quantitative grading amongst genders. Grey and white matter were dissected for protein extraction and quantification of presynaptic protein SNAP25, phosphorylated neurofilament and degraded myelin basic protein complex (dMBP) using enzyme linked immunosorbent assays (ELISA).

Results: SNAP25 expression was 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 levels were significantly increased in the white matter of females with ADD compare to their ND control counterpart ($p < 0.05$). Phosphorylated neurofilament 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.

Conclusions: These data together suggest that gender differences in ADD brain weight loss might be largely due to differential presynaptic terminal loss rather than whole neuronal and/or axonal loss. It also indicates that, as compared with males with ADD, females with ADD might not only progress more often to more severe neurofibrillary degeneration than males but might also be more susceptible to presynaptic terminal loss than males with similar levels of pathology.

Poster 70

MITOCHONDRIAL HAPLOGROUP IN COMBINATION WITH APOE GENOTYPE AS POTENTIAL PREDICTIVE BIOMARKER TO IDENTIFY RESPONDERS TO REGENERATIVE THERAPEUTIC ALLOPREGNANOLONE FOR ALZHEIMER'S DISEASE. Wang Y, Solinsky C, Hernandez G, Schneider L, Brinton RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.

Background: Late onset Alzheimer's disease (LOAD) is a systemic disease with multiple etiologies and is associated with compromised brain metabolism and regenerative capacity. Allopregnanolone has been shown to promote brain mitochondrial function, neurogenesis, and memory in mouse models, and is currently being investigated as a regenerative therapeutic for AD (NCT02221622). While genetic markers such as APOE genotype predict risk of AD, there is currently no genetic markers to predict therapeutic outcomes for AD. Because mitochondrial genetic variances and APOE genotype are known to be differentially associated with respiratory capacity and cell proliferation, in this study, we evaluate whether they can be used as potential genetic markers to predict responders for Alzheimer's disease therapeutics.

Methods: T-cells from allopregnanolone clinical trial participants were reprogrammed to iPSCs via a non-integrating, non-viral method, and then differentiated into NSCs using dual inhibition of SMAD signaling. Mitochondrial respiration and regenerative capacity were determined by metabolic analyzer and FACS. To determine mitochondrial haplogroups of the participants, DNA was extracted from whole blood of the participants, and Hypervariable region 1 and 2 of mitochondrial DNA were amplified, sequenced, and aligned to the Revised Cambridge Reference Sequence. Mitochondrial haplogroup was assigned using HaploGrep2 based on identified variants.

Results: Preliminary analysis revealed that allopregnanolone treatment preferentially increased maximum respiration in NSCs derived from participants of mitochondrial haplogroups M2, M8 and N9 compared to those from haplogroups H, HV, and J. Regardless of mitochondrial haplotype, allopregnanolone induced greater mitochondrial respiration in NSCs derived from APOE 3/4 participants relative to NSCs derived from APOE 3/3 participants. Further, NSCs derived from male APOE4 carriers exhibited significantly different proliferation patterns relative to non-APOE4 carriers following allopregnanolone treatment. Ongoing analyses will determine whether mitochondrial haplotype in combination with APOE genotype can serve as predictive biomarkers of response to allopregnanolone.

Conclusions: Mitochondrial haplotype in combination with APOE genotype is a promising predictive biomarker approach to identify potential allopregnanolone responders. Predictive biomarkers will significantly contribute to a precision medicine strategy to identify responders to therapeutic agents for Alzheimer's disease.

Poster 71

HOW DOES APOLIPOPROTEIN E REGULATE ENERGY METABOLISM IN ALZHEIMER'S DISEASE? Yin J, Reiman EM, Nielsen M, Carcione T, Beach TG, Caselli RJ, Shi J. Barrow Neurological Institute; Banner Alzheimer's Institute; University of Arizona; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Carriers of the apolipoprotein E (APOE) $\epsilon 4$ allele have a pattern of Alzheimer's disease (AD)-related cerebral hypometabolism that begins prior to the onset of cognitive impairment. Sirtuin 3 (SIRT3) plays an important role in energy metabolism, but the link between APOE variants and SIRT3 is unknown.

Methods: We characterized and correlated regional SIRT3 and peroxisome proliferator-activated receptor-gamma coactivator-1 α (PGC-1 α) in human brain samples and in 12-month-old transgenic mice with homozygous human APOE $\epsilon 4$ and $\epsilon 3$ alleles.

Results: SIRT3 and PGC-1 α levels were significantly lower in APOE $\epsilon 4$ carriers. Learning and memory, synaptic proteins, the NAD⁺/ NADH ratios, and ATP production were significantly lower in the APOE $\epsilon 4$ transgenic mice. SIRT3 knockdown reduced the oxygen consumption rate and ATP production; SIRT3 overexpression increased them.

Conclusions: Our findings suggest that SIRT3 contributes to neuronal energy metabolism, that reduced SIRT3 levels preferentially contribute to reduced neuronal metabolism in APOE $\epsilon 4$ carriers.

Poster 72

MEMBRANE-MEDIATED MECHANISMS OF NEUROTOXICITY INDUCED BY MIXTURES OF AMYLOIDOGENIC PROTEINS IN NEURODEGENERATIVE DISEASES. Younger S, Johnson NM, Downs CA, Morrison HW, Yuan JX-J, Saavedra SS, Arce FT. University of Arizona; Arizona Alzheimer's Consortium.

Background: The presence of Lewy body pathology in Alzheimer's disease (AD) is associated with a more aggressive disease course and accelerated cognitive dysfunction. A β plaques themselves are composed of various A β species. The increased neurotoxicity of heterotypic A β (1-42)/A β (pE3-42) oligomers and the enhanced pathology associated with oligomers of mixed A β / β -syn composition suggest the presence of synergistic interactions among different peptides. Increasing evidence suggests that A β oligomers form pore structures that permeabilize the membrane, causing an abrupt change in cell ionic concentration that is toxic.

Methods: Planar Lipid Bilayer Electrophysiology, Atomic Force Microscopy, Cell Culture Cytotoxicity, Cell Electrophysiology, Molecular Dynamics Simulations, Fluorescence Resonance Energy Transfer (FRET), Attenuated Total Reflection (ATR) and Acute Brain Slice Cytotoxicity.

Results: Our cytotoxicity results using mice hippocampal neurons show that A β pE3-42 oligomers incubated for 24 hours at 37C are more cytotoxic than A β (1-42) similarly treated oligomers. Significantly, and a mixture of 5% A β (pE3-42) and 95% A β (1-42) incubated together is even more cytotoxic than either amyloid individually and other A β (1-42)/A β (pE3-42) combinations. Our previous planar lipid bilayer electrophysiology results showed unincubated A β (1-42) pores have lower activity than A β (pE3-42). Our current preliminary work shows incubated A β (pE3-42) has lower activity but significantly higher conductance than similarly incubated A β (1-42).

Conclusions: Our preliminary results suggest that the higher A β pE3-42-induced neurotoxicity compared to A β 1-42 can be correlated to its increased pore conductance. Most of the previous biophysical studies have not addressed the synergistic effects of heterotypic oligomers. Our future studies will attempt to fill this knowledge gap by using an integrated set of experimental and computational approaches to correlate the neurotoxicity induced by heterotypic oligomers in different brain regions to biophysical mechanisms of membrane-mediated cytotoxicity.

Poster 73

FEASIBILITY OF QUANTIFYING AMYLOID BURDEN USING VOLUMETRIC MRI DATA: PRELIMINARY FINDINGS BASED ON THE DEEP LEARNING 3D CONVOLUTIONAL NEURAL NETWORK APPROACH. Yuan Y, Wang Z, Lee W, Thiyyagura P, Reiman EM, Chen K. Texas A&M University; Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Amyloid positron emission tomography (PET) technique has been used to image beta-amyloid (A-beta) for studies of AD. The standard uptake value ratio (SUVR) between a pre-specified mean-cortical target region and the cerebellum (or other) reference region over the amyloid PET image is routinely used as a measure of A-beta burden in the brain. On the other hand, the volumetric magnetic resonance imaging (vMRI) with information on the structural damage presumably caused by the A-beta accumulation could be potentially used to assess A-beta burden. This study examined the feasibility of using 3D convolutional neural network (3D-CNN) to estimate SUVR and to determine A-beta positivity based on only vMRI data.

Methods: vMRI data from 1072 ADNI subjects (178 AD patients, 525 MCI patients and 369 cognitively unimpaired [CU] individuals) were used (sample size for training/validation/test were 863/99/110) together with the SUVR values obtained from florbetapir PET. vMRI data were first spatially normalized. We designed the 3D-CNN structure, consisting of two convolutional layers (each followed by a max pooling layer), and two fully connected layers with the mean-square-error loss on top. To overcome data limitations (small size and noisy quality), we used (1) a denoising auto-encoder to pre-train the 3D-CNN layer-wise; and (2) batch normalization to stabilize training. The 3D-CNN estimated SUVR values were subsequently used to define amyloid positivity with a threshold previously defined (Fleisher, et al., 2011).

Results: Between 3D-CNN estimated SUVR estimation and the original SUVR, we achieve a mean absolute difference of 0.166 (std=0.111). The correlation between original SUVR and 3D-CNN estimated SUVR is 0.44 ($p=1.7e-6$). Using the traditional method as the current standard of truth, the deep learning method distinguished between positive and negative amyloid scans (i.e., florbetapir SUVR greater than or equal to 1.18) with 75% sensitivity, 70% specificity and 73% accuracy.

Conclusions: Treating our findings as preliminary, our deep-learning 3D-CNN based results pointed out the potential to provide reasonably accurate amyloid positivity from vMRI data. Additional studies are needed to improve the SUVR estimation from vMRI alone or via integrating other information into 3D-CNN and to explore the feasibility of directly using individual native-space vMRI data.

Poster 74

QUANTIFICATION OF AMYLOID BURDEN FROM FLORBETAPIR PET IMAGES WITHOUT USING TARGET AND REFERENCE REGIONS: PRELIMINARY FINDINGS BASED ON THE DEEP LEARNING 3D CONVOLUTIONAL NEURAL NETWORK APPROACH. Yuan Y, Wang Z, Lee W, VanGilder P, Chen Y, Reiman EM, Chen K. Texas A&M University; Arizona State University; Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Beta-amyloid (A-beta) is widely viewed as a major hallmark of Alzheimer's disease (AD) pathology. Standard uptake value ratio (SUVr) between a pre-specified target mean-cortical region and the cerebellum (or another) reference region is the most commonly used measurement to quantify A-beta burden for amyloid positron emission tomography (PET) technique. By utilizing a 3D convolutional neural network (3D-CNN), we examined the feasibility of estimating SUVr and determining A-beta positivity from florbetapir PET images directly without defining the target and reference regions and without extracting data from them.

Methods: Florbetapir PET data from 1072 subjects (178 AD patients, 525 MCI patients and 369 cognitively unimpaired [CU] individuals) from Alzheimer's Disease Neuroimage Initiative (ADNI) were used for this analysis. Florbetapir PET data were first spatially normalized to MNI template space. We designed the Deep Learning 3D-CNN, consisting of two convolutional layers (each followed by a max pooling layer), and two fully connected layers with the mean-square-error (MSE) loss on top. To overcome data limitations (small size and noisy quality), we use (1) a denoising auto-encoder to pre-train the 3D-CNN layer-wise; and (2) batch normalization to stabilize training. The estimated SUVr values from the 3D-CNN were subsequently used to define amyloid positivity using a previously defined threshold (Fleisher, et al., 2011).

Results: For florbetapir PET-based SUVr estimation, we achieve a mean absolute difference of 0.035, the correlation between original SUVr vs 3D-CNN estimated SUVr is 0.97 ($p=2.2e-16$). Using the traditional method as the current standard of truth, the deep learning method distinguished between positive and negative amyloid scans (i.e., florbetapir SUVr greater than or equal to 1.18) with 92% sensitivity, 98% specificity and 95% accuracy.

Conclusions: Although preliminary, our deep-learning 3D-CNN based results point out the potential to produce highly accurately SUVr from entire PET images directly without extracting data from mean-cortical and the cerebellar reference region. Additional studies are being undertaken to improve SUVr estimates and explore the feasibility of directly using native space imaging data.

Poster 75

CORRELATIONS BETWEEN REY AUDITORY VERBAL LEARNING TEST (AVLT) AND UPPER EXTREMITY DUAL TASK FUNCTION IN DETECTING COGNITIVE IMPAIRMENT. Zamrini E, Fakhoury S, Gaytan-Jenkins D, Lopez A, Ehsani H, Belden C, O'Connor K, Mohler J, Toosizadeh N. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Some worried well progress to mild cognitive impairment, while others do not. The Rey Auditory Verbal Learning Test (AVLT) is sensitive to early changes in cognition and might be useful as an early indicator of increased risk of progression. We have recently developed a novel dual-task test for cognition assessment, which incorporates sensor-based upper-extremity function (UEF) while counting backwards. The objective was to examine the association between UEF and AVLT as a screening tool for detecting early changes in cognition.

Methods: Older adults (≤ 65 years) with clinically confirmed normal cognition were recruited. Participants completed two trials of dual-task UEF (20-second rapid and 60-second self-paced), while counting backward by ones. UEF elbow angular velocity was measured using gyroscopes attached to the wrist and upper-arm. The Rey AVLT was administered measuring short- and long-term auditory-verbal memory including total learning, short and long delay recall and recognition. The UEF outcomes were elbow motion variability (pauses/delays) in motor task execution and elbow flexion overall speed. These parameters were selected to assess accuracy and speed of motor function, respectively. Pearson correlations and regression models were used to assess the association between UEF outcomes and AVLT measures.

Results: Twenty-nine participants were recruited (age= 83.3 ± 6.7 years; BMI= 25.2 ± 5.8 kg/m²; 37% male). Significant positive correlations were observed between flexion speed with AVLT short-term memory (STM) and AVLT long-term memory (LTM) scores for both normal and rapid elbow flexion ($p < 0.01$, $r = 0.56-0.62$). For motion variability, significant correlation was observed only between UEF variability in the normal speed condition and AVLT-LTM ($p = 0.02$, $r = -0.50$). Combining two UEF parameters in regression models for predicting AVLT scores, we observed a significant association between UEF models with AVLT-STM and AVLT-LTM scores for both normal and rapid tasks ($p < 0.02$, $r = 0.53-0.71$).

Conclusions: In cognitively normal older adults, the UEF normal and rapid elbow flexion speed significantly correlated with the AVLT STM and AVLT LTM while UEF motion variability in the normal speed condition correlated with AVLT LTM, suggesting a potential role for UEF tasks in enhancing assessment of early cognitive decline. Further research on the role of UEF as a rapid screen for early cognitive impairment is recommended.

Student Poster Presentations

Poster 76

CLINICAL REASONING: A 75-YEAR-OLD WOMAN WITH RAPIDLY PROGRESSIVE DEMENTIA. Aslam S, Fritz M, Sabbagh M. Barrow Neurological Institute; Earlham College; St. Joseph's Hospital and Medical Center; Arizona Alzheimer's Consortium.

