



ANNUAL REPORT

July 1, 2015 to June 30, 2016

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In memory of our dear colleague
Gerald Farin, PhD
(1953-2016)





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 about 150 researchers and support 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 several affiliated organizations, including Midwestern University, the Critical Path Institute, and the University of Arizona College of Medicine, Phoenix Campus. Established in 1998, the Consortium is intended to make a major difference in the scientific fight against AD, to engage Arizona's underserved and understudied Native American and Latino communities, and to help address the unmet needs of patients and family caregivers. The Consortium's major themes are the early detection and prevention of AD. Its primary goal is to find effective treatments to stop and end AD as quickly 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] and its Arizona Biomedical Research Commission [ABRC]), the participating institutions, a competitive Arizona AD 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 the NIA-sponsored ADCC, Richard Caselli, MD, is the ADCC's Associate Director, and Carol Barnes, PhD, chairs the Consortium's 25-member Internal Scientific Advisory Committee. Leaders from each of the seven principal institutions serve on the Consortium's Board of Directors. The Consortium's external advisors include Drs. Marilyn Albert, Zaven Khachaturian, and Bruce Miller, who are recognized for their pioneering contributions and leadership roles in the study of AD and related disorders. They conduct annual site visits, review the progress and productivity of the AAC 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, and clinical, experimental therapeutics, and neuropathology research. It has made major contributions to the scientific understanding, unusually early detection and tracking of AD, the accelerated evaluation of putative AD prevention therapies, and the scientific understanding of the aging mind and brain. It has introduced promising new care models for patients and family caregivers. It has introduced new ways for different stakeholders to work together and it has provided data, biological samples and interested research participants for researchers inside the state and around the world. It continues to attract new researchers and clinicians to its participating institutions and 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 institutional matching funds continue to provide the “glue” for this geographically distributed research program, the “fuel” needed to launch new research initiatives, and the framework needed to reach the Consortium’s over-arching goals. Funds are used to support dozens of research projects each year, almost all of which involve researchers from different scientific disciplines, and about half of which include researchers from different institutions.

The Arizona ADCC has received continuous competitive NIA grant funding since 2001. The ADCC’s Administrative, Clinical, Data Management and Statistics, Neuropathology, and Education and Information Cores and its competitive Pilot Project Program have supported researchers and projects inside and outside of the state. In place of the Education and Information Core, the proposed grant includes an Outreach and Recruitment Core and a new Research Education Component.

The ADCC’s five-year competitive renewal grant application was submitted to NIA in September 2015, it received an outstanding Impact Score and highly favorable Summary Statement comments in March 2016, and a Notification of Grant Award is expected prior to the start of the next five-year funding period in July. The Summary Statement noted our statewide programs “exceptional” track record, productivity and impact, its “outstanding scientific contributions, regional 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.

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 the Consortium’s inception in 1998, its researchers have generated more than 4,000 publications, 1,000 research grants and contracts, and a billion dollars in new investments, including more than half of those investments in the last 3 years.

Consortium researchers continue to make pioneering contributions to the scientific fight against AD, related disorders, and the aging brain:

- They have helped clarify genetic and non-genetic risk factors and disease mechanisms, offered targets at which to aim new AD treatments, provided new insights about the pathological changes associated with AD and related disorders, and proposed promising ways to treat and prevent the clinical onset of AD.
- They have played leadership roles in the earliest detection and tracking of AD and the accelerated evaluation of putative prevention therapies, and they have made use of amyloid PET and other imaging techniques in the research and clinical setting.
- They continue to clarify how different brain cells, regions, and networks, and mental operations orchestrate memory and other thinking abilities and how they are affected by AD and normal aging. They have played leadership roles in the study of normal cognitive aging.

- They continue to develop groundbreaking research methods and strategies, collaborative models and data-sharing paradigms to support these and other research endeavors.
- With several hundred million dollars in NIA, philanthropic, foundation and industry funding, their “Alzheimer’s Prevention Initiative (API)” has helped launch a new era in AD prevention research, set the stage for the field to rapidly evaluate the range of promising but unproven prevention therapies, and find ones that work as quickly as possible. API includes prevention trials in cognitively unimpaired persons who, based on their genetic background and age, are at the highest imminent risk for the clinical onset of AD; exceptionally large registries and the recently initiated “Gene Match” Program to support enrollment in prevention trials; and paradigm-changing scientific, collaborative, data-sharing, and consensus-building elements for the advancement of AD prevention research.

The past year has been marked by extraordinary progress, productivity and impact. For instance, Consortium investigators and state-supported research programs have helped to secure highly competitive funding for NIH’s primary multi-center longitudinal biomarker studies of AD in patients with Down syndrome and Chronic Traumatic Encephalopathy (CTE) in former professional and college football players. They recently secured a statewide collaborative “T32” post-doctoral training grant to advance careers in AD and cognitive aging research. They have continued to make historic contributions to the advancement of AD prevention research, the development and use of enrollment registries, and the advancement of new data sharing policies. They held the Inaugural National Conference on AD/Dementia in Native American Communities. They have set the stage for the next five years of ADCC funding, and they have continued to secure major organizational investments to advance the scientific fight against AD, related disorders and cognitive aging in Arizona.

The past year has also been marked by major change, setting the stage for dramatic growth in our research programs. It has included new organizational alignments and affiliations, major organizational investments, the recruitment of new researchers and clinicians and the development of new research programs at most of our participating organizations. For instance, the Arizona State University-Banner Neurodegenerative Disease Research Center (NDRC) was established, includes a formal commitment to build, one of the largest basic science programs in the fight against AD, Parkinson’s disease and related diseases on the University’s Tempe Campus, and is actively recruiting a leading neuroscientist to lead the effort. The University of Arizona has recently recruited Roberta Brinton, PhD, a leading basic neuroscientist in the field of AD, the aging female brain and regenerative therapeutics to establish a new Center for Innovation in Brain Science. New recruitments, clinical and research programs and strategic initiatives are underway or being planned at most of our other organizations.

What’s Next

During the next few years, the Consortium’s organizations and researchers will continue to advance several new scientific and clinical initiatives. We will do everything we can to advance the scientific fight against AD, related disorders and the aging brain, and do so in a way that served the needs of our patients, families, and underserved communities. We will try to set a new standard of dementia care for patients and family caregivers within the next five years and find treatments to postpone, reduce, or completely prevent the clinical onset of AD within a decade. There is no guarantee that we will find an effective prevention therapy within that time, since it

remains to be determined whether any of the promising but unproven prevention strategies actually work. But we now have a chance to find out.

We are extremely grateful to the state of Arizona, NIA, our participating organizations, colleagues, collaborators and advisors, and our research participants and other supporters. We are proud of our progress and excited about our plans. We are determined to make a transformational difference in the fight against AD, and do so together.

Arizona Alzheimer's Consortium
18th Annual Conference – Thursday May 19, 2016
Translational Genomics Research Institute (Host Institution)
University of Arizona College of Medicine
Virginia G. Piper Auditorium, 600 E. Van Buren Street
Phoenix, AZ 85004

POSTER PRESENTATION SET-UP CONTINENTAL BREAKFAST	7:30 – 8:50AM
WELCOME Jeffrey Trent, Ph.D. President, Research Director, Professor Translational Genomics Research Institute	8:50 – 9:00AM
INTRODUCTION Eric M. Reiman, M.D. Director, Arizona Alzheimer's Consortium	9:00 – 9:15AM
2016 JOHN THEOBALD MEMORIAL COMMUNITY SERVICE AWARD <i>Presented to Congressman Harry Mitchell</i> By Richard Caselli, M.D. Professor of Neurology Mayo Clinic Arizona	9:15 – 9:30AM
LEON THAL MEMORIAL LECTURE "The Brain I Know" Marcus E. Raichle, M.D. Professor of Radiology, Neurology, Neurobiology, and Biomedical Engineering School of Medicine Washington University in St. Louis	9:30 – 10:45AM
ORAL RESEARCH PRESENTATIONS – SESSION I	10:45 – 12:02PM
POSTER SESSION I & LUNCH	12:05 – 1:00PM
POSTER SESSION II & LUNCH	1:00 – 1:55PM
ORAL RESEARCH PRESENTATIONS – SESSION II	2:00 – 3:30PM
CLOSING REMARKS Eric M. Reiman, M.D.	3:30 – 3:40PM

Arizona Alzheimer's Consortium

Oral Research Presentations

SESSION I Moderator: Richard Caselli, M.D.