Background: Creutzfeldt-Jakob Disease (CJD) affects 1 per million worldwide annually, with 90% of afflicted patients dying within a year of symptom onset. However, many are left unaware of their condition due to clinical similarity to Alzheimer's Disease until rapid degradation of mental faculty presents, along with the host of accompanying symptoms. Even if the medical provider has suspicion of CJD, the three most commonly used methods of diagnosis are often inadequate, many studies having displayed low sensitivity in cerebrospinal fluid (CSF), MRI, and EEG testing, leaving brain biopsy as the only definitive diagnostic tool—a tool many are wary of due to its invasive nature. One study, published in 2003, found among 32 patients with verified CJD a yield of only 53% sensitivity by means of 14-3-3 protein testing. Another study, trying to outline clinical stages of progression in CJD, found a sensitivity of around 30% for EEG in 36 patients. Another case report describes a classic CJD patient who was negative for 14-3-3 testing, EEG spikes, and MRI abnormalities. Finally, a recent study found that out of 77 patients with CJD, EEG abnormalities were found in only 15 and 14-3-3 protein tests were positive in only half the patients. Here, we describe the case of a woman who presents with clinical symptoms suggestive of CJD, yet tested negative for 14-3-3 proteins, lacked EEG characteristic patterns, and had an MRI which lacked cortical ribboning, and whose diagnosis was only verified by brain biopsy.

Methods: We report a 75 year-old woman with an atypical case of CJD. We also provide an in-depth analysis of the current literature on the specificity and sensitivity of the current diagnostic tools used to confirm CJD, namely CSF, EEG, and MRI, and look at alternative methods of diagnosis.

Results: Serial MRIs failed to show cortical ribboning, serial EEGs did not show 1hz periodic waves, and CSF did not show 14-3-3 protein. With conflicting data, a brain biopsy was obtained which confirmed a diagnosis of CJD.

Conclusions: Considering the inadequate sensitivities of prior testing methods, real-time quaking-induced conversion (RT-QuIC) seems the most promising mode for future diagnosis of CJD. With a sensitivity of 96% and specificity of 100% from CSF, and the comparatively noninvasive and antemortem nature of the test—especially compared to brain biopsy—RT-QuIC should be the diagnostic tool of choice for rapidly-progressing encephalopathies to rule out CJD.

Poster 77

S6K1 ACTIVITY: ROLE AND IMPLICATIONS IN AD BRAINS. Belfiore R, Caccamo A, Oddo S. Arizona State University; University of Catania; Arizona Alzheimer's Institute.

Background: Aging is the most prominent risk factor for Alzheimer's disease (AD), the most common form of dementia. The ribosomal protein S6 kinase 1 (S6K1), a ubiquitously expressed enzyme, plays a key role in aging as it regulates protein translation and cell homeostatic systems. For example, deletion of the S6K1 gene in mice is sufficient to increase lifespan and decrease the incidence of age-dependent motor deficits, insulin resistance, and obesity. As S6K1 activity regulates aging and age-related diseases, in this study we assess to describe whether S6K1 plays a role in AD pathogenesis.

Methods: We used postmortem human AD brains and clinical data to probe for a link between S6K1 and AD pathogenesis. We also bred 3xTg-AD mice with S6K1 knockout mice to reduce the expression of S6K1. Using a multidisciplinary approach, we have collected data from aged NonTg, 3xTg-AD, and 3xTg-AD/S6K1^{+/-} mice brains.

Results: Our findings show that higher S6K1 activity correlates with increased A β levels and decreased Mini Mental State Examination (MMSE) scores in AD patients. Next, we found that reducing S6K1 levels also reduces A β and Tau pathology in 3xTg-AD/S6K1^{+/-} mice, improves spatial learning and memory deficits as well as rescues synaptic deficits. Moreover, our preliminary data show that cognitive improvements in 3xTg-AD/S6K1^{+/-} mice are linked to a decreased phosphorylation of his downstream targets, rpS6 and eEF2K proteins.

Conclusions: Our results are extremely exciting as implicate S6K1 dysregulation as a previously unidentified molecular mechanism underlying synaptic and cognitive deficits in AD. For instance, we showed that S6K1 reduction modulates specific proteins as eEF2K that regulate translation of mRNAs involved in cognition. These finding further suggest that targeting the S6K1/EF2K pathway could be a novel approach to mitigate AD pathology.

Poster 78

MULTIMODAL NEUROIMAGING REVEALS WHITE MATTER MICROSTRUCTURE RELATED COVARIANCE NETWORKS OF SUBCORTICAL GRAY MATTER VOLUMES IN HEALTHY AGING. Bharadwaj PK, Fitzhugh MC, Nguyen LA, Haws KA, Hishaw GA, Trouard TP, Moeller JR, Habeck CG, Alexander GE. University of Arizona; Columbia University; Columbia University Medical Center; Arizona Alzheimer's Consortium.

Background: Healthy aging preferentially affects selected gray matter (GM) and white matter (WM) brain regions and has been widely studied using univariate analysis methods. Multivariate network analysis of multimodal magnetic resonance imaging (MRI) data potentially improve regional characterization of age-related differences by combining information from complementary imaging modalities. Here we use this framework to investigate how differences in global WM microstructural integrity relate to regional network covariance of subcortical grey matter (SGM) volumes, including the hippocampus, amygdala, thalamus, pallidum, putamen, caudate and nucleus accumbens, and further assess how this pattern is related to age and regional white matter hyperintensity (WMH) load.

Methods: T1-weighted volumetric, diffusion weighted imaging (DWI), and T2 FLAIR 3T MRI scans were obtained in 196 healthy community dwelling older adults, 50 - 89 years of age (mean \pm sd age = 69.8 ± 10.6 ; 95F/101M). Freesurfer v5.3 was used for segmenting T1 scans and extracting SGM volumes. DWI scans were processed with TRACULA and global fractional anisotropy (FA) and mean diffusivity (MD) were computed as the average of 18 major WM tracts. WMH maps were produced by automated multispectral segmentation using SPM12's Lesion Segmentation Toolbox. A lobar atlas template was used to obtain regional WMH volumes from the four major lobes. The Scaled Subprofile Model was applied to the SGM volumes to derive their regional covariance networks in relation to global mean FA and MD.

Results: The FA-related SGM network pattern accounted for 9.8% of the variance in FA, included relative reductions in bilateral thalamus with preservation of the right caudate, but was not related to age ($p = 0.73$). The MD-related SGM network pattern accounted for 18.6% of the variance in MD, exhibited volume reductions bilaterally in hippocampus and putamen with relative preservation of left caudate and right pallidum, and was positively related to age ($r^2 = 0.29$, $p = 1.1E-16$). After adjusting for age, gender, years of education and hypertension status, the FA-SGM pattern was not related to regional WMH (FDR $p > 0.12$), while the MD-SGM pattern was positively related to WMH load in the frontal ($r^2 = 0.071$, FDR $p = 6.8E-4$), temporal ($r^2 = 0.06$, FDR $p = 1.0E-3$) and parietal ($r^2 = 0.04$, FDR $p = 7.0E-3$) lobes.

Conclusions: Together, these findings demonstrate the regionally varying impacts of differential aspects of WM integrity on subcortical GM in the context of healthy aging, providing further support for using multimodal, multivariate network analyses to more fully characterize the regionally distributed effects of brain aging.

Poster 79

USING HUMAN INDUCED PLURIPOTENT STEM CELLS TO INVESTIGATE THE CONTRIBUTION OF APOE RISK VARIANTS AND AGING TO THE ONSET AND PROGRESSION OF ALZHEIMER'S DISEASE. Brookhouser N, Brafman, DA. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: Developing therapies for the treatment of Alzheimer's disease (AD) requires an understanding of the mechanisms that cause the disease. Animal models of AD have provided important insights but do not display important AD-related pathologies and have not been useful in modeling the complex genetics associated with "sporadic" AD. Although the majority of AD patients are sporadic, multiple genetic risk variants have been identified, the most powerful and prevalent of which is the E4 variant of Apolipoprotein E (ApoE) gene. Compared to individuals with an ApoE 3/3 genotype, heterozygosity for the E4 allele increases AD risk by 3-fold, and homozygosity for the E4 allele increases risk up to 12 fold. Amyloid-dependent and -independent mechanisms have been postulated to explain the ApoE4 effect, but currently how ApoE4 modulates AD disease risk, especially during aging, remains unclear.

Methods: In collaboration with Dr. Richard Caselli (Mayo Clinic-Arizona), I have generated a pool of hiPSC lines from non-demented control (NDC) and sporadic AD (SAD) patients with various ApoE genotypes. Using these hiPSC lines, I have worked to adapt previously published cortical differentiation protocols developed in the Brafman laboratory as well as astrocyte differentiation protocols to establish 3-D cortical neuronal cultures as well as defined 3-D astrocyte-neuron co-cultures due to critical role that astrocytes play in mediating the ApoE-dependent effects of AD onset and progression. Further, I am currently adapting recently published CRIPSR/Cas9-based 'base-editing' (BE) technologies to modify the ApoE locus in hiPSCs to create isogenic hiPSC lines of varying ApoE genotypes.

Results: NDC and SAD hiPSCs display pluripotent morphology, express pluripotency markers (SOX2, OCT4, NANOG, SSEA-4), exhibit trilineage differentiation potential, and maintain a euploid karyotype. Analysis of 3-D cortical cultures at D50 revealed upregulation of mature neuronal and cortical markers. Analysis of D50+ hiPSC-derived astrocytes revealed highly pure GFAP+S100 β cultures. In addition, these astrocytes robustly produce and secrete ApoE and respond to inflammatory stimulants. Gene expression analysis of 3-D co-cultures revealed the expression of pan-neuronal markers and cortical markers were expressed at levels proportional to the number of neurons present suggesting an accessible system for controlling astrocyte:neuron ratios within the co-cultures. Finally, I have validated C => T base editing at the ApoE locus as well as other chromosomal targets in 293T cells and at the ApoE locus in hiPSCs.

Conclusions: By using a novel 3-D cortical neuronal culture model and genome-wide expression analysis (RNA-seq), we are identifying unique gene expression profiles that are independently defined by ApoE genotype, disease status, and age. Future bioinformatic analysis will reveal candidate genetic, biochemical, and signaling pathways that will provide more definitive relationships between ApoE genotype and AD onset and progression. In the future, we will investigate how modulation of these candidate target genes and pathways regulates the manifestation of AD-related phenotypes. Such future investigations will have significant impact on the design of molecularly targeted therapeutics to treat AD.

Poster 80

AGE-ASSOCIATED CHANGES IN AWAKE HIPPOCAMPAL SHARP-WAVE RIPPLES DURING SPATIAL EYEBLINK CONDITIONING. Cowen SL, Gray DT, Wiegand JL, Schimanski LA, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Sharp-wave ripples are brief (~70 ms) high-frequency oscillatory events that are generated in the hippocampus. Ripples that occur during rest periods following a learning experience are believed to support memory consolidation. Normal aging reduces the rate of occurrence of ripple events and reduces the oscillatory frequency of ripples during rest (Wiegand et al., 2016). Although ripples during rest have been implicated in memory consolidation, waking ripples also be involved in short-term planning and memory recall. It is unknown how normal aging alters features of waking ripples. Accordingly, we investigated whether characteristics of waking ripple oscillations and associated single-unit activity undergo age-dependent changes in rats.

Methods: Local-field and single-unit activity were recorded from the CA1 region of the hippocampus. Sharp-wave ripple events were examined in old (n = 5) and young (n = 6) F344 male rats as they performed a place-dependent eyeblink conditioning task.

Results: Comparisons between ripples occurring during rest and waking behavior and between aged and young animals revealed two effects. First, although ripples in aged rats had a significantly lower oscillatory frequency relative to young rats during rest ($p < 0.01$, t-test, n aged = 5, n young = 6), there was no difference between aged and young rats on this measure during behavior ($p = 0.83$). Second, the modulation of principal neuron firing activity by waking ripples was reduced in aged animals when compared to young rats (aged: n = 233 neurons, young: n = 167 neurons, Wilcoxon rank sum test, $p < 0.001$). Modulation was measured as the difference between the mean firing rate during the ripple compared to the mean firing rate during 100 ms intervals that preceded and followed each ripple (+/- 350 to 450 ms). Even though ripple oscillatory frequency was normalized in aged rats during behavior, modulation of single cell activity within a ripple was reduced.

Conclusions: Given the involvement of waking ripples in memory recall, these changes in the dynamics of waking ripples could contribute to age-associated memory loss.

Poster 81

INVESTIGATING THE MECHANISMS OF A MULTI-STATE MODEL OF WNT SIGNALING. Cutts J, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: The WNT signaling pathway plays a critical role in many developmental processes as well as the maintenance of tissue homeostasis in adults. In addition, dysfunction in WNT signaling results in numerous human diseases. Canonical WNT signaling is classically described by the 'two-state' model. This model posits that in the 'off' state in the absence of a WNT ligand, cytoplasmic β -catenin is continuously degraded by the action of the APC/Axin/GSK-3 β destruction complex. In the 'on' state in the presence of WNT ligands, this protein destruction complex is disrupted, allowing β -catenin to translocate into the nucleus where it interacts with the DNA-bound TCF/LEF proteins to regulate target gene expression. However, this 'two-state' model does not adequately explain the mechanisms by which WNT signaling can elicit distinct patterns of target gene expression and cell responses at specific signaling thresholds. For example, in the development and patterning of many tissues, the WNT pathway attains different levels of activity through gradients of WNT signaling activity. In turn, the positional information supplied by these WNT signaling gradients produces the appropriate spatial pattern of cellular differentiation. Elucidating the mechanisms of how a graded WNT signal leads to precise changes in transcriptional responses has been difficult because the lack of an in vitro model where WNT signaling molecules cause distinct cellular phenotypes at different concentrations.

Methods: We have developed an in vitro human pluripotent stem cell (hPSC)-based model that recapitulates the same in vivo developmental effects of the WNT signaling gradient on the anterior-posterior (A/P) patterning of the neural tube during early development. By precisely manipulating the amount of WNT signaling hPSCs receive during neural differentiation we are able to generate forebrain, midbrain, and hindbrain neural progenitor cells (NPCs) and neurons.

Results: Using this model along with genome-wide expression analysis (RNA-seq) and DNA binding analysis (ChIP-seq), we are uncovering the mechanisms by which specific levels of WNT activity translate into precise transcriptional responses and cell identities.

Conclusions: Overall, the new insights gained from this research will lead to the better understanding of how various WNT pathway activity levels lead to cancer or other pathological conditions. In addition, findings will enable the understanding of transcriptional regulation of the specification of regionalized neurons, which will facilitate study of potential pathogenic roles in the development of neurodegenerative diseases.

Poster 82

ADVANCED TECHNIQUES IN DIFFUSION MR IMAGE ANALYSIS FOR CHARACTERIZING NEUROLOGICAL CHANGES WITH AGE. Do L, Bernstein A, Bharadwaj P, Lindley M, Wheeler G, Alexander G, Barnes C, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Background: Diffusion magnetic resonance imaging (DMRI) has the potential to characterize neurological processes, such as healthy cognitive aging. Rodent models are important tools for seminal investigations of such processes, however methods designed for analysis of human DMRI data have not been well translated to rodents. The purpose of this study is to use a variety of methods to preprocess rodent brain imaging to remove distortions, eddy currents and other artifacts that are created when acquiring data with single shot EPI DMRI sequences.