- 10:45 - 10:57AM **Regeneration in a degenerating brain: allopregnanolone as the first regenerative therapeutic for Alzheimer's disease.** Roberta Brinton. University of Arizona; Arizona Alzheimer's Consortium.
- 10:58 – 11:10AM **Novel immunomagnetic reduction platform provides ultra-sensitivity for measuring plasma tau and amyloid beta 42 to distinguish Alzheimer's dementia patients from normal controls.** Lih-Fen Lue. Arizona State University; Barrow Neurological Institute; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
- 11:11 – 11:23AM **Developing new insights into preventing A β deposition by harnessing CNS-parasite interactions.** Anita A. Koshy. University of Arizona; Arizona Alzheimer's Consortium.
- 11:24 – 11:36AM **Alzheimer's Prevention Registry and the Genematch program: shared resources to the scientific community to facilitate enrollment in studies.** Jessica Langbaum. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
- 11:37 – 11:49AM **Histopathology and Florbetaben PET in patients incorrectly diagnosed with Alzheimer's disease.** Marwan Sabbagh. Barrow Neurological Institute; Piramal Imaging GmbH, Berlin, Germany; Banner Sun Health Research Institute; Tokyo Metropolitan Geriatric Hospital; Tokyo Metropolitan Institute of Gerontology; Fukushima Hospital, Toyohashi, Japan; Nagoya City University, Aichi, Japan; Mihara Memorial Hospital, Ise, Japan; University of Melbourne, VIC, Australia; Florey Institute of Neuroscience and Mental Health, Australia; Leipzig University, Germany; Charité Berlin, Berlin, Germany; Stanford School of Medicine; Bioscript Group, Macclesfield, UK; Georg-August University Göttingen, Germany; Molecular Neuroimaging, New Haven, CT; Arizona Alzheimer's Consortium.
- 11:50 – 12:02PM **Deep brain stimulation of the fornix for Alzheimer's disease - the ADvance trial.** Francisco Ponce. University of Toronto, Toronto, Ontario Canada; Functional Neuromodulation Ltd, Minneapolis, MN; Douglas Mental Health University Institute, Montreal, Quebec, Canada; McGill University, Montreal Quebec Canada; Johns Hopkins University School of Medicine; Clintara LLC; Butler Hospital; Alpert Medical School of Brown University; Rhode Island Hospital; Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; Banner Alzheimer's Institute; University of Arizona College of Medicine, Phoenix; University of Pennsylvania; University of Florida; Arizona Alzheimer's Consortium.

Alzheimer's Consortium

Oral Research Presentations

SESSION II Moderator: Heather Bimonte-Nelson, Ph.D.

- 2:00 - 2:12PM **C9orf72: bridging the gap between dementia and motor neuron disease.** Rita Sattler. Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; Johns Hopkins University; Mayo Clinic Jacksonville; Arizona Alzheimer's Consortium.
- 2:13 – 2:25PM **The mTOR/p70S6K pathway plays a key role in the pathogenesis of Alzheimer's disease.** Salvatore Oddo. Arizona State University; Arizona Alzheimer's Consortium.
- 2:26 – 2:38PM **Behavioral evidence for enhanced interference during working memory and associative learning tasks in aged macaques.** Daniel Gray. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.
- 2:39 – 2:51PM **Patch-based sparse coding and multivariate surface morphometry for predicting amnesic mild cognitive impairment and Alzheimer's disease in cognitively unimpaired individuals.** Cynthia Stonnington. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
- 2:52 – 3:04PM **Identification of TREM2 agonists as a therapeutic avenue for Alzheimer's disease.** Isabelle Schrauwen. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
- 3:05 – 3:17PM **Digital biomarkers: building a regulatory science roadmap towards biomarker qualification for clinical trial use in presymptomatic Alzheimer's disease and related dementias.** Stephen P. Arneric. Critical Path Institute; Oregon Health Science University; Arizona Alzheimer's Consortium.

Arizona Alzheimer's Consortium

Poster Presentations

1. **Phenothiazine analogues: therapeutic agents for mitochondrial and neurodegenerative diseases.** Bandyopadhyay I, Chowdhury SR, Khmour OM, Hecht SM. Arizona State University; Arizona Alzheimer's Consortium.
2. **Age-associated regional network pattern of MRI gray matter in the bonnet macaque.** Bharadwaj PK, Burke SN, Trouard TP, Chen K, Moeller JR, Barnes CA, Alexander GE. University of Arizona; University of Florida; Banner Alzheimer's Institute; Columbia University; Arizona Alzheimer's Consortium.
3. **Depression and anxiety in the aging ASD cohort: relationships with cognition and social networks.** Braden BB, Smith CJ, Glaspy T, Thompson A, Deatherage BR, Wood E, Vatsa D, Baxter L. Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona Alzheimer's Consortium.
4. **Dissecting the role of NRF2 in Alzheimer's disease.** Branca C, Caccamo A, Dave N, Negrich C, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
5. **Cholinergic dysfunction and muscarinic receptor uncoupling in Alzheimer's disease.** Burkart A, Hamada M, Arthur K, Jones D. Midwestern University; Arizona Alzheimer's Consortium.
6. **Understanding Toxoplasma gondii's neuroprotection against A β deposition.** Cabral C, Franco J, MacDonald WR, Koshy AA. University of Arizona; Arizona Alzheimer's Consortium.
7. **Comparison of three FDG PET analysis techniques in the tracking of Alzheimer's disease and evaluation of disease-modifying treatments.** Chen K, Kuang X, Luo J, Roontiva A, Lee W, Thiyyagura P, Bauer III R, Devadas V, Reiman EM. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
8. **Allopregnanolone promotes neural stem cells differentiation to neurons and oligodendrocyte precursor cells.** Chen S, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
9. **Differential pattern of altered gene expression among brain regions in aging and Alzheimer's disease.** Coleman PD, Mastroeni D, Delvaux E, Nolz J, Berchtold N, Cotman C. Arizona State University; Banner Sun Health Research Institute; University of California, Irvine; Arizona Alzheimer's Consortium.
10. **An interdisciplinary music-based intervention for people with advanced ADRD.** Coon DW, Rosas V, Frye M, McCarthy M, O'Toole L, Rio R, Bontrager V, Todd M, Burleson M. Arizona State University; Dignity Health/St. Joseph's Medical Center; The Phoenix Symphony; Arizona Alzheimer's Consortium.

11. **Lenalidomide to modulate brain BACE1 expression.** Decourt B*, Grover AC, Macias MP, Walker A, Gonzales A, Malek-Ahmadi M, Sabbagh MN. Arizona State University; Banner Sun Health Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
12. **Multivariate analysis of gene expression of peripheral blood leukocytes differentiates persons at risk for Alzheimer's disease from persons not at risk.** Delvaux E, Mastroeni D, Nolz J, Marshall F, Coleman PD. Arizona State University; Banner Sun Health Research Institute; University of Rochester Medical Center; Arizona Alzheimer's Consortium.
13. **Evidence for lymphocyte infiltration during perimenopausal transition: implications for prodromal phase of Alzheimer's disease.** Desai MK, Yin F, Mao Z, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
14. **Enhanced beta band activity in the aged amygdala during probabilistic decision making.** Duarte L, Samson RD, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
15. **Cultural bias in memory screening of American Indian individuals in Arizona.** Ewbank C, Dougherty J, Lomay V. UA College of Medicine Phoenix; Banner Alzheimer's Institute; Salt River Pima Indian Community; Arizona Alzheimer's Consortium.
16. **Identification of learning-induced changes in protein networks in the hippocampi of 3xTg-AD mice.** Ferreira E, Shaw DM, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
17. **Density assessment of synucleinopathy-affected nerve fibers in submandibular gland biopsies of Parkinson's disease subjects.** Glass M, Adler CH, Serrano G, Intorcchia A, Filon J, Sue LL, Garcia A, Callan M, Walker J, Maarouf C, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
18. **Emotional memory: a pre-clinical cognitive marker of Alzheimer's disease?** Grilli MD, Woolverton CB, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.
19. **Formative evaluation of the National Family Caregiver Outreach program.** Han E, Park M, Han D, Kim Y, Lee J. Health Insurance Policy Research Institute; Chungnam National University, Daejeon, South Korea; Arizona State University; Ministry of Health & Welfare, KAIST Graduate Program for Future Strategy; Arizona Alzheimer's Consortium.
20. **Alzheimer's Prevention Registry: a shared resource to the scientific community to facilitate enrollment in studies.** High N, Gordon D, Nichols J, Aisen PS, Albert MS, Comer M, Cummings JL, Manly JJ, Petersen RC, Sperling RA, Strobel G, Weiner MW, Reiman EM, Tariot PN, Langbaum JB. Banner Alzheimer's Institute; University of California San Diego; Johns Hopkins University School of Medicine; Geoffrey Beene Foundation Alzheimer's Initiative; Cleveland Clinic Lou Ruvo Center for Brain Health; Columbia University; Mayo Clinic; Harvard Medical School; Alzforum; University of California San Francisco; Arizona Alzheimer's Consortium.