Methods: Fisher 344 rats (n=12) underwent 3D T2-weighted RARE (150 micron isotropic) and 64 direction diffusion weighted single shot echo planar imaging sequence at $b=1000, 2000, \text{ and } 3000 \text{ s/mm}^2$, and a resolution matched T2 weighted anatomical reference on a 7T Bruker Biospec MRI scanner. DMRI data were semi-automatically brain extracted with ITKsnap and MRICron, bias field corrected with N4ITK implemented in ANTs, EPI distortion corrected using TORTOISE (NIH), eddy current distortion correction with EDDY within FSL and de-noised with local principal component analysis (PCI) in MATLAB. Diffusion tensors were estimated using a weighted linear least squares fit of the data and derived scalar maps including fractional anisotropy, mean diffusivity and return to origin probability were computed with MRTrix.

Results: Manual brain extraction of the 3D RARE images took 4 ± 1 hours whereas the semi-automated method took 4 ± 0.5 min. Manual brain extraction of the T2 sequences took 20 ± 10 min whereas automated method took 4 ± 4 min. The combination of TORTOISE, EDDY and Matlab PCI took 8 ± 1 hrs per animal to correct for the artifacts and the corrected DMRI images showed marked improvement compared with other software such as FSL. 3D RARE image comparisons showed dice coefficients (DC) that were better between manual and semi-automated methods revealed that after bias correction, the semi-automated method was indeed much more in line with manual brain extraction. Applying non-parametric Wilcoxon Signed Rank Test revealed significance between the DCs (Z-score = -2.366, $p = 0.018$). Eddy current correction and TORTOISE effectively eliminated distortions between DMRI scans but failed to completely remove the signal pile up artifact at the brain sinus junction.

Conclusions: Results show semi-automated brain extraction in both 3D RARE and resolution matched T2 anatomical reference images are similar in accuracy with the manual brain extraction with a significant reduction in analysis time. Furthermore, distortion correction, eddy current corrections, and noise reduction in bias corrected images show marked improvement in image quality in DMRI images. Further testing is needed with a larger sample size and testing with and without reverse phase encoding sequence for improvement of pile up artifact in TORTOISE by registering the images to a T2 anatomical space. Performing a bias field correction prior to semi-automated brain extraction maintained accuracy and also reduces time to completion in T2-weighted 3D RARE data and low resolution T2-weighted in plane resolution matched data. Preprocessing of DMRI data show that TORTOISE, EDDY and Matlab PCI should be implemented for rat brain data to minimize distortions resulting from the collection scheme but hopefully methods of reducing processing time can be implemented in the future.

Poster 83

DYNAMIC EXPRESSION OF RNA STRESS GRANULE COMPONENTS IN AGING BRAINS: FROM FLIES TO RATS. Eck R, Siddegowda B, Chawla MK, Yao S, Barnes CA, Zarnescu DC. University of Arizona; Arizona Alzheimer's Consortium.

Background: RNA stress granules are dynamic cytoplasmic structures that assemble in response to various cellular insults. In the process, these non-membrane bound organelles sequester specific mRNAs causing inhibition of translation initiation, with the goal of protecting the cell from spending precious resources during times of stress. Upon stress removal, RNA stress granules disassemble and translation is reinitiated. These dynamic changes in RNA stress granules have been linked mechanistically to age-related neurodegenerative diseases suggesting that they be playing key roles in the aging process. Despite some existing reports that translation inhibition changes with aging, it remains unclear whether RNA stress granules are undergoing dynamic changes as organisms grow older.

Methods: To shed light on this question, we began by profiling the expression of RNA binding proteins associated with RNA stress granules including TIAR, PABP, FMRP, Gcn2 as well as the translation initiation factor eIF2alpha in aging fly and rat brains.

Results: Analyses of both transcript and protein expression of these RNA stress granule/translation initiation markers indicate dynamic changes in aging fly and rat brains. While Gcn2 and phospho-eIF2alpha expression decline, there is an increase in TIAR levels with age. In addition, the expression of TAR DNA binding protein (TDP-43), a key RNA binding protein implicated in neurodegeneration exhibits a reduction in expression in both fly and rat brains, during aging.

Conclusions: These findings support the hypothesis that RNA stress granules undergo dynamic changes during aging. Current experiments including polysome fractionations and expression profiling are aimed at elucidating the role of cellular stress responses in aging brains from the perspective of RNA stress granules.

Poster 84

FUNCTIONAL CONNECTIVITY CHANGES AND HEARING LOSS IN OLDER ADULTS. Fitzhugh MC, Baxter LC, Rogalsky C. Arizona State University; Barrow Neurological Institute & St. Joseph's Medical Center; Arizona Alzheimer's Consortium.

Background: Approximately one third of adults over the age of 60 experience a hearing loss (HL), with this number doubling in individuals 70 years and older (Lin et al., 2011). Central hearing loss in older adults has been linked to an increased risk for cognitive decline and dementia (Loughrey et al., 2017), declines in speech comprehension, and decreases in quality of life (Bainbridge and Wallhagen, 2014). Despite these findings, few aging studies measure hearing levels and consider their role in cognitive aging. The few studies that have investigated neural changes associated with HL report structural declines and reduced activity in auditory regions, and increased activation in frontal and parietal regions (Cardin, 2016). One previous study that investigated functional connectivity (FC) and hearing loss focused on the dorsal attention and default mode networks, finding decreases in FC between the dorsal attention network, left insula, and postcentral gyrus, and FC increases between the default mode network and left middle frontal gyrus (Husain et al., 2014). The present study examined the effects of hearing loss on brain FC across and within several well-characterized, stable brain networks and primary auditory cortex (Heschl's gyrus) in a cohort of older adults.

Methods: Sixteen adults aged 60 to 80 years (mean(sd)=69.75(6.78) years; 12 female; mean(sd) education=16.84(2.28) years) were recruited from the community. Participants were all native English-speaking, right-handed, and cognitively intact (MMSE mean(sd)=28.63(1.17)). Pure tone audiometry was obtained for each participant over test frequencies 125, 500, 1, 2, 4, and 8 kHz (mean(sd) threshold over both ears=26.25(9.31) dB, min=15 dB, max=45.83 dB). A 10-minute resting-state fMRI using the ADNI 3 protocol was obtained on a Phillips Ingenia 3T scanner. The data were preprocessed in the CONN Toolbox using SPM12 functions. CONN's default seed regions for the Language, Frontoparietal, Dorsal Attention, Salience, and Default Mode networks and bilateral Heschl's gyri were selected. FC between seeds was correlated with participant hearing level, controlling for age with a $p < .05$ FDR-corrected significance threshold applied.

Results: Participants' hearing abilities ranged from normal hearing to moderate HL. Significant decreases in intra-network FC were observed within the Language network. Inter-network connectivity decreases were also observed between the anterior cingulate in the Salience network and the posterior cingulate and lateral parietal region of the Default Mode network. The anterior cingulate also exhibited FC decreases with the superior parietal region of the Frontoparietal network and the left posterior temporal region of the Language network. Additional decreases in FC correlated with HL were found between portions of the Dorsal Attention network and the Language and Salience networks. No FC differences were observed between left or right Heschl's gyrus and any of the networks investigated.

Conclusions: We examined FC between and within brain networks critical to social and cognitive functions in a cohort of healthy older adults. We found FC decreases associated with HL in all networks but not in primary auditory regions. Since hearing loss is linked to cognitive decline, this work demonstrates the importance of considering and/or directly studying the effect that HL has on functional brain changes with age. Future studies are needed to explore the causal relationship between HL and FC within and between brain networks and how this benefit hearing and cognitive interventions.

Poster 85

RELATION OF PHYSICAL SPORT ACTIVITY TO REGIONAL WHITE MATTER INTEGRITY IN OLDER ADULTS. Franchetti MK, Bharadwaj PK, Nguyen LA, Klimentidis YC, Haws KA, Fitzhugh MC, Hishaw GA, Trouard TP, Raichlen DA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Physical activity (PA) have an important role in maintaining cerebral white matter (WM) integrity in healthy aging. We sought to determine whether high levels of self-reported physical sport activity are associated with better WM integrity.

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). T1 and diffusion weighted 3T MRIs were processed using Freesurfer v5.3 and TRACULA for tractography to compute fractional anisotropy (FA) and mean (MD), radial (RD), and axial (AD) diffusivity for 18 WM tracts. ANCOVA tested age group (young-old group (YO) = 50-69 years; old-old group (OO) = 70-89 years), PA group, and interaction effects after controlling for hypertension status.

Results: No main effects for PA group (p 's > 0.05) were observed across all four diffusion metrics. For FA, results revealed main effects for age group for four WM tracts (0.001, p , ≤ 0.034) such that, for three tracts, the OO had lower values. All age group effects for MD, RD, and AD revealed that the OO had higher diffusion than the YO. For MD, we found age effects for all but one bilateral WM tract ($6.3E-6$, p , ≤ 0.036). For RD, we found age effects for all but one bilateral and two individual WM tracts (0.001, p , ≤ 0.035). For AD, effects for all but one bilateral and three individual WM tracts ($7.9E-8$, p , ≤ 0.043) were observed. We found an age by PA interaction in one tract for FA, the left inferior longitudinal fasciculus (ILF; $p = 0.012$). An interaction was observed for the same tract (left ILF) for MD ($p = 0.006$) and RD ($p = 0.002$). Interactions were observed for the same two tracts, the superior longitudinal fasciculus-parietal (SLFP) and temporal (SLFT) bundles, bilaterally for MD (0.011, p , ≤ 0.02) and RD (0.012, p , ≤ 0.038). For AD, interactions were observed for bilateral SLFP (0.022, p , ≤ 0.049) and in left tracts of SLFT ($p = 0.028$). An interaction was observed for the right cingulum cingulate gyrus (CCG) for MD ($p = 0.042$) and AD ($p = 0.022$). Interactions were observed in right tracts of the anterior thalamic radiation (ATR) for RD ($p = 0.045$) and in left tracts for AD ($p = 0.013$). An interaction was observed in the right uncinate (UNC) for RD ($p = 0.046$). Simple effect analyses revealed that for the OO, those with lower PA had lower FA ($p = 0.009$) and for the low PA group, the OO had lower FA ($p = 3.5E-5$). Effects for MD, RD, and AD showed that among those with low PA, the OO had higher diffusion (p , ≤ 0.001). In the OO, those with low PA had higher diffusion in all but one tract for MD, three tracts for RD, and two tracts for AD (0.002, p 's, ≤ 0.027). After adding gender as an additional covariate for main and interaction effects, the regional findings were consistent.

Conclusions: These results suggest that reporting high levels of physical sport activity be associated with greater WM integrity in the context of healthy aging.

Poster 86

INTERACTIVE EFFECTS OF FAMILY HISTORY OF ALZHEIMER'S DISEASE AND GENDER ON BRAIN VOLUMES AMONG COGNITIVELY HEALTHY OLDER ADULTS. Gallegos N, Stickel A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Both a family history of Alzheimer's disease (AD) and female gender increase risk for the disorder. However, there is little information about the interactions between family history and gender as it pertains to risk for AD. Even among cognitively healthy adults, those at greater risk for AD often have structural brain differences (e.g., smaller brain volumes) compared to those with low risk. The present study investigated the interaction between family history and gender on brain volumes in a sample of cognitively healthy older adults.

Methods: Thirty-four individuals with a family history of AD and 35 individuals without a family history between the ages of 53 and 89 years were matched on age, education, gender, and apolipoprotein e4 status. Nine and 7 males were included in the family history and no family history groups, respectively. All participants underwent magnetic resonance imaging which included a high-resolution scan. Whole brain voxel-based morphometry analysis was performed to identify brain regions in which volumes were significantly predicted by the interaction between family history and gender, controlling for age and intracranial volumes. A minimum cluster size of 10 voxels with a family-wise error of $p < 0.05$ was used.

Results: Volumes in two regions within the left superior frontal lobe and the left middle frontal gyrus were modulated by the interaction between family history and gender. Specifically, males without a family history had significantly higher volumes in both regions than males with a family history as well as compared to both female groups. The latter three groups did not differ in brain volumes.

Conclusions: In sum, volumetric differences were detected among groups of cognitively healthy older adults based on AD risk. Specifically, females with and without a family history did not differ from one another, nor did they differ from males with a family history of AD. However, males without a family history had larger brain volumes than all other groups, suggesting protection specific to that group. Future studies should include a larger sample of males and investigate whether volumetric differences between females with and without a family history would be detected at earlier ages.

Poster 87

THE IMPACT OF DEPRESSIVE SYMPTOMS ON COGNITION AMONG HISPANICS COMPARED WITH NON-HISPANIC WHITES. Gregolynskyj A, Stickel A, McKinnon A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Depression is associated with poorer learning and memory. Although Hispanics are the largest ethnic demographic in the United States, there is little research on the impact of depression on cognition among Hispanics. Further, Hispanics live longer than non-Hispanic Whites (NHWs), on average, despite having poorer access to health care services. It is unclear whether cognition is protected from the negative impacts of depression among Hispanics relative to NHWs.

Methods: Participants included Hispanics and NHWs between the ages of 50 and 94 years from the National Alzheimer's Coordinating Center (NACC; Hispanics (n = 48); NHWs (n = 46)) and the Alzheimer's Disease Neuroimaging Initiative (ADNI; Hispanics (n = 34); NHWs (n = 34)) databases*. Individuals with dementia were excluded. Ethnic groups were matched on age, education, gender, mild cognitive impairment status, and apolipoprotein e4 status. Depression was measured using the 15-item Geriatric Depression Scale. WMS Logical Memory Immediate and Delayed Story Recall tasks were administered to participants from the NACC database, and the Auditory Verbal Learning Test list learning and 30-minute delay recall tasks were administered to participants from the ADNI database. Four general linear models (two per database sample) were performed to test the interaction between depressive symptoms and ethnicity on learning as well as memory, controlling for age and education.

Results: Among the NACC participants, higher depression scores were significantly associated with poorer immediate story recall and marginally poorer delayed story recall across both ethnic groups. The interaction between ethnicity and depression was nonsignificant. In contrast, among ADNI participants higher depression scores predicted better list learning and memory scores among Hispanics whereas they predicted lower scores among NHWs.

Conclusions: Taken together, we found mixed evidence for differential impacts of depression on cognition among Hispanics compared to NHWs, and results differed by participant database. Specifically, depressive symptoms had a similar negative impact on learning and memory across both ethnic groups in the NACC sample. However, higher depressive symptoms were unexpectedly associated with better cognition among ADNI Hispanics but were related to poorer performance among ADNI NHWs. Several factors (e.g., demographic differences, cognitive task differences) have contributed to the observed differences between databases and should be investigated in future studies. *The NACC database is funded by NIA/NIH Grant U01 AG016976. ADNI Data collection and sharing was funded by the NIH Grant U01 AG024904 and DOD award number W81XWH-12-2-0012.