21. **Adding reference memory to a working memory maze task alters the pattern of age-related impairment in rats: associations with choline acetyltransferase activity in discrete brain regions.** Hiroi R, Prakapenka AV, Poisson M, Kirshner Z, Castaneda AJ, Gibbs RB, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium; Barrow Neurological Institute; University of Pittsburgh School of Pharmacy.
22. **Long-term storage effects on immunohistochemical and histochemical neurodegenerative diagnostic staining of archived paraffin sections.** Intorcia A, Garcia A, Glass M, Filon J, Walker J, Maarouf C, Callan M, Sue LI, Beach TG, Serrano G. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
23. **Regulation of LXR and PXR mechanisms by allopregnanolone to promote clearance of amyloid-beta and cholesterol homeostasis: therapeutic potential for Alzheimer's disease.** Irwin RW, Swanson HM, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
24. **Specificity of pan-fungal PCR primers for detection of fungal pathogens in Alzheimer's disease patient tissue.** Jentarra G, Chavira B, Potter P, Vallejo J, Jones B, Tullot T. Midwestern University; Arizona Alzheimer's Consortium.
25. **Disparate expression of inflammatory genes in cortex and hippocampus of APOE4-targeted replacement mice.** Jones TB, Vallejo J, Chavira B, DeVera C, Castro M, Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.
26. **Optical clearing and 3D-histology of murine testis.** Kaufman JA, Castro MJ, Ruiz SA, Rodriguez-Sosa JR. Midwestern University; Arizona Alzheimer's Consortium.
27. **Nuclear, but not mitochondrial encoded OXPHOS genes are altered in aging, mild cognitive impairment, and Alzheimer's disease.** Khdour OM, Delvaux E, Nolz J, Olsen G, Berchtold N, Cotman C, Hecht SM, Coleman PD, Mastroeni D. Arizona State University; Banner Sun Health Research Institute; University of California, Irvine; Arizona Alzheimer's Consortium.
28. **Head-to-head comparison of SUVR methods in amyloid cross-sectional and longitudinal studies.** Klein G, Sampat M, Staewen D, Lemon C, Suhy J, Reiman EM, Chen K. BioClinica; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
29. **Mechanistic pathways linking mitochondrial oxidative stress and white matter degeneration in the aging mammalian female brain.** Klosinski LP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
30. **Mentally stimulating activities in late-life and the risk of incident mild cognitive impairment: a prospective cohort study.** Krell-Roesch J, Roberts R, Pink A, Stokin G, Mielke M, Vemuri P, Christianson T, Knopman D, Petersen R, Geda Y. Mayo Clinic Arizona; Mayo Clinic Minnesota; International Clinical Research Center, Brno, Czech Republic; Arizona Alzheimer's Consortium.

31. **Preliminary patient and partner outcomes in a randomized trial of two cognitive rehabilitation interventions for mild cognitive impairment.** Locke DEC, Cuc AV, Snyder CH, Fields JA, Smith GE, Chandler M. Mayo Clinic Arizona; Mayo Clinic Minnesota; University of Florida; Mayo Clinic Florida; Arizona Alzheimer's Consortium.
32. **The effects of APOE genotype on A β levels in human liver.** Maarouf C, Garcia A, Walker J, Intorcchia A, Filon J, Glass M, Callan M, Walker D, Sue LI, Beach TG, Dugger B, Serrano G. Banner Sun Health Research Institute; Arizona State University; University of California, San Francisco; Arizona Alzheimer's Consortium.
33. **The use of reliable change index to characterize cognitive composite score decline as an outcome for Alzheimer's disease prevention trials.** Malek-Ahmadi M, Chen K. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
34. **Neuritic and diffuse plaque associations with cognition in elderly persons without cognitive impairment.** Malek-Ahmadi M, Perez SE, Chen K, Mufson EJ. Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
35. **Sex-dependent bioenergetic and metabolic gene expression in the hippocampus: female brain ages differently from male brain.** Mao Z, Zhao L, Yao J, Ding F, Cadenas E, Brinton RD. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.
36. **Increased 5-hydroxymethylation levels in the sub ventricular zone of the Alzheimer's brain.** Mastroeni D, Chouliaras L, Van den Hove DL, Rutten BPF, Delvaux E, Coleman PD. Arizona State University; Banner Sun Health Research Institute; Maastricht University Medical Centre, Maastricht, The Netherlands; University of Oxford, Oxford UK; Arizona Alzheimer's Consortium.
37. **A paradigm shift in microglial expression profiles in human brain.** Mastroeni D, Sekar S, Delvaux E, Nolz J, Liang W, Coleman PD. Arizona State University; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
38. **Does body fat predict cognition better than body mass index in a group of cognitively healthy older adults?** Meyer A, Stickel A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
39. **Medin amyloid peptide enhances β -amyloid fibrillation and induces human arteriole dysfunction.** Migrino RQ, Davies H, Truran S, Karamanova N, Franco DA, Serrano G, Callan M, Burciu C, Beach TG, Madine J. Phoenix VA Health Care System; University of Arizona College of Medicine-Phoenix; University of Liverpool; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
40. **Amyloid- β , neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a prospective cohort study.** Neureiter J, Krell-Roesch J, Pink A, Stokin G, Roberts R, Mielke M, Christianson T, Spanghel K, Lowe V, Jack C, Knopman D, Boeve B, Petersen R, Geda Y. Paracelus Medical University, Salzburg, Austria; Mayo Clinic Arizona; International Clinical Research Center, Brno, Czech Republic; Mayo Clinic Minnesota; Arizona Alzheimer's Consortium.

41. **The mTOR/p70S6K pathway plays a key role in the pathogenesis of Alzheimer's disease.** Oddo S, Caccamo A, Shaw D, Branca C. Arizona State University; Arizona Alzheimer's Consortium.
42. **Developing an individualized web based dementia caregiver support program.** Park M. Chungnam National University, Daejeon, South Korea; Arizona State University; Arizona Alzheimer's Consortium.
43. **Genome-wide expression and methylation profiling in medial temporal gyrus reveals concordant patterns of downregulation/hypermethylation in key molecular processes involved in the pathogenesis of Alzheimer's disease.** Piras IS*, Krate J*, Delvaux E, Nolz J, Mastroeni D, Jepsen W, Beach TG, Persico AM, Coleman PD, Huentelman MJ. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona State University; University Campus Bio-Medico, Rome, Italy; University of Arizona; Arizona Alzheimer's Consortium.
44. **The mild cognitive impairment of primary progressive aphasia: a case series.** Powell J, Lendrum J, Huff R, Belden C, Sabbagh MN, FAAN. Banner Sun Health Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
45. **Relationships between baseline biomarkers and subsequent cognitive decline in cognitively unimpaired PSEN1 E280A mutation carriers from the Colombian kindred with autosomal dominant Alzheimer's disease.** Quiroz YT, Protas H, Chen K, Roontiva A, Thiyyagura P, Fagan AM, Shah A, Gutierrez M, Londono M, Giraldo M, Munoz C, Tirado V, Velilla L, Garcia G, Jaimes SY, Langbaum JB, Tariot PN, Sperling RA, Lopera F, Reiman EM. Universidad de Antioquia, Medellin, Colombia; Massachusetts General Hospital; Banner Alzheimer's Institute; Washington University School of Medicine; Knight Alzheimer's Disease Research Center; Brigham and Women's Hospital, Harvard Medical School; Athinoula A Martinos Center for Biomedical Imaging; Arizona Alzheimer's Consortium.
46. **Differences in resting state functional connectivity between aerobic athletes and sedentary young adults.** Raichlen DA, Bharadwaj PK, Fitzhugh MC, Haws KA, Torre GA, Trouard TP, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.
47. **Relation between social interaction and cognitive functioning in older adults: a feasibility study using the EAR technology.** Robbins R, Glisky E, Mehl M. University of Arizona; Arizona Alzheimer's Consortium.
48. **Aging with traumatic brain injury: age at injury effects on behavioral outcome following diffuse brain injury in rats.** Rowe RK, Ziebell JM, Harrison JL, Law LM, Adelson PD, Lifshitz J. Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona College of Medicine; Arizona State University; Arizona Alzheimer's Consortium.
49. **Histopathology and Florbetaben PET in patients incorrectly diagnosed with Alzheimer's disease.** Sabbagh MN, Schäuble B, Richards D, Anand K, Beach TG, Murayama S, Akatsu H, Takao M, Rowe CC, Masters CL, Sabri O, Barthel H, Gertz H-J, Peters O, Rasgon N, Booth DR, Schulz-Schaeffer WJ, Seibyl J. Barrow Neurological

Institute; Piramal Imaging GmbH, Berlin, Germany; Banner Sun Health Research Institute; Tokyo Metropolitan Geriatric Hospital; Tokyo Metropolitan Institute of Gerontology; Fukushima Hospital, Toyohashi, Japan; Nagoya City University, Aichi, Japan; Mihara Memorial Hospital, Isesaki, Japan; University of Melbourne, VIC, Australia; Florey Institute of Neuroscience and Mental Health, Australia; Leipzig University, Germany; Charité Berlin, Berlin, Germany; Stanford School of Medicine; Bioscript Group, Macclesfield, UK; Georg-August University Göttingen, Germany; Molecular Neuroimaging, New Haven, CT; Arizona Alzheimer's Consortium.

50. **Enhanced single unit firing to unexpected large rewards in aged amygdala neurons.** Samson RD, Duarte L, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
51. **Identification of TREM2 agonists as a therapeutic avenue for Alzheimer's disease.** Schrauwen I, Sereduk C, Yin H, Huentelman M. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
52. **Transcriptional changes in the hippocampus related to aging and cognition.** Siniard AL, De Both MD, Piras IS, Chawla M, Ianov L, Guzman-karlsson M, Kennedy A, Day J, Young J, Blanton S, Wright C, Sweatt D, Foster T, Moroz L, Barnes C, Huentelman MJ. Arizona Alzheimer's Consortium; University of Arizona; Translational Genomics Research Institute; University of Florida; University of Miami; University of Alabama.
53. **The effect of statins on rate of cognitive decline in mild cognitive impairment.** Smith KB, Kang P, Sabbagh MN, The Alzheimer's Disease Neuroimaging Initiative. Barrow Neurological Institute; Arizona Alzheimer's Consortium.
54. **Lower frontal amyloid burden in antidepressant users: preliminary findings from persons with and without post-traumatic stress disorder in the ADNI DOD study.** Snyder N, Chen K, Luo J, Thiyyagura P, Devadas V, Chen Y, Bauer III R, Sheline YI, Jagust WJ, Neylan T, Landau SM, Weiner MW, Reiman EM. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of Pennsylvania; University of California Berkeley; University of California San Francisco; Translational Genomics Research Institute; University of Arizona.
55. **Predicting progression to mild cognitive impairment in cognitively unimpaired individuals using neuroimaging biomarkers.** Stonnington CM, Lee W, Bauer III RJ, Shariieff S, Chen Y, Caselli RJ, Locke DEC, Reiman EM, Chen K. Mayo Clinic Arizona; Banner Alzheimer's Institute; Midwestern University; Arizona Alzheimer's Consortium.
56. **Palmitic acid-induced endothelial dysfunction in human leptomenigeal and adipose arterioles.** Truran S, Karamanova N, Serrano G, Franco D, Burciu C, Beach TG, Roher A, Migrino RQ. Phoenix VA Health Care System; Banner Sun Health Research Institute; University of Arizona College of Medicine Phoenix; Arizona Alzheimer's Consortium.
57. **Maternal choline supplementation as a preventive therapeutic option with transgenerational altering properties for Alzheimer's disease pathology.** Velazquez R, Ferreira E, Tran A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

58. **PIMI inhibition as a novel therapeutic strategy for Alzheimer's disease.** Velazquez R, Shaw DM, Caccamo A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.
59. **The quest for a robust and reliable reference region (RR). Exploring RR stability across clinical categories, across A β status and across time for five different A β radiotracers.** Villemagne VL, Bourgeat P, Doré V, Macaulay L, Williams R, Ames D, Martins RN, Salvado O, Chen K, Reiman EM, Masters CL, Rowe CC. Austin Health, Melbourne, Australia; The Florey Institute of Neuroscience and Mental Health, Parkville, Australia; CSIRO, Brisbane, Australia; CSIRO, Melbourne, Australia; The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia; National Ageing Research Institute, Melbourne, Australia; Hollywood Private Hospital, Perth, Australia; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
60. **What are activated microglia doing in Alzheimer's disease brains?: search for additional functional markers.** Walker DG, Tang T, Tsang A, Lue, LF. Arizona State University; Arizona Alzheimer's Consortium.
61. **The Alzheimer's Prevention Registry Genematch program.** Walsh T, Langbaum JB*, Karlawish J, Bradbury A, McCarty Wood B, Roberts JS, Kim S, Patrick-Miller L, Blacker D, Caselli RJ, Marchant GE, Zallen D, Langlois C, Gordon D, Reiman EM, Tariot PN. Banner Alzheimer's Institute; University of Pennsylvania; University of Michigan School of Public Health; National Institutes of Health; University of Chicago; Harvard University; Mayo Clinic Arizona; Arizona State University; Virginia Tech University; Arizona Alzheimer's Consortium.
62. **Retrospective review of dementia specialist experience with amyloid PET imaging: impact on clinical decision-making in diagnosis and patient management.** Weidman DA, Sabbagh MN, Jacobson SA, Burke A, Belden C, Powell J, Seward J, Roontiva A, Thiyyagura P, Kuang X, Bhalla N, Chen K, Zamrini E, Reiman EM. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
63. **Higher BMI is associated with greater cerebral glucose metabolism in late middle aged and elderly subjects regardless of APOE ϵ 4 genotype.** Weise CM, Chen K, Chen Y, Goradhia D, Savage C, Caselli R, Krakoff J, Reiman EM. Klinik und Poliklinik für Neurologie; Universität Leipzig; Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona State University; University of Arizona; Mayo Clinic; NIDDK; Arizona Alzheimer's Consortium.
64. **Automatic prediction of linguistic decline from writings of patients with dementia.** Weissenbacher D, Johnson T, Wojtulewicz L, Dueck A, Locke D, Caselli RJ, Gonzalez G. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
65. **Prevalence of autistic traits in a cognitively normal aging cohort.** Woodruff B, Caselli R, Locke D. Mayo Clinic; Arizona Alzheimer's Consortium.
66. **Highly multiplexed single cell *in situ* analysis with cleavable fluorescent probes.** Xiao L, Mondal M, Liao R, Guo J. Arizona State University; Arizona Alzheimer's Consortium.