Poster 88

THE IMPORTANCE OF PHYSICAL ACTIVITY AMONG THE ELDERLY. Hindosh Z, Stipho F, Tirambulo C, Sutherland-Mills C, Sween A, Golden T, Toosizadeh N, Mohler J. University of Arizona; Arizona Alzheimer's Consortium.

Background: Physical activity (PA) and cognitive performance are associated, especially among the elderly. Although the role of PA in cognitive impairments is unclear, recent studies suggest it facilitates neuroplasticity and cognitive function. We investigated the association of PA on cognitive health as measured by the validated, modified Minnesota Leisure-time Physical Activity Questionnaire and the Montreal Cognitive Assessment (MoCA) among older adults.

Methods: We performed the MoCA and administered the Fried Frailty assessment in the NIH-funded Arizona Frailty Cohort of community-dwelling adults aged >65 years. The Minnesota Leisure-time Physical Activity Questionnaire was used to assess physical activity, using the guidelines for moderate-intense activities and beneficial exercise set by the Centers for Disease Control and Prevention (CDC). Moderate-intense activities including walking, moderately strenuous household chores, gardening, biking, exercise cycle, aerobic exercise, general exercise, and dancing were assessed. The total minutes of PA within a two-week duration was calculated for each participant, and the total minutes of PA > 300 minutes was used to identify beneficial physical activity, as defined by the CDC physical activity guidelines. A MoCa cut-off score <25 (range: 0-30) was used to identify participants with mild cognitive impairments. Using total minutes of PA as the independent variable and MoCA scores as the dependent variable, a linear regression (adjusted with age, gender, and BMI) was used to assess the association between PA and cognition.

Results: Eighty-five older adults (mean age: 79.3±7.7, range: 65-95), 58% female were assessed, among which 43 (51%, mean age: 81.5±7.7) were cognitively impaired. Overall, cognitive score and physical activity were significantly associated ($p < 0.05$).

Conclusions: Increased physical activity was associated with the absence of cognitive impairment. An understanding of this relationship between physical activity and cognition can help inform clinical screening practices, management, and interventions. Older adults with decreased physical activity are at an increased risk of having cognitive impairment and should be routinely screened for cognitive impairment in primary care.

Poster 89

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

Background: We studied a familial case of late-onset Alzheimer's disease. DNA sequencing was conducted on all surviving members of a single generation (3 affected females, 1 unaffected female, 1 unaffected male), from which we identified a rare, dominant mutation in ABCC1 (chr16:16216007 A>G, p.Y1189C). A recently deceased, affected female family member was autopsied, and neuropathology was consistent with AD. In vitro work demonstrated that ABCC1 WT skews APP processing towards the α -secretase pathway, but the Y1189C mutation results in higher A β production, possibly through modulation of the TIMP3/ADAM pathway.

Methods: Exome sequencing was conducted on three affected females and one unaffected male. Sanger sequencing was used to genotype one unaffected female. The neuropathology report included H & E, Gallyas, Campbell-Switzer, and thioflavin S staining methods and a comprehensive gross examination. In vitro, BE(2)-m17 neuroblastoma cells were modified to overexpress APP using the Sleeping Beauty Transposon system. This cell line was used to generate a control line, and two experimental lines: pSBbi-PUR, pSBbi-PUR-ABCC1(WT), and pSBbi-PUR-ABCC1(Y1189C). ELISAs and RNA-seq were performed on cells or supernatant under identical, standard culture conditions at various passages.

Results: Relating specifically to A β , neuropathology revealed frequent senile plaques (diffuse and neuritic) in all cerebral cortex regions, as well as the striatum and thalamus, with moderate to frequent plaques in the substantia nigra. In vitro, overexpression of ABCC1 reduced extracellular A β 1-40 and A β 1-42, with a reduced effect in the Y1189C mutant cell line. Furthermore, RNA-seq and ELISA analysis of the cell lines revealed significantly lower expression of TIMP3 mRNA and protein in the ABCC1(WT) cell line, again with a reduced effect in the Y1189C line. Treatment of the cells with thiethylperezine (a drug believed to activate ABCC1-mediated export of A β across the BBB): 1) decreased extracellular A β 1-40 in all cell lines 2) decreased A β 1-42 in the control and WT, but not the Y1189C line, and 3) resulted in increased extracellular levels of TIMP3 in the control and WT line, but not the Y1189C line.

Conclusions: We have identified a rare, dominant ABCC1 mutation associated with increased A β 1-40 and A β 1-42 in a familial case of late-onset AD. In vitro, ABCC1 WT overexpression resulted in lower levels of TIMP3, which is known to inhibit the α -secretase activity of ADAM10 and ADAM17. This effect on TIMP3 is reduced at the mRNA level, and nearly absent at the protein level, in the Y1189C mutant. Interestingly, in our standard 2D culture, treatment of the cells with thiethylperezine reduced A β 1-40 in all cell lines but had no effect on A β 1-42 or extracellular TIMP3 levels in the Y1189C mutant. Our data show that increased ABCC1 expression results in lower A β levels in an in vitro model, and that the Y1189C variant of ABCC1 likely increases amyloidogenesis in carriers. To our knowledge, this is the first germline mutation in ABCC1 to ever be associated with disease, and the first identification of a late-onset familial Alzheimer's disease gene.

Poster 90

DEFICITS IN AGED RATS ON THE W-TRACK CONTINUOUS SPATIAL ALTERNATION TASK SUGGEST IMPAIRED HIPPOCAMPAL-PREFRONTAL INTERACTIONS. Kapellusch AJ, Lester AW, Schwartz BA, Brewster JR, Barnes CA.
University of Arizona; Arizona Alzheimer's Consortium.

Background: The hippocampus and the PFC are part of a functional system involved in memory-guided decision making, a cognitive process particularly vulnerable to age-related decline in human and animal models of aging.

Methods: Groups of young and old rats were tested on a continuous spatial alternation task (Frank et al., 2000) in which they learned to alternate arm visits on a W-shaped track to receive a food reward. There are two interleaved components of this task: (1) an "outbound" or alternation component (working-memory) and (2) an "inbound" component, requiring the animal to remember to return to the center arm (spatial memory). The inbound component is primarily hippocampus dependent. The outbound component, in contrast, likely utilizes both the PFC to maintain a working memory of the previously visited arm, as well as the hippocampus to localize the currently rewarded position in absolute space. Rats with hippocampal lesions are impaired in learning both components of the task and show a pattern of perseverative inbound errors during initial learning (Kim & Frank, 2009). Although lesioning the hippocampus results in slower learning rates, animals are still able to reach learning criterion with time, suggesting adaptive compensation among parallel cognitive networks. Additionally, both aged rats and those with lesions to the mPFC show delayed learning on a T-maze spatial alternation task which also requires rats to maintain a working memory of the previously visited feeder (Ramos et al., 2003; Divac & Wikmark, 1975).

Results: In the present study, aged rats made more outbound errors throughout testing, resulting in significantly more days to reach learning criterion, as compared to young rats. Furthermore, while all animals were able to learn the hippocampus-dependent inbound component of the task, 4 of 6 aged animals remained at or near chance level on the outbound component, even after extended testing days.

Conclusions: Aged rats be more impaired on the outbound part of the task because it requires cooperation of both the hippocampus and mPFC, each of which is compromised with age. In addition, there are striking individual differences among aged animals in their ability to learn this task. The next step in the study will be to perform dual-region ensemble recordings from both the hippocampus and the mPFC while animals complete the alternation task to answer how age impacts network dynamics between these two regions, as well as identify the source of significant variation in performance among aged rats.

Poster 91

MAZE COMPLEXITY AND TASK LEARNING ORDER AFFECTS MEMORY PERFORMANCE IN ESTROGEN-TREATED RATS. Koebele SV, Quihuis AM, Lavery CN, Plumley ZMT, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging and menopause onset are each associated with changes in memory. Menopause symptoms can become exacerbated with surgical menopause, particularly if the surgery occurs in adulthood. Estrogen-containing hormone therapy is often prescribed during the menopause transition to treat symptoms like hot flashes and might also ameliorate some of the memory problems many women report. Evidence in human literature also suggests that completing complex cognitive exercises to keep the brain active be neuroprotective during aging. The complexity of cognitive tasks, as well as previous experience on cognitively-challenging tasks, can alter memory outcomes. This experiment systematically assessed whether the level of cognitive demand involved in performing maze tasks, and the order in which the tasks are presented, impacts spatial learning and memory in middle-aged ovariectomized (Ovx) rats receiving vehicle or estrogen treatment.

Methods: 60 middle-aged female rats underwent Ovx. One week later Alzet osmotic pumps were inserted subcutaneously to deliver tonic Vehicle, Low-17-estradiol (E2), or High-E2. Half of the rats in each treatment group were first tested on the water radial-arm maze (WRAM), a high-cognitive demand spatial task involving an increasing memory load, and then tested on the delayed match-to-sample (DMS), a low-cognitive demand spatial task without a memory load component. The other half of the rats were first tested on the low-cognitive demand task (DMS), followed by the high-cognitive demand task (WRAM).

Results: Performance within each treatment group was analyzed separately to assess whether experience on a low- or high- cognitive demand task impacts subsequent task performance. Low-E2-treated rats that had previously experienced the low-cognitive demand task made fewer working memory errors when memory load was taxed during the latter portion of testing on the subsequent high-cognitive demand task, compared to naïve Low-E2-treated rats. Low-E2-treated rats with previous experience on the high-cognitive demand task learned faster than their naïve counterparts on the subsequent low-cognitive demand task. Neither Vehicle- nor High-E2-treated rats showed a significant response to prior maze experience; this was true for low-cognitive demand experience before testing on a subsequent high-cognitive demand task, as well as for high-cognitive demand experience before testing on a subsequent low-cognitive demand task.

Conclusions: Results indicate that a tonic low circulating level of E2 in a surgically menopausal background enhances the cognitive flexibility to learn novel maze tasks when subjects have prior experience with another task, regardless of the task complexity level. Specifically, surgically menopausal rats treated with a low dose of E2 that had previous experience on a task with either level of cognitive demand showed enhanced learning and memory on novel tasks of varying complexity, compared to rats naïve to the task. For surgically menopausal rats devoid of estrogen, prior cognitive practice of any type did not impart cognitive benefits when learning a novel task. Dose-dependent effects of E2 and delayed memory retention will also be discussed. Overall, it is important to understand how experience on maze tasks of varying complexity can impact performance on subsequent maze learning, and whether estrogen treatment impacts outcomes following surgical menopause, so that these factors are taken into account when evaluating hormone effects on cognition during aging.

Poster 92

IMPACT OF $\alpha 5$ NICOTINIC RECEPTOR SUBUNIT IN ALCOHOL-INDUCED ALTERATIONS OF HIPPOCAMPAL STRUCTURE AND FUNCTION. Li S, Gao M, Shen J, Wu J. Shantou University Medical College; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Alcoholism is a serious public health problem and has been identified as the third major cause of preventable mortality in the world. It has been reported that alcohol and nicotine are often co-abused, which suggests that neuronal nicotinic acetylcholine receptors (nAChRs) contribute to alcohol's abusive properties. The genetic variation in nAChR $\alpha 5$ (CHRNA5) has been associated with increased risk of the addiction-associated phenotype in humans, suggesting the nAChR $\alpha 5$ subunit involve in alcohol's effects in the brain. However, the impact of nAChR $\alpha 5$ subunit in EtOH-induced alterations in hippocampal synaptic function and animal behaviors is still unclear.

Methods: Hippocampal CA3-CA1 synaptic function were determined using field potential recordings in hippocampal slices prepared from wild type (WT) and nAChR $\alpha 5$ subunit knockout (KO) mice. EtOH were administrated by bath-perfusion or mouse gavage. Animal behavioral tests include to measure mouse loss of righting reflex (LORR) and mouse conditioned place preference (CPP). The t-test or One-Way ANOVA statistical analysis was used based on the data compared.

Results: Field potential recordings in hippocampal slices (CA1 area) showed that $\alpha 5$ KO mice did not show the altered synaptic input-output (I-O) relationship curve and paired-pulse facilitation (PPF) but reduced the theta-burst-induced initiation of long-term potentiation (LTP) compared to WT mice. Acute bath-infusion of EtOH (8.6 mM) to record slice shifted I-O curve to left and reduced LTP but did not affect PPF in WT mice. In $\alpha 5$ KO mice, these effects of EtOH were absent. When high dose (4g/Kg) of EtOH was given via gavage, WT mice show LORR with 928 ± 345 sec (n=6) while 80% $\alpha 5$ KO mice (8/10) did not show LORR with the same EtOH gavage. Field potential recordings from these mice showed that compared to WT, $\alpha 5$ KO mice exhibited enhanced I-O curve and LTP maintenance. CPP tests showed that EtOH (2g/Kg, i.p.) induced CPP in WT but not in $\alpha 5$ KO mice.

Conclusions: We have demonstrated for the first time that $\alpha 5$ KO mice show significant changes on the effect of EtOH on hippocampal synaptic function, suggesting an important impact of the nAChR $\alpha 5$ subunit on the effect of EtOH on brain function.

Poster 93

EFFECTS OF AGING AND APOE E4 ON THE RELATIONSHIP BETWEEN WHITE MATTER INTEGRITY AND COGNITION. Matijevic S, Walther K, Huentelman M, Ryan L. University of Arizona; University of Erlangen; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: White matter microstructural changes with age have been found to moderate the relationship between age and cognitive function, such that poorer white matter tract integrity accounts for cognitive declines in older adults. Apolipoprotein (APOE) $\epsilon 4$, a risk factor for Alzheimer's Disease, has also been associated with both poor cognitive performance and white matter integrity in healthy older adults, and some studies have suggested that the influence of E4 on white matter partly explain the relationship between E4 and cognition. In the following longitudinal study, we evaluate the effects of aging and APOE E4 status on changes in tract integrity, cognitive performance, and the relationship between certain tracts and cognition.

Methods: We obtained neuropsychology measures and diffusion weighted images for 50 healthy older adults (54-91 at time 1) at two time points across a period of on average 2.7 years. Composite scores for memory and executive function were calculated based on the method described in Glisky & Kong (2008). Within-subject templates were created from the diffusion images of each participant using DTI-TK, and a group template was then bootstrapped from all within-subject templates to allow for normalization of each time point image to a common space. The JHU ICBM81 atlas was registered to the group template with ANTS and used to extract fractional anisotropy (FA) values for 14 tracts from each time point image: genu, callosum body, splenium, L/R inferior longitudinal fasciculus, L/R superior longitudinal fasciculus, fornix, L/R cingulum, L/R parahippocampal cingulum, and L/R uncinate.

Results: For all analyses, a Repeated Measures GLM was used with APOE $\epsilon 4$ status as a between-subjects factor and age at time point 1, years of education, and sex as covariates. For memory, there was a significant Time x Sex interaction ($p = 0.01$) and a main effect of Age ($p < 0.01$). There was a significant main effect of Time for the L SLF ($p = 0.015$), Time x Age effect for the right SLF ($p = 0.025$), and Time x Education effect for the left ILF ($p = 0.04$). Age was associated with poorer FA for all tracts but the bilateral uncinate (p 's < 0.05). There was a main effects of Sex for the fornix, bilateral cingulum, bilateral SLF and right uncinate, such that females had lower FA values than males in these tracts. Percent change values for the tracts were added as predictors in the memory and executive functioning models - only callosum body FA interacted with time to predict memory ($p < 0.000$).