67. **The perimenopausal bioenergetic transition in the female brain: implications for prodromal phase of Alzheimer's.** Yin F, Yao J, Sancheti H, Feng T, Melcangi RC, Morgan TE, Finch CE, Pike CJ, Mack WJ, Cadenas E, Brinton, RD. University of Arizona; Arizona Alzheimer's Consortium.
68. **Patch-based sparse coding and multivariate surface morphometry for predicting amnesic mild cognitive impairment and Alzheimer's disease in cognitively unimpaired individuals.** Zhang J, Wang Y, Li Q, Shi J, Bauer III RJ, Chen K, Reiman EM, Caselli RJ, Stonnington CM. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

STUDENT POSTER PRESENTATIONS

69. **Transcriptional and epigenomic changes across perimenopause: implications for prodromal phase of Alzheimer's disease.** Bacon ER, Desai M, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
70. **Effects of multiband acceleration on high angular resolution diffusion imaging data collection, processing, and analysis.** Bernstein AS, Pisner D, Klimova A, Umaphathy L, Do L, Squire S, Killgore S, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.
71. **Using human induced pluripotent stem cells to investigate the contribution of risk variants and aging to the onset and progression of Alzheimer's disease.** Brookhouser N, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
72. **Sex differences in brain metabolism and therapeutic response in the 3xTgAD mouse model.** Caldwell CC, Wong K, Stefanko D, Yin F, Mao Z, Deng Q, Jakowec M, Cadenas E, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
73. **A novel Drosophila model of Alzheimer's disease based on TDP-43.** Chaung M, Kraft R, Zarnescu DC. University of Arizona; Arizona Alzheimer's Consortium.
74. **Species- and age-related differences in learning and performance on working memory tasks in two species of macaque monkeys.** Comrie AE, Gray DT, Burke SN, Smith AC, Barnes CA. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.
75. **Investigating the mechanisms of a multi-state model of Wnt signaling.** Cutts J, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
76. **Cerebellar differences associated with fine motor dysfunction in an aging autism cohort.** Deatherage BR, Braden BB, McBeath MK, Baxter LC. Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; Arizona State University; Arizona Alzheimer's Consortium.
77. **Behavioral evidence for enhanced interference during working memory and associative learning tasks in aged macaques.** Gray DT, Ashford SL, Pyon W, Burke SN, Smith AC, Barnes CA. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.

78. **An orderly interaction? Maze order impacts the outcome of estrogen effects on memory.** Koebele SV, Quihuis AM, Lavery CN, Plumley ZMT, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.
79. **Behavioral impact of long-term chronic implantation of neural recording devices in the rhesus macaque.** Kyle CT, Permenter MR, Vogt JA, Barnes CA. University of Arizona; University of California, Davis; Arizona Alzheimer's Consortium.
80. **Recognition memory context effects in aging.** Lawrence A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
81. **Age-related changes in external cue-based navigation in the medial entorhinal-hippocampal network.** Lester AW, Koutia AJ, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
82. **Using bioengineering approaches to generate a three-dimensional (3-D) human induced pluripotent stem cell (HIPSC)-based model of Alzheimer's disease (ad).** Lundeen R, Petty F, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
83. **Epigenetic and endosomal-lysosomal dysfunction in the basal forebrain during the progression of Alzheimer's disease.** Mahady L, Nadeem M, He B, Perez SE, Mufson EJ. Barrow Neurological Institute; Rush University; Arizona State University; Arizona Alzheimer's Consortium.
84. **Transitions in the inflammatory phenotype during the perimenopause: implications for prodromal phase of Alzheimer's disease.** Mishra A, Brinton, RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.
85. **Relation of white matter hyperintensity volume to cognitive performance in older adults.** Nguyen LA, Bharadwaj PK, Haws KA, Fitzhugh MC, Trouard TP, Hishaw GA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.
86. **Generation of isogenic APOE variants to investigate Alzheimer's disease risk and progression.** Potts C, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
87. **Generation of HIPSC-based model of progerin-induced aging.** Raman S, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
88. **Relation between social interaction and cognitive functioning in older adults: a feasibility study using the EAR technology.** Robbins R, Glisky E, Mehl M. University of Arizona; Arizona Alzheimer's Consortium.
89. **Characterization of circular RNAs in the posterior cingulate in Alzheimer's disease.** Sekar S, McDonald J, Cuyugan L, Craig DW, Liang WS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
90. **Conformal invariants for shape analysis in brain morphometry study.** Shi J, Zhang W, Tang M, Caselli RJ, Wang Y. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

91. **Development of iPSC-based biomarkers to identify the patient population responsive to allopregnanolone.** Solinsky CM, Hennes V, Park JA, Chui HC, Blurton-Jones M, Ichida JK, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
92. **White matter integrity in young and aged bonnet macaques assessed using diffusion MRI.** Umapathy L, Burke SN, Thome A, Plange K, Engle JR, Bernstein A, Do L, Trouard TP, Gothard KM, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
93. **Enhancement of delivery to the brain using ultrasound.** Valdez M, Fernandez E, Matsunaga T, Witte R, Furenid L, Romanowski M, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.
94. **A robust vitronectin-derived peptide (VDP) substrate for the scalable long-term expansion and neuronal differentiation of human pluripotent stem cell (HPSC)-derived neural progenitor cells (HNPCS).** Varun D, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
95. **Mitochondrial gene expression during perimenopause and chronological aging: implications for prodromal stage of Alzheimer's disease.** Wang Y, Brinton RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.
96. **Time-dependent decrease in the peak frequency and power of hippocampal sharp-wave ripples and high-gamma events during post-behavior sleep in aged and young rats.** Wiegand J-P, Gray DT, Schimanski LA, Lipa P, Barnes CA, Cowen SL. University of Arizona; Arizona Alzheimer's Consortium.
97. **Patch analysis based sparse-coding system for predicting future cognitive decline.** Zhang J, Stonnington CM, Li Q, Shi J, Bauer III RJ, Gutman BA, Chen K, Reiman EM, Caselli RJ, Thompson PM, Ye J, Wang Y. Arizona State University; Mayo Clinic Arizona; University of Southern California; Banner Alzheimer's Institute; University of Michigan; Arizona Alzheimer's Consortium.
98. **Studying ventricular abnormalities in mild cognitive impairment with sparse coding on hyperbolic space.** Zhang J, Stonnington CM, Shi J, Li Q, Gutman BA, Chen K, Reiman EM, Caselli RJ, Thompson PM, Ye J, Wang Y. Arizona State University; Mayo Clinic Arizona; University of Southern California; Banner Alzheimer's Institute; University of Michigan; Arizona Alzheimer's Consortium.
99. **Cognitive declination affects the morphometric properties of hippocampus and lateral ventricle.** Zhang W, Shi J, Stonnington C, Bauer III RJ, Gutman BA, Chen K, Thompson PM, Reiman EM, Caselli RJ, Wang Y. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer's Institute; University of Southern California; Arizona Alzheimer's Consortium.

2016 Oral Research Presentation

Abstracts

REGENERATION IN A DEGENERATING BRAIN: ALLOPREGNANOLONE AS THE FIRST REGENERATIVE THERAPEUTIC FOR ALZHEIMER'S DISEASE. Brinton RD.
University of Arizona; Arizona Alzheimer's Consortium.

Background: Allopregnanolone (Allo), a neurosteroid, has emerged as a promising promoter of endogenous regeneration in brain (1). In a mouse model of Alzheimer's disease, Allo induced neurogenesis, oligodendrogenesis, white matter generation and cholesterol homeostasis while simultaneously reducing β -amyloid and neuroinflammatory burden (1). Mechanistically, Allo activates gene expression and signaling pathways required for regeneration of neural stem cells and their differentiation into neurons (1). In parallel, Allo activates systems to promote cholesterol homeostasis and reduce β -amyloid generation (1)

Methods: Discovery, IND enabling translational and clinical analytics to advance therapeutic development of allopregnanolone (Allo) as the first regenerative therapeutic for Alzheimer's disease.

Results: Allopregnanolone induced generation and survival of new neurons in the hippocampus of both normal aged and transgenic AD mice which was accompanied by restoration of associative learning and memory function. In 3xTgAD mice, allopregnanolone increased liver X receptor and pregnane X receptor expression, reduced amyloid- β and microglial activation, and increased markers of myelin and white matter generation. Therapeutic windows for efficacy were evident in both the AD and normal aging brain. Allopregnanolone dose and a regenerative treatment regimen of intermittent allopregnanolone exposure were determining factors regulating therapeutic efficacy.

Conclusions: Gender, genetic risks, stage and burden of disease are critical determinants of efficacy Targeting systems of endogenous regeneration and repair require dosing and treatment regimens specific to regenerative systems biology. Allopregnanolone serves as proof of concept for therapeutics that target endogenous regeneration, windows of therapeutic opportunity for regeneration, and critical system biology factors that will determine the efficacy of regeneration. Based on substantial preclinical and translational science, a Phase 1b/2a clinical trial of allopregnanolone in persons with mild cognitive impairment or early Alzheimer's disease is currently underway.

<https://clinicaltrials.gov/ct2/show/NCT02221622?term=brinton+allopregnanolone&rank=1>

1. Brinton, RD Neurosteroids as regenerative agents in the brain: therapeutic implications. Nature Rev Endocrinol. 2013, 9(4):241-50.

Research supported by US NIH National Institute on Aging (U01 AG031115; UF1AG046148) and the Alzheimer Drug Development Foundation.

NOVEL IMMUNOMAGNETIC REDUCTION PLATFORM PROVIDES ULTRA-SENSITIVITY FOR MEASURING PLASMA TAU AND AMYLOID BETA 42 TO DISTINGUISH ALZHEIMER'S DEMENTIA PATIENTS FROM NORMAL CONTROLS. Lue L, Sabbagh M, Walker D, Schmitz C, Snyder N, Belden C, Chen K, Reiman EM. Arizona State University; Barrow Neurological Institute; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Importance: Ultra-sensitive assays have the potential to provide blood-based biomarkers of Alzheimer's disease (AD).

Objective: To evaluate the ability of ultra-sensitive immunomagnetic reduction (IMR)-based assays and compare levels of plasma total tau (t-tau), amyloid- β (A β 42), and A β 40 levels, and the ratios and products of these measures in patients with the clinical diagnosis of late-onset Alzheimer's dementia and cognitively normal older adults.

Methods: Venous blood was drawn, centrifuged at 2,500 RPM, and used to extract plasma samples from 32 adults, 82 \pm 1 years of age, including 16 patients with the clinical diagnosis of moderate Alzheimer's dementia and 16 normal control (NCs). IMR assays were performed to characterize plasma t-tau, A β 42, and A β 40 levels blind to the subjects' classification or demographic features. For comparative purposes, ultra-sensitive single-molecule enzyme-linked immunosorbent (SIMOA) assays were performed to characterize plasma tau levels in 10 ADs and 10 NCs.

Main outcomes and measures: IMR-measured plasma t-tau, A β 42, and A β 40 levels, alone or in combination, were compared in the patient and NC groups. Receiver Operation Characteristic (ROC) analysis was used to determine the ability to distinguish patient from NC group using levels of t-tau and A β species measured by IMR. Results of tau measurement by IMR and SIMOA platforms were compared within sample, between disease groups, and by area under curve of ROC analysis.

Results: Probable AD group had significantly higher plasma t-tau levels (P=0.001), a trend for higher plasma A β 42 levels (P=0.06), and significantly lower plasma A β 40 levels (P=0.01) than NCs. None of these markers correlated with dementia severity ratings in the patient group.

In an exploratory analyses, the product of plasma t-tau and A β 42 levels distinguished patients from controls with 93.75% sensitivity and 81.25% specificity. IMR- and SIMOA-assayed plasma t-tau levels were comparable in classifying patient from NC groups in terms of area under curve from the ROC analysis (AUC for IMR = 0.93; AUC for SIMOA = 0.75; p = 0.2192).

DEVELOPING NEW INSIGHTS INTO PREVENTING A β DEPOSITION BY HARNESSING CNS-PARASITE INTERACTIONS. Cabral CM, Franco J, MacDonald WR, Koshy AA. University of Arizona; Arizona Alzheimer's Consortium.

Alzheimer's disease (AD) affects over 5 million people in the US alone. Genetic and pathologic data suggest that the generation and aggregation of beta-amyloid (A β) is a major initiator and potentiator of AD pathology. To gain new insights into A β modulation, we sought to harness the co-evolution between the neurotropic parasite *Toxoplasma gondii* and the mammalian brain. A prior study in a human amyloid precursor protein (hAPP) mouse model showed that chronic infection with *T.gondii* improved cognition and reduced A β plaque burden by > 80%. This protection was attributed to *T.gondii*-associated increases in CNS levels of the anti-inflammatory cytokines TGF β and IL-10. To test this hypothesis and develop a better mechanistic understanding of *T.gondii*-associated protection against A β , we infected J20 hAPP mice with one of three canonical strains of *T.gondii* (type I, type II, or type III) and evaluated the CNS of these mice and uninfected hAPP mice at 6 months post infection (9 months of age) for A β deposition, immune cell infiltration, global cytokine environment, and parasite burden. We found that only infection with the type II *Toxoplasma* strain was protective against A β deposition (>80% reduction in A β plaque burden), despite both type II and type III strains establishing a chronic CNS infection and inflammatory response. Compared to control mice, hAPP mice infected with either type II or type III parasites showed increased T-cell infiltration and elevated CNS pro-inflammatory cytokines, including IFN- γ . Neither group showed a > 2-fold elevation of TGF β or IL-10 compared to uninfected hAPP mice, suggesting that these cytokines alone do not account for protective effect of the type II infection. Preliminary work in non-hAPP mice suggest that type II and III infection may alter different parts of the A β processing pathway and may differentially affect T cell and macrophage polarization. Type I-infected mice, which only experience an acute infection, showed no differences in any measured parameter compared to control mice.

In summary, we have determined that the *T.gondii*-induced protection against A β deposition requires a chronic infection and only occurs with *T.gondii* type II-infection. Current work focuses on using unbiased approaches to identify CNS host pathways and immune cell changes specifically associated with type II-infection and protection against A β deposition. Understanding the cellular and molecular mechanisms that underlie the type II effect on A β may offer novel therapeutic targets for preventing A β deposition and improving outcomes for patients with AD.

ALZHEIMER’S PREVENTION REGISTRY AND THE GENEMATCH PROGRAM: SHARED RESOURCES TO THE SCIENTIFIC COMMUNITY TO FACILITATE ENROLLMENT IN STUDIES. Langbaum JB, High N, Walsh T, Gordon D, Nichols J, Reiman EM, Tariot PN. Banner Alzheimer’s Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer’s Consortium.

Background: The Alzheimer’s Prevention Initiative (API) is a collaborative funded by the NIH, philanthropy, and industry to conduct preclinical Alzheimer’s disease (AD) trials in people who, based on age and genetics, are at elevated risk of developing AD symptoms. To support these and other trials, we developed the web-based Alzheimer’s Prevention Registry (“Registry”) and GeneMatch to provide shared resources to the AD scientific community to facilitate enrollment in preclinical studies and to complement and enhance local recruitment efforts.

Methods: Prior to creating the Registry, a national survey of 1,024 adults age 18-75 was conducted for planning purposes to help guide Registry development and outreach strategy. Interested adults of all ages, with and without memory and thinking problems, are eligible to join at www.endALZnow.org. 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 first name, last name, email address, zip code and year of birth; after enrollment they can complete additional contact and demographic information at their convenience and discretion. 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. A/B testing is used to refine messaging and collection of demographic information to increase enrollment. Beginning in Q3 2016, Registry members will be given the opportunity to share his/her contact information with study site staff in order to be contacted about their study interest. GeneMatch is a trial-independent program of the Registry, performing APOE genotyping in individuals age 55-75 to enrich referrals to prevention studies. GeneMatch uses buccal swab kits sent via mail and does not disclose APOE results to participants, either directly or inadvertently through referral to studies. Recruiting studies, however, may ask or invite individuals to learn their APOE results.

Results: The national survey found that 60% were likely to join the Registry, with the biggest motivators to joining being to prevent themselves (73%) or a loved one (77%) from developing AD and believing that clinical trials are key to medical breakthroughs (72%). The Registry was launched in May 2012; as of March 2016, over 213,000 individuals have joined. GeneMatch was launched in a pilot phase in November 2015; as of March 2016 over 2,000 individuals have joined.

Conclusion: The Registry and GeneMatch are key elements of the API, facilitating enrollment into a range of research studies. Both programs have been well-received and enrollment in each continues to increase. We continue to explore novel approaches for increasing enrollment and engagement of enrollees, as well as collaborating with researchers to help promote relevant studies taking place in their catchment areas.

HISTOPATHOLOGY AND FLORBETABEN PET IN PATIENTS INCORRECTLY DIAGNOSED WITH ALZHEIMER'S DISEASE. Sabbagh MN, Schäuble B, Richards D, Anand K, Beach TG, Murayama S, Akatsu H, Takao M, Rowe CC, Masters CL, Sabri O, Barthel H, Gertz H-J, Peters O, Rasgon N, Booth DR, Schulz-Schaeffer WJ, Seibyl J. Barrow Neurological Institute; Piramal Imaging GmbH, Berlin, Germany; Banner Sun Health Research Institute; Tokyo Metropolitan Geriatric Hospital; Tokyo Metropolitan Institute of Gerontology; Fukushima Hospital, Toyohashi, Japan; Nagoya City University, Aichi, Japan; Mihara Memorial Hospital, Isesaki, Japan; University of Melbourne, VIC, Australia; Florey Institute of Neuroscience and Mental Health, Australia; Leipzig University, Germany; Charité Berlin, Berlin, Germany; Stanford School of Medicine; Bioscript Group, Macclesfield, UK; Georg-August University Göttingen, Germany; Molecular Neuroimaging, New Haven, CT; Arizona Alzheimer's Consortium.