Conclusions: Contrary to other studies, we did not find an effect of APOE E4 on FA values nor cognition. One possible interpretation of these results is that the influence of E4 on healthy older adults be more subtle than previous work has suggested; however, there are confounds in this study that have concealed existing effects. The limited number of male E4 carriers in this sample prevented us from testing for an E4 x Sex interaction, which be a critical confound given the evident sex differences in memory performance and various white matter tract FA values.

Poster 94

CEREBRAL AMYLOID ANGIOPATHY CORRELATES WITH SEMANTIC MEMORY IN NON-COGNITIVELY IMPAIRED OLDER ADULTS. Methuku V, Malek-Ahmadi M, Chen K, Perez SE, Mufson EJ. BASIS Peoria; Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Cerebral amyloid angiopathy (CAA) is a vascular neuropathology, resulting by the accumulation of beta amyloid ($A\beta$) in small blood vessels and commonly reported in non-cognitively impaired (NCI), mild cognitive impairment (MCI) and Alzheimer's disease (AD) brains. Although previous studies report that the presence of CAA affects cognition in MCI and AD subjects, its impact on cognition in non-demented who do not progress to MCI or AD remains unclear.

Methods: Data from 112 older deceased and autopsied persons in the Rush Religious Order Study were analyzed. All subjects died with a premortem clinical diagnosis NCI. Linear regression analyses with CAA severity as a predictor of cognition (global cognitive score (GCS), MMSE, episodic, working, semantic, and visuospatial memory, and perceptual speed) were performed. Negative binomial regression analyses determined whether CAA severity was associated with neuritic plaques (NP), diffuse plaques (DP), and neurofibrillary tangles (NFT). All models adjusted for age at death, gender, education, and APOE $\epsilon 4$ carrier status.

Results: CAA was significantly associated with semantic memory ($\beta = -0.19$, SE = 0.06, $p = 0.001$). Group-wise analyses of this association indicated that those with Moderate or Severe CAA had significantly worse performance than those with no CAA ($p = 0.007$). GCS ($\beta = -0.05$, SE = 0.04, $p = 0.19$), MMSE ($\beta = -0.08$, SE = 0.16, $p = 0.63$), episodic memory ($\beta = -0.06$, SE = 0.06, $p = 0.25$), working memory ($\beta = -0.003$, SE = 0.06, $p = 0.96$), visuospatial ($\beta = 0.04$, SE = 0.07, $p = 0.59$), and perceptual speed ($\beta = 0.002$, SE = 0.08, $p = 0.98$) were not associated with CAA severity. For the negative binomial regression models, CAA was positively associated with neuritic plaques (NP) ($\beta = 0.48$, SE = 0.21, $p = 0.02$) and diffuse plaques (DP) ($\beta = 0.52$, SE = 0.22, $p = 0.02$). Similarly, CAA severity correlated with higher Braak stage ($p = 0.013$) and higher CERAD diagnosis ($p < 0.001$).

Conclusions: In the present study we found that CAA severity was associated with semantic memory decline, increased $A\beta$ plaque pathology and NFT Braak stage suggesting that $A\beta$ accumulations in blood vessels, together with tangle pathology play a role in cognitive decline during aging. Therefore, understanding the impact of CAA on cognition in preclinical cohorts will be important, as the development of anti-amyloid therapies for pre-clinical AD continues.

Poster 95

SEX DIFFERENCES IN METABOLIC AND INFLAMMATORY AGING OF THE BRAIN IN HUMANIZED APOE- ϵ 4 KNOCK-IN RATS. Mishra A, Yin F, Mao Z, Shang Y, Do L, Trouard TP, Brinton RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.

Background: Women APOE- ϵ 4 carriers are susceptible to accelerated aging and undergo faster rates of cognitive decline from mild cognitive impairment to Alzheimer's disease. Using humanized APOE- ϵ 4 knock-in rat model, we conducted a longitudinal study to characterize the individual and combined impact of sex and APOE- ϵ 4 genotype on the brain aging process.

Methods: APOE- ϵ 4 and wildtype (WT), male and female rats, were assessed at four aging windows during the study: 7-8 months (m), 9-10m, 12-13m and 15-16m. Reproductive cyclicity in female rats was assessed by vaginal lavages. During the longitudinal follow-up, we conducted 18FDG-microPET/CT(18-fludeoxyglucose micro Positron Emission Tomography/Computational Tomography) to measure brain glucose uptake and established peripheral metabolic and inflammatory profile consisting of ketone bodies, triglycerides, insulin, lipidomics and, circulating cytokines and chemokines. Hippocampal RNA-Seq and brain mitochondrial function assessment was conducted in the rats that underwent 18FDG-microPET/CT. Magnetic resonance imaging (MRI) using 3-dimensional high resolution T2-weighted sequence and diffusion-weighted MRI was also carried out. Regional brain volume assessment using atlas-based analysis and white matter integrity assessment using diffusion parameters related tissue microstructure are currently underway.

Results: Longitudinal analyses indicate female and male APOE- ϵ 4 rats had significantly higher triglyceride and ketone body plasma levels. Female APOE- ϵ 4 underwent an age-related decline in insulin levels and increase in ketone body levels. At 16m, APOE- ϵ 4 males had higher brain glucose uptake than APOE- ϵ 4 females. Age did not affect the brain glucose uptake in APOE- ϵ 4 males. In comparison to WT-females, APOE- ϵ 4 females exhibited significant decline in brain glucose uptake at 12-13m, after reproductive senescence. Analyses correlating the transcriptional profile with brain glucose uptake and mitochondrial function are underway. Quantitative assessment of regional brain volume and correlation with inflammatory and metabolic biomarkers are also underway.

Conclusions: Aging did not affect brain glucose uptake in male APOE- ϵ 4 rats, while female APOE- ϵ 4 rats underwent a significant decline following menopausal transition. This longitudinal study demonstrates that APOE- ϵ 4 in combination with endocrine transition states worsens the metabolic trajectory of the aging female brain. Outcomes of this study will contribute to identifying optimal intervention windows for APOE- ϵ 4 carriers and peripheral markers predictive of neurological decline. Supported by NIA-P01AG026572; Alzheimer's Association: SAGA-17-419459 & AAC to RDB.

Poster 96

EXPLORE-EXPLOIT BEHAVIOR IN OLDER ADULTS. Mizell J-M, Wang S, Franchietti M-K, Keung J, Alexander G, Wilson RC. University of Arizona; Arizona Alzheimer's Consortium.

Background: The explore-exploit tradeoff is a fundamental behavioral dilemma faced by all adaptive organisms. Should we explore new options in the hopes of finding a better meal, a better house or a better investment vehicle for our savings, or should we exploit the options we currently believe to be best? Striking the right balance between exploration and exploitation is crucial for optimal performance, while getting the balance wrong has been associated with mental illness and cognitive decline (Strauss et al. 2011; Wilson et al., 2002; Wilson et al., 2007). Recently, we have shown that young adults solve the explore-exploit dilemma using a mixture of two strategies: "directed exploration", in which a competition between information seeking and risk aversion drives exploration by choice, and "random exploration", in which adaptive behavioral variability drives exploration by chance. Despite this progress, almost nothing is known about the neural and cognitive processes underlying explore-exploit decisions in old age, which given the ubiquity of these decisions in daily life and their possible relationship to cognitive decline, is a critical omission if we are to fully understand decision making in older adults. The current study is the first to study random and directed exploration in older adults.

Methods: Participants will be 20 healthy older adult participants between the age of 65 and 74. Directed and random exploration will be quantified using our previous published Horizon Task. In this task, participants make decisions between explore options that yield more information and exploit options that are better known. The key manipulation in this task is the number of trials in each game, the horizon, which determines how valuable it is to explore. When the horizon is short (1 trial), exploration has no value since there is no opportunity to use new information in the future. When the horizon is long (6 trials) it is often worth exploring at first to gain information about the exploratory option. Thus by contrasting behavior between horizon 1 and horizon 6 on the first choice of each game we can quantify the components of behavior that are related to exploration.

Results: Preliminary data from 2 participants shows increased risk aversion in horizon 1, suggesting that older adults avoid uncertain options even when they are, on average, more rewarding. While our current sample size is obviously small, it is nevertheless notable that these two older adults were more risk averse than any of the younger adults that we have run on this task! Despite this change in risk Anderson in horizon 1, our data show no change in information-seeking in horizon 6 compared to young adults. This suggests that older adults show a huge increase in information-seeking between Horizon 1 and Horizon 6 suggesting that they adjust their information seeking more strategically than younger adults. That is they show more directed exploration than younger adults. Despite this difference in directed exploration there appear to be no differences in random exploration between these two age groups.

Conclusions: While these results are preliminary, when taken together with our data in adolescents and middle-aged participants, they suggest that risk aversion and directed exploration increase with age, while random exploration is constant across the life span. This also adds to the evidence that random and directed exploration are at least somewhat neurally dissociable.

Poster 97

EFFICIENT DIFFERENTIATION OF HUMAN PLURIPOTENT STEM CELL DERIVED ASTROCYTES ON A DEFINED SUBSTRATE. Morgan D, Brookhouser N, Brafman DA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Human pluripotent stem cell (hPSC) derived neural progenitor cells (hNPCs) beneficially have the capability of self-renewing and differentiating into several different cell types of the central nervous system (CNS). Developing stronger disease models or cell therapies for neurodegenerative disease will require robust and clinically relevant differentiations of hNPCs into cell types aside from neurons including astrocytes. This could be particularly useful in modelling neurodegenerative diseases such as Alzheimer's Disease.

Methods: Previously completed work within the lab identified a completely defined synthetic peptide substrate, vitronectin derived peptide (VDP) that is able to support the long-term expansion and differentiation of hNPCs derived from hPSCs. In this investigation, hNPCs were differentiated into astrocytes for at least fifty days on VDP coated plates in a commercially available differentiation media.

Results: VDP allowed for the differentiation of hNPCs into astrocytes that were morphologically similar to astrocytes differentiated on typical extracellular matrix protein-based substrates. Immunofluorescent staining showed expression of the astrocyte markers, glial fibrillary actin protein and S100 calcium-binding protein B. Astrocytes showed an elevated inflammatory response when treated with lipopolysaccharide. Lastly, these cells demonstrated measurable secretion of apolipoprotein E.

Conclusions: As shown, VDP serve as the substrate in a defined system for generating astrocytes from hPSC derived hNPCs. Astrocytes differentiated on the synthetic peptide, VDP, will be useful in well-defined disease models which more closely recapitulate disease phenotypes by accounting for the heterogeneity of the microenvironment. Additionally, a xeno-free substrate will allow for possible use in clinical applications such as cell-based therapies.

Poster 98

REGIONAL COVARIANCE PATTERNS OF WHITE MATTER MICROSTRUCTURE IN HEALTHY AGING. Nguyen LA, Bharadwaj PK, Fitzhugh MC, Haws KA, Hishaw GA, Moeller JR, Habeck CG, Trouard TP, Alexander GE. University of Arizona; Columbia University; Arizona Alzheimer's Consortium.

Background: Diffusion tensor imaging (DTI), a non-invasive method for characterizing microstructural white matter, has been used to evaluate white matter differences in aging. Previous studies have primarily applied univariate approaches for evaluating relations between age and DTI metrics of white matter integrity, with prominent results showing associations between advancing age and decreases in fractional anisotropy (FA) and increases in mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD).

Methods: We applied a multivariate method, the Scaled Subprofile Model (SSM; Alexander & Moeller, 1994), to identify separate white matter regional network patterns for each diffusivity measure that optimally predicted age in a sample of 196 neurologically healthy community-dwelling older adults, ages 50-89. Additionally, we assessed the contributions of common vascular risk factors, including white matter hyperintensities (WMH), hypertension, and homocysteine, to each covariance pattern. We used TRACULA for automated probabilistic tractography to reconstruct 18 major white matter pathways and to generate estimates of FA, MD, RD, and AD. We used a multivariate model of regional network covariance, SSM, to identify regional patterns of white matter integrity associated with aging.

Results: We found distinct age-related regional patterns of white matter tracts for each diffusivity metric ($5.3E-9 \leq p \leq 0.001$). Additionally, there were no interactive effects of vascular risk factors and age on the covariance patterns. Only WMH volume showed an additive effect on the white matter integrity network patterns for FA, MD, and AD ($0.019 \leq p \leq 0.029$) but hypertension and homocysteine did not show contributory effects.

Conclusions: Together, these findings suggest that in the context of healthy aging, damage to white matter microstructural tracts differentially predict advancing age through region-specific effects and be further influenced by macrostructural white matter lesion load.

Poster 99

AN EVALUATION OF SHORT-TERM AND LONG-TERM OVARIAN HORMONE DEPRIVATION IN THE APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE: IMPACTS OF SPATIAL WORKING AND REFERENCE MEMORY. Palmer JM, Strouse IM, Koebele SV, Woner VE, Willeman M, Peña V, Winslow W, Oddo S, Bimonte-Nelson HA. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: With no known cure, Alzheimer's disease (AD) is the most common form of dementia, affecting more than 5.5 million Americans. The population is not affected by AD equally; women are at a greater risk for developing AD than their age-matched men. This disproportionate risk is thought to be associated with the changes in the female hormone profile that occur during menopause. Further, there is evidence that women who undergo surgical menopause (i.e., oophorectomy, or removal of the ovaries) before the onset of natural menopause are at a greater risk for AD. This greater relative risk of developing AD is thought to be linked to the ovarian-hormone deprivation associated with surgical menopause.

Methods: The current studies evaluated the behavioral changes after a short-term (Study 1) or a long-term (Study 2) period of ovarian hormone deprivation in a mouse model of AD. At three months of age, wildtype (Wt) mice and transgenic (Tg) mice expressing clinical mutations in the APP and PS1 genes (herein referred to as APP/PS1 mice) underwent either a sham surgery or an ovariectomy (Ovx) surgery, which is the surgical removal of the ovaries in rodents. Study 1 consisted of a short-term cohort that was tested on a battery of behavioral tasks involving the utilization of spatial reference memory and spatial working memory one month following surgery and subsequent hormone deprivation. These tasks included the Morris water maze, the delayed match-to-sample water maze, and the visible platform task. Study 2 consisted of a long-term cohort that was behaviorally tested three months following surgery and subsequent hormone deprivation on the same cognitive behavior battery.

Results: Results from Study 1 revealed that genotype interacted with surgical menopause status, such that after a short-term deprivation, no genotype effect was present after sham surgery, while Ovx induced a genotype effect, with Tg mice showing poorer cognitive scores relative to their Wt counterparts. Results from Study 2 showed a similar pattern of effects, with a comparable interaction between genotype and surgical menopause status.

Conclusions: These findings indicate that ovarian hormone deprivation exacerbates cognitive deficits in APP/PS1 mice. Future neuropathological evaluations will allow us to determine relationships between surgical menopause status, cognition, and AD-like pathology.

Poster 100

TOGETHER, BUT NOT FOR BETTER? EVALUATING THE COGNITIVE EFFECTS OF ETHINYL ESTRADIOL AND DROSPIRENONE GIVEN INDIVIDUALLY AND IN COMBINATION IN SURGICALLY MENOPAUSAL RATS. Peña VP, Poisson ML, Koebele SV, Croft C, Patel S, Strouse IM, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Among women ages 15-44 who use some form of contraception, approximately 28% of users take oral contraceptives, of which combined oral contraceptives (COCs) are most prevalent (Mosher & Jones, 2010). COCs are comprised of an estrogen and progestogen component. For the past decade, a popular COC formulation has been composed of ethinyl estradiol (EE) and drospirenone (DRSP). Using the rat model, our laboratory has demonstrated that EE administration resulted in dose-dependent spatial working memory impairments and decreased ChAT-positive cells in the basal forebrain, which correlated with poorer working memory performance (Mennenga et al., 2015). We have also shown that some clinically-used synthetic progestins, such as medroxyprogesterone acetate and norethindrone acetate, impair cognition in the rat (Braden et al., 2010, 2011, 2017). Natural progesterone administration can attenuate the beneficial cognitive effects and growth factor increases due to exogenous 17-estradiol (E2) treatment in preclinical models (Bimonte-Nelson et al., 2004, 2006). DRSP is a fourth generation progestogen that is more closely related to endogenous progesterone compared to other synthetic progestins. DRSP has anti-androgenic and anti-mineralocorticoid effects without glucocorticoid activity, thus potentially resulting in differential cognitive effects compared to other synthetic progestins. It is currently unknown whether EE and DRSP interact to produce unique effects on cognition than either one alone. Given that most women take COCs for an extended time period, it is important to model this preclinically and investigate how combined EE and DRSP impact cognitive performance when given chronically.

Methods: Young Fischer-344-CDF rats were ovariectomized (Ovx). Rats received daily injections of vehicle, DRSP, EE, or a combination of EE plus DRSP. They were tested on a battery of behavioral tasks: the water radial-arm maze (WRAM; spatial working and reference memory), Morris maze (spatial reference memory), and open field task (anxiety like and locomotor behavior).

Results: Results suggest that DRSP treatment alone enhanced WRAM acquisition compared to vehicle treatment. Further, low dose EE plus DRSP impaired spatial working memory on the WRAM compared to low dose EE alone.

Conclusions: Prior work from our and other laboratories indicates that progesterone attenuates E2-related cognitive benefits; the current results extend these interactive findings to include clinically-relevant synthetic hormones commonly used in COCs. Further investigation into the differential cognitive effects of independent and combined estrogen and progestogen administrations are currently underway.

Poster 101

MEMORY IMPAIRMENTS FROM 17 β -ESTRADIOL PLUS LEVONORGESTREL HORMONE THERAPY ARE DEPENDENT ON THEIR RATIO. Prakapenka AV, Berns-Leone C, Peña VL, Northup-Smith S, Melikian R, Patel S, Ladwig DS, Hiroi R, Mann AL, Valenzuela-Sanchez MJ, Sirianni RW, Bimonte-Nelson HA. Arizona State University; Red Mountain High School; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: 17 β -estradiol (E2) and Levonorgestrel (Levo) are two hormones clinically used in hormone therapy to alleviate symptoms associated with menopause. Our and other laboratories have previously shown that E2 alone and Levo alone can have beneficial effects on cognition in a rodent model of surgical menopause. However, because E2 and Levo are typically given in the clinic together (e.g., ClimaraPro), it is vital to understand how different E2 to Levo combination ratios impact cognitive performance following a decrease in circulating ovarian hormone levels. Thus, two studies were conducted with the overarching aim of examining the cognitive effects of E2 plus Levo hormone combination treatments using a rat model of surgical menopause.

Methods: In both studies, middle-aged female rats were ovariectomized and randomly assigned to receive daily subcutaneous injections of either vehicle or hormone treatment. To evaluate cognitive performance, the water-radial arm maze (WRAM) was used to assess spatial working and reference memory and the Morris water maze was used to assess spatial reference memory. The goal of the first study was to determine how E2 treatment dose impacted cognitive performance. Findings from this study revealed that the low E2 dose enhanced working memory performance compared to both vehicle control and high E2 dose treatments. Consequently, the low E2 dose was used in combination with varying doses of Levo in the second study; this allowed us to examine the cognitive effects of 5:1, 3:1, and 1:2 E2 to Levo combination ratios.

Results: We found that the addition of a high dose of Levo to E2 (a 1:2 E2 to Levo ratio) impaired spatial memory performance on the WRAM. The hormone ratio found in ClimaraPro, 3:1 E2 to Levo, also tended to impair spatial memory performance. Indeed, there was a linear dose response effect indicating that spatial working and spatial reference memory performance was incrementally impaired as Levo dose increased when combined with E2. Western blot analyses on brain regions involved in cognitive function are currently being completed to elucidate neuromechanisms mediating the cognitive effects seen with the hormone treatments tested in these two studies.

Conclusions: Together, the behavioral results suggest that the E2 plus Levo combination is likely not neutral for cognitive function, even though each hormone on its own has been previously shown to be cognitively beneficial, in a model of surgical menopause. Moreover, cognitive impairment tended to increase with the addition of increasing Levo dose to a cognitively beneficial E2 dose, indicating that the ratio of estrogen (E2) to progestin (Levo) hormone combination is a critical contributing factor to cognitive outcomes.

Poster 102

COGNITIVE DECLINE AND ITS RELATIONSHIP TO PERCEIVED QUALITY OF LIFE IN PARKINSON'S DISEASE. Pulaski S, Ponce F, Hanson K, Troster AI. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus (GPi) has been shown to be effective in reducing the motor symptoms in patients with medically-refractory Parkinson's disease. However, the effects of DBS on cognitive and psychiatric functioning, and subsequent quality of life, remain inconclusive. A recent meta-analysis¹ of randomized controlled trials comparing STN DBS and GPi DBS in Parkinson's disease found that STN DBS result in post-operative reductions in global cognition, attention, working memory, processing speed, verbal fluency, and memory. Despite an increased risk for cognitive decline following STN DBS, this same meta-analysis found no significant differences in rates of post-operative depression, anxiety, or perceived quality of life in Parkinson's disease patients who underwent STN DBS or GPi DBS. However, research has suggested that a subset of individuals with Parkinson's disease perceive reduced quality of life following DBS surgery. The goal of this study was to examine whether there was a relationship between post-operative cognitive decline and perceived reduction in post-operative quality of life.

Methods: 83 patients (Mean age 67.1 years; Mean education 14.8 years) underwent unilateral (n=17) or bilateral (n=66) subthalamic nucleus (STN) or globus pallidus (GPi) DBS for treatment of motor symptoms of PD. Patients completed neuropsychological testing pre- and post-DBS. ANCOVAs were conducted to identify if: 1. Those with postoperative memory, verbal fluency, or confrontation naming declines (≥ 0.5 SD) reported greater reduction in QOL (PDQ-39 Cognition or Communication, as appropriate) in comparison to those showing cognitive test score increments of ≥ 0.5 SD. Partial correlation analyses address whether depression moderates the relationships between postoperative verbal memory, verbal fluency, and naming impairments and perceived cognitive and communication aspects of QOL.

Results: Each ANCOVA yielded nonsignificant results ($p > .50$). Partial correlations examining depression as a moderator for the relationship between postoperative memory and language impairments and cognitive QOL and communication QOL were nonsignificant ($p > .30$). Only the relationship between postoperative depression and cognitive QOL was significant ($p < 0.05$).

Conclusions: Perceived QOL is not significantly impacted by objective changes in postoperative memory or language functioning following DBS surgery in patients with PD although significant cognitive changes are rare. Those with more depression symptoms report poorer QOL related to cognition. Findings support prior suggestions that, generally, cognitive alterations after DBS are well tolerated. Those with more depressive symptoms are more apt to be dissatisfied with cognition-related QOL, emphasizing importance of control of depression for optimal QOL outcomes after DBS.

Poster 103

DEVELOPING A CLINICALLY RELEVANT IN VITRO MODEL OF ALZHEIMER'S DISEASE USING PROGERIN INDUCED AGING. Raman S, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: An in vitro model of Alzheimer's disease (AD) is required to study the poorly understood molecular mechanisms involved in the familial and sporadic forms of the disease. Reprogramming patient samples to human induced Pluripotent Stem Cells (hiPSCs) presents an opportunity to study AD in a dish. However, AD hiPSC derived neurons do not faithfully reflect all the molecular characteristics and phenotypes observed in the aged cells with the neurodegenerative disease. The truncated form of nuclear protein lamin-A, progerin, has been implicated in premature aging and is found in increasing concentrations as normal cells age. The overexpression of progerin in AD hiPSC derived forebrain neurons therefore can be used to model AD in a dish.

Methods: We develop a lentivirus-based system to introduce an inducible progerin-GFP transgene that allows for its overexpression in undifferentiated patient-derived neural progenitor cells (NPCs) and derived neurons. The lentiviral construct also confers antibiotic resistance that allows us to enrich for transduced hNPCs that express GFP tagged progerin. Age-related phenotypes like abnormalities in nuclear morphology are confirmed through epifluorescence microscopy. Flow cytometry is used to quantify mitochondrial reactive oxidation species (ROS) and repressive histone methylation marks. A genome wide expression analysis of the generated model using RNA-seq will reveal its ability to induce the AD related phenotype in differentiated neurons.

Results: We have confirmed progerin overexpression using a lentiviral system in undifferentiated NDC and AD NPCs using RT-qPCR. Also, we are verifying the presence of various age-related phenotypes such as abnormal nuclear structure and the loss of nuclear lamina associated proteins to characterize 'aging' in NPCs and derived neurons. Progerin expressing AD/NDC NPCs are being differentiated using an established protocol into forebrain/cortical neurons followed by gene expression analysis and measurement of dendrite branching to confirm an aged neuronal phenotype.

Conclusions: By overexpressing progerin we can reintroduce some age and disease associated neurodegenerative effects in reprogrammed hiPSCs, allowing us to develop a clinically relevant model of AD.

Poster 104

AGING HIPPOCAMPAL NEURAL STEM CELL FUNCTION AND NRF2. Reed A, Ray S, Corenblum MJ, Anandhan A, Ortiz F, Zhang DD, Barnes CA, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Redox mechanisms are emerging as essential to stem cell function given their capacity to influence a number of important signaling pathways governing stem cell survival and regenerative activity. In this context, our recent work identified the reduced expression of nuclear factor (erythroid-derived 2)-like 2, or Nrf2, in mediating the decline in subventricular zone neural stem progenitor cell (NSPC) regeneration during aging (Corenblum et al., 2016, Aging Cell). Since Nrf2 is a major transcription factor at the heart of cellular redox regulation and homeostasis, we investigated the role that it play in the aging of NSPCs that reside within the other major mammalian germinal niche located in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus.

Methods: Using male rats from multiple aging stages ranging from newborn to old age, and aging male Nrf2 knock-out mice, we studied Nrf2 expression, NSPC viability, and proliferative capacities throughout the aging continuum in both the SVZ and DG. In congruence, we also looked at neurogenesis related hippocampal dependent behaviors via the Morris water maze and pattern separation tasks.

Results: We first determined that, in contrast to SVZ NSPCs, Nrf2 expression does not significantly affect overall DG NSPC viability with age. However, DG NSPCs resembled SVZ stem cells in that Nrf2 expression controlled their proliferation and the balance of neuronal versus glial differentiation particularly in relation to specific critical period during middle-age (13-15 mos). Importantly, this Nrf2-based control of NSPC regeneration was found to impact functional neurogenesis-related hippocampal behaviors, particularly in the Morris water maze and in pattern separation tasks. Furthermore, the enrichment of the hippocampal environment via the transplantation of Nrf2 overexpressing NSPCs was able to mitigate the age-related decline in DG stem cell regeneration during the critical middle-age period, and significantly improved pattern separation abilities. Moreover, preliminary data from female rats indicate that the decline in neurogenesis in females occurs early (by 9mos), which is well before the 13-15 mos critical period noted in males, and Nrf2's involvement here is currently being analyzed.

Conclusions: Overall, these results emphasize the importance of Nrf2 in DG NSPC regeneration, and support Nrf2 upregulation as a potential approach to advantageously modulate DG NSPC activity with age.

Poster 105

ELUCIDATING THE EFFECTS OF PRAS40 ON LEARNING AND MEMORY. Sarette P, Velazquez R, Rodin A, Caccamo A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: The mammalian target of rapamycin (mTOR) is integral in regulating cell growth as it maintains a homeostatic balance of proteins by modulating their synthesis and degradation. In the brain, mTOR regulates protein-driven neuroplastic changes that modulate learning and memory. Nevertheless, upregulation of mTOR can cause detrimental effect in spatial memory and synaptic plasticity. The proline-rich Akt-substrate 40 kDa (PRAS40) is a key negative regulator of mTOR, as it binds mTOR and directly reduces its activity

Methods: To investigate the role of PRAS40 on learning and memory, we generated a transgenic mouse model in which we used the tetracycline-off system to regulate the expression of PRAS40 specifically in neurons of the hippocampus.

Results: After induction, we found that mice overexpressing PRAS40 performed better than control mice in the Morris Water Maze behavioral test. We further show that the improvement in learning and memory was associated with a decrease in mTOR signaling and an increase in dendritic spines in hippocampal pyramidal neurons, and an increase in the levels of brain-derived neurotrophic factor (BDNF), a neurotrophin necessary for learning and memory. This is the first evidence that shows that increasing PRAS40 in the mouse brain enhances learning and memory deficits.

Conclusions: We showed that spatial memory was significantly improved in TgPRAS40 mice, which also showed reduced mTOR-signaling. This improvement might be attributed to increased synaptic density and formation of dendritic spines. Taken together, our data suggest that PRAS40 overexpression is a novel approach to improving learning and memory during aging and in neurodegenerative diseases.

Poster 106

CIRCULAR RNAs IN FUNCTIONALLY DISTINCT REGIONS OF HEALTHY AGED HUMAN BRAIN. Sekar S, Geiger P, Serrano GE, Sue LI, Beach TG, Liang WS. Translational Genomics Research Institute; Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Circular RNAs (circRNAs) represent a class of endogenous, non-coding RNAs that are formed when exons back-splice to each other and are pervasively expressed in the mammalian brain. While the functional role and impact of circRNAs remains to be clarified, they have been found to regulate micro-RNAs (miRNAs) as well as parental gene transcription and might thus have key roles in transcriptional regulation. The goal of this study was thus to systematically identify and characterize circRNA expression and evaluate the predicted impact on regulatory networks in five functionally distinct cortical regions of healthy aged human brain - cerebellum (BC), inferior parietal lobe (IPL), middle temporal gyrus (MTG), occipital cortex (OC) and superior frontal gyrus (SFG).