Background: Correct diagnosis in patients with cognitive decline can be challenging, with a high incidence of misdiagnosis and implications for patient management. We describe a series of patients from a Phase 3 study who were found to be negative for amyloid beta (A β) on post-mortem histopathology and florbetaben positron emission tomography (PET) scan, despite a clinical diagnosis of Alzheimer's disease (AD).

Methods: Patients were end-of-life individuals who participated in an open-label Phase 3 study comparing florbetaben PET imaging with post-mortem histopathology (ClinicalTrials.gov: NCT01020838).

Results: Of 74 individuals in the original study, 57 were clinically diagnosed with AD, of whom 13 (23%) were negative for A β on histopathology. These patients presented with memory loss, cognitive dysfunction, behavioural and psychological problems, and inability to carry out activities of daily living. At post-mortem histopathology, a wide range of different non-AD conditions was identified, including frontotemporal dementia (FTD), argyrophilic grain dementia, and dementia with Lewy bodies. Florbetaben PET scans were classified as negative for A β in 11 patients based on visual analysis and in all 12 evaluable cases based on composite standardized uptake value ratios.

Conclusions: The diagnostic accuracy of a clinical diagnosis of AD is 77%. Florbetaben PET can assist physicians in the differential diagnosis of neurodegenerative disorders by reliably excluding amyloid pathology.

DEEP BRAIN STIMULATION OF THE FORNIX FOR ALZHEIMER'S DISEASE - THE ADVANCE TRIAL. Lozano AM, Fosdick L, Mallar Chakravarty M, Leoutsakos J, Munro C, Oh E, Drake KE, Lyman CH, Rosenberg PB, Anderson WS, Tang-Wai DF, Pendergrass JC, Salloway S, Asaad WF, Ponce FA, Burke A, Sabbagh M, Wolk DA, Baltuch G, Okun MS, Foote KD, McAndrews M, Giacobbe P, Targum SD, Lyketsos CG*, Smith G*. University of Toronto, Toronto, Ontario Canada; Functional Neuromodulation Ltd, Minneapolis, MN; Douglas Mental Health University Institute, Montreal, Quebec, Canada; McGill University, Montreal Quebec Canada; Johns Hopkins University School of Medicine; Clintara LLC; Butler Hospital; Alpert Medical School of Brown University; Rhode Island Hospital; Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; Banner Alzheimer's Institute; University of Arizona College of Medicine, Phoenix; University of Pennsylvania; University of Florida; Arizona Alzheimer's Consortium.

Background: This report describes the surgical safety and one-year cognitive outcomes in a cohort of patients with mild probable Alzheimer's disease who underwent bilateral deep brain stimulation (DBS) of the fornix as part of the ADvance Trial.

Methods: The ADvance Trial is a multicenter, 12-month, double-blind, randomized, controlled feasibility study that was conducted to evaluate the safety and tolerability of DBS of the fornix in patients with mild probable Alzheimer's disease. Intraoperative, perioperative, and cognitive data were collected to assess treatment effect size prospectively. Adverse events (AEs) were reported to an independent clinical events committee and adjudicated to determine relationship between the AE and the study procedure.

Results: Between June 6, 2012, and April 28, 2014, a total of 42 patients with mild probable Alzheimer's disease were treated with bilateral fornix DBS at 7 study sites. These patients underwent surgery (mean age 68.2 ± 7.8 [range 48.0-79.7], 19 women and 23 men). The mean interval from diagnosis was 2.3 years (range 0-5.9 years). There were 20 serious adverse events. No patients experienced neurological deficits as a result of the study and there were no mortalities. Implanted subjects had baseline mean ADAS-cog-13 and CDR-SB scores of 28.9 (SD 5.2) and 3.9 (SD 1.6), respectively. There were no significant differences between the groups at 12 months in the entire cohort. However, in a subgroup of subjects 65 or older (n=15 in each group) ADAS Cog-13 worsened by 7.8 vs 3.7 while CDR-SB scores worsened by 3.5 vs 2.1 in the "off" vs "on" group respectively.

Conclusions: Patients with mild probable Alzheimer's disease treated as part of the ADvance Trial tolerated DBS to the fornix well. While there were no differences in cognitive outcomes for participants as a whole, participants aged ≥ 65 years demonstrate a trend toward slowing of clinical decline supporting continued evaluation of DBS of the fornix in older AD patients.

C9ORF72: BRIDGING THE GAP BETWEEN DEMENTIA AND MOTOR NEURON DISEASE. Lorenzini I, Mendez E, Chew J, Petrucelli L, Sattler R. Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; Johns Hopkins University; Mayo Clinic Jacksonville; Arizona Alzheimer's Consortium.

In 2011, a mutation in the C9orf72 (C9) gene has been identified in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). This discovery strengthened the already known, yet largely neglected symptomatic and genetic overlap between a uniformly fatal motor neuron disease and the second-most common early-onset form of dementia. Our laboratory is interested in studying the molecular mechanisms of cognitive impairments found in the ALS/FTD disease continuum using human in vitro cell models and novel C9orf72 mouse models. We hypothesize that progressive synaptic loss and dysfunction, often described as synaptopathy, is an early event during disease development, which has long-lasting effects for cognitive function. In support of this, we have preliminary evidence of synaptic loss and dendritic remodeling in human cortical neurons differentiated from C9 ALS patient-derived human induced pluripotent stem cells (hiPSCs). In addition, we have evidence that the glutamate receptor subunit GluA2 is mis-edited at its Q/R editing site in C9 patient tissue, C9 hiPSC neurons and novel C9 mouse models. Lack of editing at the GluA2 Q/R site makes GluA2-containing AMPA receptors permeable to Ca²⁺, which has been associated with vulnerability of neurons to excitotoxicity, a hallmark mechanism of neuronal cell death in ALS and a well-described mechanism for deficits in synaptic transmission. A basic understanding of synaptic dysfunction in ALS and FTD, especially at early pre-symptomatic time points, could lead to the identification of specific therapeutic targets aimed at stratified patient populations to enable better and more successful clinical trials.

THE MTOR/P70S6K PATHWAY PLAYS A KEY ROLE IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE. Oddo S, Caccamo A, Shaw D, Branca C. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging is the major risk factor for Alzheimer's disease (AD); however, little is known as to how the aging process facilitates the development of AD. Changes that occur in the brain as a function of age may facilitate the development of AD. Reducing the activity of the mammalian target of rapamycin (mTOR), and its downstream target p70S6K, increases lifespan and health-span in several genetically different species. mTOR is a protein kinase that plays a key role in regulating protein translation (via p70S6K) and degradation. Therefore, mTOR is key in controlling protein homeostasis, a process that is altered in AD and other proteinopathies. The goal of this work is to assess the role of the mTOR/p70S6K pathways in the pathogenesis of AD.

Methods: Using several mouse models, we employed multidisciplinary approaches to dissect the role of the mTOR/p70S6K signaling in AD.

Results: We will show that genetic and pharmacologic reduction of mTOR and p70S6K signaling reduced amyloid- β and tau pathology and rescued memory deficits. Mechanistically, the reduction in mTOR signaling led to an increase in autophagy induction and restored the hippocampal gene expression signature of the Tg2576 mice to wild type levels.

Conclusions: Given that mTOR and p70S6K regulate lifespan and health span, the data presented here have profound clinical implications for aging and Alzheimer's disease and provide the molecular basis for how aging may contribute to AD pathology. Our results implicate hyperactive mTOR/p70S6K signaling as a previous unidentified signaling pathway underlying gene-expression dysregulation and cognitive deficits in Alzheimer's disease.

BEHAVIORAL EVIDENCE FOR ENHANCED INTERFERENCE DURING WORKING MEMORY AND ASSOCIATIVE LEARNING TASKS IN AGED MACAQUES. Gray DT, Ashford SL, Pyon W, Burke SN, Smith AC, Barnes CA. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.