Methods: We extracted total RNA from 100 mg of frozen cortex from each brain region (N = 6 non-demented donors for each region) and treated with RNase R, an exoribonuclease that selectively degrades linear molecules but leaves behind circular ones. We prepared RNA sequencing (RNAseq) libraries and performed paired end next generation sequencing on the Illumina HiSeq. Raw fastqs generated were analyzed using six different circRNA prediction algorithms: find_circ, CIRI, DCC, Mapsplice, KNIFE and CIRCexplorer and differentially expressed circRNAs in each brain region were identified using DESeq2. Further, given their potential role in regulating miRNAs, we predicted circRNA-miRNA-mRNA regulatory networks in each region using the miRanda and RNAHybrid miRNA target prediction algorithms.

Results: We sequenced a total of thirty samples from BC, IPL, MTG, OC and SFG brain regions to generate a median of 103,003,950 reads across all samples. Samples from two of the six donors were dropped from further analysis due to outliers in circRNA detection. Overall, we detected a union of 28,220 circRNAs across all samples with at least two supporting reads. Among these, 752, 3496, 355, 1357 and 3478 were detected by at least three of the six tools in all four samples in BC, IPL, MTG, OC and SFG, respectively. CDR1as, a widely reported circRNA, was detected by two of the tools - DCC and find_circ, with a median of 539 supporting reads across all samples. Further, 1923, 106, 99, 113 and 93 circRNAs were differentially expressed in BC, IPL, MTG, OC and SFG, respectively. CircRNA-miRNA-mRNA networks were predicted for these differentially expressed circRNAs and Ingenuity pathway analysis was performed on genes from each of these networks. Enriched pathways include neuregulin signaling, axonal guidance signaling, neuroinflammation signaling, insulin receptor signaling, NRF2 (nuclear factor erythroid 2-related factor 2) mediated oxidative stress response and glucocorticoid receptor signaling.

Conclusions: In this study, we evaluated the abundance of circRNAs in five brain regions of healthy elderly individuals using circRNA enriched RNAseq data. Given our identification of differentially expressed circRNAs in each brain region and enriched signaling pathways, the circRNAs we identified be associated with key regional functions. Using these analyses, we establish a reference dataset of circRNA expression profiles and regulatory networks in healthy elderly individuals in a region-specific manner. This resource along with existing databases such as circBase will be invaluable in advancing circRNA research as well as understanding their role in transcriptional regulation and various neurological conditions.

Poster 107

A NEW LINK BETWEEN ARTHRITIS AND ALZHEIMER'S DISEASE? Squire M, Alkoul MF, Anderson M, Castro M, Al-Nakkash L, Broderick TL, Plochocki JH. Midwestern University; Arizona Alzheimer's Consortium.

Background: Recently, systemic inflammation has been implicated in the pathogenesis of Alzheimer's disease (AD). This inflammation has the ability to exacerbate both motor and cognitive symptoms of the disease through increasing amounts of inflammatory markers like TNF- α and C-Reactive Protein, as well as amyloid plaque depositions within many areas throughout the body, including articular cartilage of synovial joints. These inflammatory markers and amyloid plaques are related to the development of arthritis. In fact, arthritis is a risk factor for cognitive impairment in the elderly. For this reason, we hypothesize inflammatory mediators associated with the development of AD also affect articular cartilage metabolism, specifically hypertrophy-like changes induced by chondrocyte activation by inflammatory cytokines.

Methods: We compared expression of type X collagen (col10a1), a standard marker for chondrocyte hypertrophy, in tibiofemoral joint articular cartilage of 7-month-old male wild type mice with mice of the 3xTg-AD model for AD. Murine proximal tibias were decalcified, formalin-fixed and paraffin-embedded. Ten micron sections were obtained using a microtome and placed on charged slides. The tissue was tagged with collagen (COL10a1 Biorbyt orb373500) antibody and a complementary secondary fluorophore (Life Technologies AF647). Dapi was also added as a nuclear stain. A refractive index matching solution (RIMS) was used as the mounting media. Slides were imaged on Leica confocal microscope.

Results: Results show that expression of col10a1 in mice with the Alzheimer's phenotype is significantly reduced in comparison with the wild type mice ($P < 0.05$). This reduction is consistent with inhibited col10a1 expression by chondrocytes identified in arthritic cartilage.

Conclusions: Our exploratory study suggests neurodegenerative and arthritogenic changes identified in many AD patients be linked to a common systemic inflammatory process and warrants further investigation.

Poster 108

MEMORY AND PROCESSING SPEED PREDICT FUNCTIONAL INDEPENDENCE DIFFERENTIALLY IN NON-HISPANIC AND HISPANIC WHITE MIDDLE AGED AND OLDER ADULTS. Stickel A, McKinnon A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Hispanics live longer, on average, than non-Hispanic Whites, yet little is known about cognition and aging among Hispanics. Among non-Hispanic Whites, cognitive functioning is predictive of maintenance of functional independence. The present study compared the relationships between cognition and functional independence in aging (50-94 years old) Hispanics and NHWs.

Methods: Eighty-five Hispanics and 97 non-Hispanic Whites were selected from the National Alzheimer's Coordinating Center (NACC) and Alzheimer's Disease Neuroimaging Initiative (ADNI) databases*. Ethnic groups were matched on age, education, gender, and apolipoprotein e4 status. Functional independence was measured with the Functional Activities Questionnaire (FAQ). Participants completed a neuropsychological battery. Test scores of interest included Logical Memory Long Delay free recall, Trails Making Test A speed, and Trails Making Test speed difference (B - A). General linear models tested the interaction between ethnicity and cognitive function on FAQ scores, controlling for age and education.

Results: Poorer performances on Logical Memory and Trails A were associated with lower functional independence. Further, an interaction between ethnicity and cognition indicated that slowing on Trails A was associated with lower functional independence among non-Hispanic Whites but not Hispanics. Trails B - A was not predictive of functional independence.

Conclusions: These results suggest that associations between cognition and functional independence are not uniform across ethnic groups. Although memory be a more generalizable predictor of functional independence, processing speed is not. *The NACC database is funded by NIA/NIH Grant U01 AG016976. ADNI Data collection and sharing was funded by the NIH Grant U01 AG024904 and DOD award number W81XWH-12-2-0012.

Poster 109

PATHOLOGICALLY CONFIRMED AD IN APOE E2 HOMOZYGOTES IS RARE BUT DOES OCCUR. Stipho F, Jackson R, Sabbagh MN. University of Arizona; Arizona Alzheimer's Consortium.

Background: Homozygous APOE ϵ 4 status is a well-known risk factor in the development of Alzheimer's disease (AD). However, other genotypes of APOE have not yet been found to have equal clinical significance. There is a paucity of reports regarding clinically or pathologically described AD in APOE ϵ 2 homozygotes compared to the other alleles. Objective: To notify clinicians that patients with homozygous APOE ϵ 2 are also at risk of developing Alzheimer's disease based on results from the largest prospectively gathered registry of brain samples to date.

Methods: We queried the National Alzheimer's Coordinating Center (NACC) database for autopsy-confirmed AD cases. Of the Uniform Data Set (UDS) participants who are deceased, 5,779 were diagnosed with dementia at their last UDS visit prior to death, and autopsy data are available for 3518. Seven of those were found to have the APOE ϵ 2/ ϵ 2 isoform and two of those seven had confirmed pathological AD.

Results: Of the brains in the NACC database with pathologically confirmed dementia, seven were found to be homozygous for APOE ϵ 2, which represents only 0.2% of the autopsy-confirmed sample. Furthermore, pathology-confirmed AD represents 29% of the APOE ϵ 2/ ϵ 2 patients diagnosed with dementia.

Conclusions: Although rare, autopsy-confirmed AD can be present in APOE ϵ 2/ ϵ 2 carriers and, most importantly, was seen more frequently than previously believed.

Poster 110

TICK-TOCK, DON'T FORGET THE CLOCK: WHY FREQUENCY OF 17 β -ESTRADIOL TREATMENT MATTERS FOR WORKING MEMORY AND SPATIAL ACCURACY DURING MENOPAUSE. Strouse IM, Valenzuela-Sanchez MJ, Prakapenka AV, Quihuis AM, Sirianni RW, Bimonte-Nelson HA. Arizona State University; Barrow Neurological Institute; Red Mountain High School; Arizona Alzheimer's Consortium.

Background: Both preclinical and clinical research indicates that 17 β -estradiol (E2), the most potent endogenous estrogen used in menopausal hormone therapy (HT), can affect cognition. Whether frequency of E2 administration impacts efficacy is unclear. This study evaluated whether E2 administration frequency impacts cognition in a rat model of surgical menopause.

Methods: Middle-aged rats were ovariectomized and given subcutaneous injections of either a vehicle, or daily, weekly, or biweekly E2 regimen. They were subsequently tested on the water-radial-arm-maze (WRAM) to evaluate spatial working and reference memory. An additional novel form of error entry analysis was implemented. Errors were quantified as either 1-arm, 2-arms, 3-arms, or 4-arms away from the nearest platformed arm, enabling assessment of whether arm choices were a near-miss or extreme-miss from the correct spatial location; indeed, an incorrect arm choice further from a correct platformed-arm choice would be a greater failure of localization as compared to an incorrect arm choice that was closer to a correct platformed-arm choice.

Results: Rats given the daily E2 regimen made fewer working memory errors than those given the vehicle control. Rats given weekly E2 made more 1-arm-away errors than all other groups, suggesting this group made errors reflecting arm choices that were closest to a correct spatial location.

Conclusions: These results indicate that daily E2 treatment benefited working memory the most and led to fine-tuned spatial localization, while weekly E2 treatment resulted in more errors than daily treatment, but more near-misses when errors were made compared to the other treatment groups. This suggests that the errors made with the weekly E2 regimen were close to the target spatial location, indicating accurate spatial localization to the general vicinity of the target, with localization not as fine-tuned as that with daily E2 treatment. Understanding specific parameters of estrogenic effects, including temporal regimens and cognitive intricacies, will aid the development of HTs that promote beneficial cognitive aging in women.

Poster 111

COGNITIVE-UPPER-EXTREMITY FUNCTION DUAL TASK CHALLENGE IN HEALTHY ADULTS USING fMRI. Tirambulo C*, Sutherland-Mills C*, Toosizadeh N, Lindley M, Golden T, Chen N-K, Mohler J, Chou Y-H. University of Arizona; Arizona Alzheimer's Consortium.

Background: Cognitive-motor dual-tasking is a sensitive measure of cognitive impairment in older adults, however the neural correlates of dual-task processes are not fully understood. We used functional magnetic resonance imaging (fMRI) to investigate the difference between brain activation in cognition, motor, and dual-task conditions comparing healthy younger (HY) adults and healthy older adults (HO), to explore the effects of cognitive challenge difficulty during dual-tasking.

Methods: We performed fMRI using blood oxygenation level-dependent (BOLD) contrast echoplanar imaging using a 3-Tesla MRI. We implemented a blocked paradigm procedure consisting of: resting (30 sec), single cognition (counting backwards by count-1 or count-3: 30 sec), single motor (upper-extremity function (UEF) - elbow flexion and extension: 30 sec), and dual-task (combined motor UEF and cognitive challenge: 30 sec) with rests between tasks. Each paradigm was repeated twice. The data were analyzed using FSL FEAT. First, data were preprocessed with MCFLIRT, BET, and a Gaussian kernel of 5 mm FWHM. Next, functional data were registered to structural images and MNI standard space. For individual analyses, Z-statistical images were determined using a threshold of $z > 2.3$, $p < 0.05$ (whole-brain cluster-wise-corrected) for each task (i.e., cognition, motor, dual-task). Nine contrasts (i.e., dual-task vs. cognition, dual-task vs. motor) were performed for count-1 and count-3 conditions. Finally, results were entered into higher-level analyses using FLAME to compare mean brain activation in HY and HO.

Results: Sixteen participants were recruited. Five females and four males were HY (mean age: 20.7 ± 1.3 , range: 18-22 years); three females and four males were HO (mean age: 73 ± 3.5 ; range: 68-79 years). We found HO display more brain activation compared to HY for all tasks. For both count-1 and count-3 conditions in HY and HO, mean brain activation was greatest in cognition, followed by dual-task, and motor respectively. Dual-task for count-3 showed the greatest number of statistically significant clusters. Mean differences in activation at each cluster of voxels under cognition, motor, and dual-task challenge indicated the functioning of distinct neural tracts between count-1 and count-3 conditions in both HY and HO.

Conclusions: We found our UEF gait-equivalent procedure to be feasible for fMRI dual-task testing with MCFLIRT-based motion correction (absolute mean displacement value < 1 mm). We better specified dual-task activation norms in a group of HY and HO. Further investigation will explore the specific neural networks associated with the significantly different voxel clusters in mild cognitively impaired older adult subjects to better understand the effects of dual-task challenge in cognitive impairment.

Poster 112

MOVEMENT OF MOLECULES THROUGH GAP-JUNCTION CHANNELS: AN ALTERNATIVE MECHANISM FOR THE SPREADING OF ALZHEIMER'S DISEASE PATHOLOGY? Tran L, Chu P, Murthy A, Weidang L, and Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common type of dementia seen in elderly patients. Amyloid plaques and neurofibrillary tangles are the hallmarks of AD pathology, but the mechanisms that induce this pathology are still poorly defined. Development of AD pathology follows a relatively predictable pattern of progression through various regions of the brain. It has been proposed that this characteristic spreading of pathology results from transcellular movement of amyloid beta peptides or tau protein from one neuron to another via exocytosis from one cell and endocytosis into a neighboring cell. This mechanism has been described, particularly in the case amyloid beta, to be prion-like in nature. We hypothesized that there be another mechanism by which small triggering molecules or short peptides could spread from cell to cell. We are testing the ability of a small peptide to transfer from one cell to another via connexon gap junction channels, also referred to as electrical synapses. Transfer of peptides less than 1 kDa in size has been previously described in immunological cells for the purpose of antigen presentation but has not been tested in other cell types.

Methods: HeLa cells overexpressing wild-type connexon 43 (Cx43-WT) and non-functional connexon 43 (Cx43-T154A) are being used as a model system to test the ability of non-immunological cells to transfer peptides. Functionality of connexon channels in the Cx43-WT cell line was first verified using a fluorescent dye, Calcein AM, to load donor cells. This dye is known to transfer through connexon channels and should move readily into recipient Cx43-WT cells. Cx43-T154A cells were used as negative control recipient cells to confirm that the connexon channels are the avenue by which Calcein AM is being transferred between cells. To determine whether transmission of peptides can occur through Cx43 channels in this HeLa cell model, we are loading fluorescently-tagged 10 amino acid peptides (LDRLDRLDRK) into Cx43-WT cells. As with the Calcein AM, these loaded donor cells will be dropped onto a monolayer of Cx43-WT cells. Cx43-T154A recipient cells will again be used as a negative control. The ratio of donor to recipient cells in all experiments is 1:100. Both donor and recipient cells are co-cultured together for 7 hours to allow transfer. Then the donor and recipient cells are fixed using 4% PFA and the transmission of fluorescent dyes and peptides between cells through Cx43 channels is observed using the fluorescent microscope.

Results: Calcein-AM was found to transfer between cells when Cx43-WT cells were used as both the donor and recipient, verifying the functionality of the connexon 43 channels. Transfer was blocked when Cx43-T154A cells were used as the recipients, confirming that transfer of the dye was occurring through the connexon channels. Data will also be presented for the peptide transfer experiments, which are still on-going.

Conclusions: Our preliminary data confirm that Cx43-WT channels are functional and capable of transferring small molecules like Calcein-AM, which is less than 1 kD, from cell to cell. We are awaiting the results of peptide transfer experiments before determining if peptides can transfer readily through the connexon 43 gap junction channels of our model cell line.

Poster 113

DIAGNOSTIC AND THERAPEUTIC POTENTIAL OF ANTIBODY FRAGMENTS SELECTIVE FOR HUMAN AD BRAIN DERIVED TAU VARIANTS. Venkataraman L, He P, Beach TG, Peltz C, Yaffe K, Sierks MR. Arizona State University; Banner Sun Health Research Institute; University of California San Francisco; Arizona Alzheimer's Consortium.

Background: Protein aggregation is a common feature in many neurodegenerative diseases. Small oligomeric variants of proteins including tau, alpha-synuclein and amyloid-beta, have been implicated in the pathogenesis & spread of various neurodegenerative diseases. Reagents that can selectively recognize specific tau variants associated with onset & progression of Alzheimer's disease (AD) can be effective diagnostic & therapeutic tools.

Methods: A novel atomic force microscopy (AFM) based biopanning protocol was used to isolate a pool of single chain variable fragment (scFvs) that selectively bind tau variants present in human AD but not cognitively normal age matched brain tissue. The scFvs were screened with postmortem human brain tissue from the mid temporal gyrus (MTG) of either 2 early stage AD (Braak stage III), 5 late stage AD (Braak stage V), or 2 healthy age matched controls. To identify scFvs with potential value for identifying blood-based biomarkers of AD, sera samples from human postmortem AD & control cases were also analyzed.

Results: The selected scFvs against tau variants in AD tissue did not bind healthy control tissue and some showed differential binding to AD Braak stage III & V tissue suggesting that different tau variants are generated at different stages of AD. The anti-tau scFvs also readily selected AD over control sera samples indicating that the targeted tau variants are present in blood & are promising biomarkers and therapeutic targets for AD.

Conclusions: 1) Generated a pool of scFvs that are selective for tau variants uniquely present in human post-mortem AD brain tissue. 2) Anti-tau scFvs selectively bind pooled AD brain tissue homogenates compared to age-matched cognitively normal controls. 3) Different anti-tau scFvs selectively bind early stage (Braak stage III) or late stage (Braak stage V) AD brain tissue samples. 4) Anti-tau scFvs readily select AD sera samples over healthy controls indicating potential application of tau variants as blood based biomarkers for AD. 5) Selective targeting of tau variants reduces toxicity of AD brain tau preparations indicating potential therapeutic value.

Poster 114

AGE-RELATED DIFFERENCES IN EXECUTIVE NETWORK FUNCTIONAL CONNECTIVITY AND RELATIONSHIPS WITH SOCIAL COMMUNICATION IMPAIRMENTS IN AUTISM SPECTRUM DISORDER. Walsh MJM, Baxter LC, Smith CJ, Braden BB. Arizona State University; Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona Alzheimer's Consortium.

Background: Research suggests adults with autism spectrum disorder (ASD) use executive functions to compensate for social communication impairments. Given hallmark age-related declines in executive functioning, there is concern that older adults with ASD experience declines in social communication abilities. We hypothesized older adults with ASD will have greater social communication impairments than young adults with ASD, and that behavioral and neural mechanisms of executive functioning underlie this age-related difference.

Methods: Participants included young and middle-aged adults with and without ASD of average intelligence. We assessed social communication impairments via the Social Responsiveness Scale-2 (SRS-2). We evaluated behavioral executive function via the Tower of London (ToL), and neural executive function via the resting-state executive network (EN). Correlations were investigated between SRS-2 scores, EN functional connectivity, and ToL moves.

Results: Middle-aged adults with ASD had higher scores on the SRS-2 Cognitive Subscale than young-adults. The EN demonstrated exacerbated age-related declines in functional connectivity of the left dorsolateral prefrontal cortices in adults with ASD, compared to neurotypicals. There was a significant correlation between hypo-connectivity of the EN and higher SRS-2 scores in middle-aged adults with ASD. Furthermore, there was a significant relationship between worse performance on the ToL and higher SRS-2 Cognitive Subscale scores in both groups of adults with ASD.

Conclusions: Our findings suggest cognitive aspects of social communication impairments and EN hypoconnectivity get worse with age in adults with ASD. Further, exacerbated age-related EN hypoconnectivity be the mechanism of increased social communication impairments in older adults with ASD.

Poster 115

THE EFFICIENCY OF GENERATIVE AND DIRECT RETRIEVAL OF EPISODIC AUTOBIOGRAPHICAL MEMORIES IN HEALTHY AGING. Wank AA, Andrews-Hanna J, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: The retrieval of episodic autobiographical memories (EAMs) is our ability to recall unique life events, which is a reconstructive process involving the mental search for, selection, and elaboration of life experiences. Each stage places heavy demands on executive and memory resources, both of which experience decline in normal cognitive aging. To date, no study has examined the effects of healthy aging on the mental search phase of EAM retrieval, the step that is required before a memory can be selected and elaborated. According to theoretical models, this critical search phase can follow either a generative or a direct route. In the generative route, semantic details are initially retrieved and used to cue retrieval of more specific spatiotemporal details until a unique event is recovered, a process that exerts executive resources. When an EAM is directly retrieved, a unique event is selected virtually instantaneously, requiring the rapid recombination of specific details to reconstruct an EAM. Given the cognitive processes thought to support these routes of EAM retrieval, both generative and direct retrieval be compromised among cognitively healthy older adults.

Methods: We recruited twenty young and twenty older adults to investigate age-related differences in the search phase of EAM retrieval. Participants were presented with cue words and were asked to retrieve EAMs. A think aloud paradigm was used to capture the mental search process and a scoring procedure evaluating spatiotemporal specificity was implemented to categorize the steps taken to reach an EAM. Participants received a small neuropsychological battery assessing generative ability, relational processing, working memory, and inhibition.

Results: Results indicated that young adults directly retrieved specific memories more frequently than older adults. During generative retrieval, young adults more often retrieved a specific memory in comparison to older adults, with older adults often ending the search prematurely at an abstract fact level. However, the two age groups exhibited comparable performance in the level at which EAM search was initiated and the number of steps taken to reach a specific event. Inhibition ability was associated with all three significant findings.

Conclusions: These results suggest that older adults experience difficulty with direct recovery of EAMs and making contact with an EAM after mentally filing through personal semantic information (i.e., generative retrieval), often terminating search prematurely. Difficulty in generative retrieval be related to lower inhibitory processing by allowing irrelevant semantic contents to disrupt memory search. Future work should focus on understanding neural mechanisms underlying these observed age-related effects and elucidating differences between normal and abnormal aging in the efficiency EAM search routes.

HIPPOCAMPUS MORPHOMETRY STUDY ON PATHOLOGY-CONFIRMED ALZHEIMER'S DISEASE PATIENTS WITH SURFACE MULTIVARIATE MORPHOMETRY STATISTICS. Wu J, Zhang J, Shi J, Chen K, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: One of the hallmarks of Alzheimer's Disease is the accumulation of beta-amyloid plaques ($A\beta$) in human. While a variety of research has been devoted to studies on the group difference or personal diagnosis with sMRI analysis, limited research has been conducted on those $A\beta$ positive AD patients and $A\beta$ negative cognitively unimpaired subjects.

Methods: We applied surface-based subcortical morphometry analysis to a cohort consisting of patients with dementia due to AD (defined $A\beta$ positive and the presence of clinical symptoms) and $A\beta$ negative cognitively unimpaired subjects (not individuals at preclinical stage of AD). Surface tensor-based morphometry (TBM) is an intrinsic surfer statistic that examines spatial derivatives of the deformation maps that register brains to a common template and construct morphological tensor maps. We recently proposed a multivariate TBM (mTBM) and later further combined radial distances (RD, distance between each surface points to its medical center) and mTBM into surface multivariate morphometry statistics (MMS). Then, we adopt surface MMS of hippocampi as imaging biomarkers and designed two different experiments for validation. The first experiment is to calculate the group difference between $A\beta+$ AD and $A\beta-$ NL. With Mahalanobis distance, the group difference was computed by the Hotelling's T^2 test and corrected by the multiple comparisons with a 10000-time permutation test. We set the threshold as $p < 0.05$. The second experiment classified these two groups based on the features, of which the dimension was reduced. The meshes for each subject were converted into 1008 patches and the dictionary was initialized by random selection of these patches. The dictionary and sparse codes were learned by Stochastic Coordinate Coding (SCC) and the features were reduced to a reasonable size by max-pooling method. The two groups were discriminated by a weak classifier, Adaboost, with the dimension-reduced features.

Results: We achieved results that support that MMS can be used as a valid biomarker of pathology-confirmed AD patients. For the first experiment, the global differences, of which the p-values are less than 0.0001, are significant on both sides of the hippocampi. We also made permutation test on left hippocampal volume and hippocampal surface area measures. The result shows the features of hippocampal volume and area are equally effective with MMS for group difference study. As for the second experiment, to estimate classification accuracy, we used 10-fold leave-one-out cross-validation method. The result shows that the classification accuracy of our features, MMS, reached 90.48%, which is higher than the linear-SVM classification result (80.09%) of hippocampal volume as well as the area (78.44%). Our work achieved relatively good sensitivity (91.67%), specificity (88.89%), and negative predictive value (88.89%). The area under the curve (AUC) of our work is 0.9213, which is also better than those of volume (0.8927) and area (0.8742).

Conclusions: We used a surface-based subcortical morphometry analysis on a cohort consisting of $A\beta+$ AD and $A\beta-$ cognitively unimpaired subjects and the two aforementioned experiment results demonstrated our surface MMS can be applied as a potential biomarker for pathology-confirmed AD analysis.

PROXIMITY-AWARE LONGITUDINAL ORDER PRESERVING DICTIONARY LEARNING FOR PROGNOSIS OF SUBJECTIVE COGNITIVE IMPAIRMENT. Zhang J, Wu J, Chen K, Reiman EM, Caselli RJ, Wang Y. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Subjective cognitive impairment (SCI) is subjective memory or cognitive complaints not corroborated objectively by psychometric tests. While many people with SCI are anxious and depressed (SCI-psych), a subset might be correctly self-identifying early cognitive decline (SCI-neuro). Early and accurate identification of SCI-neuro might reduce unnecessary medical costs and offer earlier therapeutic opportunities than mild cognitive impairment (MCI).

Methods: We propose the multi-source order preserving dictionary learning (MopDL) framework to leverage the advantage of multi-source dictionary learning with the time order information of the longitudinal data. Our novel proximity-aware longitudinal order preserving algorithm is rooted in online dictionary learning, which scale up gracefully to large incomplete data being collected in ongoing clinical trials. Multi-source dictionary learning uses shared and individual dictionaries to encode both consistent and changing imaging features along longitudinal time points. Additionally, we designed a proximity-aware penalty term which ensure higher correlations between neighboring time points than those of non-neighboring time points and guarantee features temporally ahead of those of succeeding time points. In the regression stage, we use unsupervised learning to deal with the missing clinical score problem with respect to incomplete data matrices. We use stochastic coordinate coding to solve the above dictionary learning problem, it can dramatically reduce the computational cost of the sparse coding while keeping a comparable performance.

Results: In order to evaluate the model, we randomly split the data into training and testing sets using a 9:1 ratio and used 10-fold cross-validation to avoid data bias. Lastly, we evaluated the overall regression performance using weighted correlation coefficient (wR) and root mean square error (rMSE) for task-specific regression performance measures. The smaller rMSE, the bigger wR mean the better results. We report the mean and standard deviation based on 50 iterations of experiments on different splits of data. We compared MopDL with multi-source multi-target (MSMT) method, ODL: the single-task online dictionary learning followed by Lasso, as well as directly use Lasso and Ridge on the same feature settings. We used hippocampal surface multivariate morphometry statistics (MMS) as learning features, consisting of surface multivariate tensor-based morphometry, which is computed from the conformal grid and describes surface deformation on a local surface region, and radial distance, which measures the surface deformation along the surface normal direction. We followed the same protocol as Shi et al. and extract vertex-wise hippocampal morphometry features, consisting of 4*1 vectors on each vertex of 30,000 vertices on every pair of hippocampal surfaces.

Dictionary learning methods (ODL, MSMT and MopDL) outperformed Lasso method. MSMT achieved better result than ODL since it better models feature-feature relationship by multi-task framework. Finally, the newly proposed MopDL achieved the best results since it explicitly integrated temporal information in the formulation.

Conclusions: We developed a novel proximity-aware longitudinal order preserving algorithm MopDL. Experiments on MR image of 111 SMCs subjects show that MopDL achieves higher correlation and lower root mean square error comparing with previous methods, which demonstrate MopDL has a great potential to assist early stage of AD diagnosis and prognosis.

Additional Abstracts

A SHARED RESOURCE FOR THE EVALUATION OF BLOOD-BASED BIOMARKERS OF AMYLOID- β PLAQUE DEPOSITION. Jansen WJ, Reiman EM. Banner Alzheimer's Institute; Maastricht University; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: A major obstruction to the therapeutic development and clinical trial design for Alzheimer's disease (AD) is the lack of an accessible, inexpensive and noninvasive biomarker. The development of a blood-based biomarker for an early pathological event in AD, amyloid- β plaque deposition, would overcome these issues. However, lack of access to large samples from multiple sites including people with varying characteristics limits further testing of newly developed promising blood-based markers. This study aims to promote the further development of blood-based amyloid- β biomarkers by providing a shared resource of blood samples and clinical data and to examine the impact of age, APOE4 gene dose, clinical severity on performance of the blood-based biomarkers.

Methods: Research centers from multiple sites are encouraged to share blood samples and clinical data of cognitively impaired and unimpaired persons with known amyloid- status for the purpose of testing promising newly discovered blood-based biomarkers for amyloid- plaque deposition. Promising, newly developed amyloid- blood-based biomarkers will be tested using samples and data from this resource. Brain amyloid- burden measured by PET, CSF or neuropathological examination and dichotomized according to center-specific cut-offs will be used as the reference amyloid- burden. 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. We will 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.

Results: To date 7 studies have committed to sample and data sharing. In total, we aim to include samples and data of 5,000 participants in the first year of this study. Two research groups that have developed plasma biomarkers of Amyloid- β 42 and the Amyloid- β 42/40 ratio measured by refined mass spectrometry assays will use samples and data of the resource with the goal of replicating and extending their findings.

Conclusions: This study will result in a large repository of blood samples and clinical data that can be used by the worldwide research community for the further development of a blood-based amyloid- β biomarker. This would help the rapid development of a blood test to monitor individuals for their risk of amyloid- β pathology and have a profound impact on the prevention of AD.