Background: The ability to protect ongoing cognitive processes from distracting stimuli is known as interference control. Human studies investigating this phenomenon have revealed that despite impressive flexibility in most cognitive domains, there is a severe capacity limitation in the ability to perform multiple tasks simultaneously. Efforts to develop behavioral paradigms for animal models to study interference control at the single-neuron level have recently led to insights into the neuronal mechanisms behind these limitations. For example, Wantanabe and Funahashi (2014) demonstrated that during a spatial attention task, neurons in the lateral prefrontal cortex show a decreased ability to represent task-relevant information proportional to the cognitive demand of a competing task. During normal aging this capacity limit is further reduced, but our understanding of the neural basis underlying these age-related declines is minimal.

Methods: A colony of young and aged bonnet macaques performed two behavioral paradigms that test different forms of memory interference. The first paradigm is a novel computer-controlled associative learning task with varying levels of interference, and the second is a manually-presented working memory interference task (adapted from Clapp et al., 2009). Learning of these tasks are characterized using a state-space modeling algorithm (Smith et al., 2004).

Results: In the associative learning interference task, the ability of monkeys to form associations between novel images and rewards was significantly reduced as the number of associations to simultaneously learn increased. This interference effect was proportionally greater in aged than in young monkeys. During the working memory interference task, interruptions presented in the delay period of a delayed nonmatching-to-sample task decreased the performance of aged monkeys significantly more so than young monkeys.

Conclusions: Together these data suggest that older macaque monkeys, like older humans, exhibit age-related deficits in interference control. As with the associative learning paradigm, the working memory interference task is currently being implemented under computer control to facilitate the temporal precision required to monitor behavior in relation to electrophysiological recordings, which will provide a novel opportunity to study age-related deficits in interference control at the single-neuron level.

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PATCH-BASED SPARSE CODING AND MULTIVARIATE SURFACE MORPHOMETRY FOR PREDICTING AMNESTIC MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE IN COGNITIVELY UNIMPAIRED INDIVIDUALS. Zhang J, Wang Y, Li Q, Shi J, Bauer III RJ, Chen K, Reiman EM, Caselli RJ, Stonnington CM. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Neuroimaging biomarkers in combination with classification methods have shown promise as a tool for predicting progression to the clinical stage of Alzheimer's disease (AD). The hippocampus is affected in late preclinical and early clinical stages of AD. We previously described a method capable of detecting subtle changes in hippocampal surfaces, based on the surface fluid registration and multivariate tensor-based morphometry (mTBM) statistics. We now describe a method for distinguishing between cognitively unimpaired older adults who do or do not subsequently progress to amnesic Mild Cognitive Impairment (aMCI) using our new patch-based sparse-coding system with surface multivariate morphometry statistics (MMS) from the hippocampus.

Methods: From the Arizona APOE cohort, a longitudinal study of cognitively unimpaired persons with two, one and no copies of the apolipoprotein E (APOE4) allele with a reported first degree family history of possible AD dementia, we examined volumetric MRI data from 18 cognitively unimpaired participants approximately 2 (1.8 ± 0.8) years before progression to the clinical diagnosis of aMCI and 35 participants who were matched for age and sex and remained unimpaired for ≥ 4 years. We segmented each individual MRI scan with FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>), parameterized the hippocampal surfaces as described previously, and generated the surface MMS consisting of mTBM and radial distance (RD). We constructed a collection of overlapping patches on the surface as the initial sparse coding dictionary. Stochastic Coordinate Coding was then applied to learn a dictionary and sparse codes. We used the max-pooling algorithm on the newly learned high-dimensional features to obtain a final set of low-dimensional features. Finally, an AdaBoost classifier was applied to categorize aMCI and cognitively unimpaired individuals with 5-fold leave-one-out cross validation adopted to evaluate classification accuracy, sensitivity, specificity, positive and negative predictive values.

Results: The best prediction result of aMCI was achieved with our MMS features, with 96% accuracy, 100% sensitivity, 95% specificity, 86% positive and 100% negative predictive values.

Conclusions: While our findings should be considered preliminary, sparse coding with the sensitivity of surface multivariate morphometry may be applied to volumetric MRIs to predict imminent progression from the preclinical to clinical stages of AD with great accuracy.

IDENTIFICATION OF TREM2 AGONISTS AS A THERAPEUTIC AVENUE FOR ALZHEIMER'S DISEASE. Schrauwen I, Sereduk C, Yin H, Huentelman M. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The global prevalence of dementia is projected to increase in the coming decades as the population ages. Alzheimer's disease (AD) is a leading cause of dementia, and current FDA-approved drugs for AD do not prevent or reverse the disease, and provide only modest symptomatic benefits. Alterations in both astrocytes and microglia, reflecting underlying changes in innate immune activation within the brain, are invariant pathological features of AD as well as other neurodegenerative disorders.

Methods: Several studies have demonstrated that genetic variants in triggering receptor expressed on myeloid cells 2 (TREM2), a known regulator of microglial activation and phagocytosis, confer substantial risk to several forms of dementia and neurodegenerative disease. This evidence is further strengthened by the first report of a nonsense mutation we recently identified in a family with behavioral variant frontotemporal lobar degeneration (bvFTLD). TREM2 function may affect AD pathology through the phagocytosis of amyloid plaque deposits and other debris, and recent studies overexpressing TREM2 in vitro and in vivo support this hypothesis. We hypothesize that agonists of TREM2 could increase the clearance of amyloid- β , apoptotic neurons and other debris in the brain and may therefore act to prevent or to slow disease progression when administered during the optimal timeframe.

Results: We have developed a reporter cell line that can detect the activation of TREM2 to identify compounds that can stimulate TREM2 in high throughput. The luciferase reporter cell-line stably expresses TREM2, TYROBP and NFAT Luciferase. We will screen 2,400 compounds from the well characterized Prestwick and LOPAC libraries at two doses (5 and 20 μ M), All positive hits will be further validated using an NFAT-Luc counter-screening approach and TREM2 selective blocking. Results will be presented at the meeting.

Conclusions: This cell-based high throughput assay for TREM2/TYROBP dependent signaling and agonist discovery program are aimed at laying the foundation for the detection of potent and selective compounds for future in vitro and in vivo development to prevent/halt AD progression and other forms of dementia.

DIGITAL BIOMARKERS: BUILDING A REGULATORY SCIENCE ROADMAP TOWARDS BIOMARKER QUALIFICATION FOR CLINICAL TRIAL USE IN PRESYMPTOMATIC ALZHEIMER'S DISEASE AND RELATED DEMENTIAS. Americ SP, Aviles E, Hudson LD, Kern VD, Kaye JA. Critical Path Institute; Oregon Health Science University; Arizona Alzheimer's Consortium.

Background: Interest in identifying, evaluating and qualifying innovative technologies for use in drug development is growing. While FDA guidance documents exist for pursuing novel Drug Development Tools (DDTs) and Medical Devices Development Tools (MDDTs) for Qualification, the use of Digital Biomarkers (i.e., measured biological events or patient function captured through a device or sensor technology) for use in clinical development remains ill-defined. FDA issued in 4Q2015 a Federal Register request [Federal Register Docket No. FDA-2015-N-3579] for comments that could accelerate the assessment of innovative drug treatments.

Methods: The Coalition Against Major Diseases (CAMD), a consortium within the Critical Path Institute, aims to accelerate the development of tools that increase the efficiency of delivering innovative treatments for Alzheimer's Disease and related dementias. This presentation highlights our use of digital biomarkers in clinical trials, the challenges faced, and the need for:

Data Standards: Consensus on standardized ways to record, structure and report data generated by digital biosensors, employing CDISC standards to provide the consistent data model/structure to enable data sharing across technology platforms.

Digital Biomarkers as Drug Development Tools: Development of standards for validating the analytic performance of devices.

Context of Use (COU) Statements: Implementation of COU statements based on the current state-of-evidence for their application in the drug development process.

Results: CAMD's perspective supports the use of digital biomarkers in clinical trials for:

Function: Electronic monitoring of activities in and outside of home (patterns of sleep, eating, drug adherence, walking, social interactions via phone and computer, cognitive task assessments, etc.) and fine motor skills (e.g., typing or keystroking on computer or smartphone).

Physiological measures: ECG, EEG, movement (accelerometer), speech/voice analysis, etc.

Symptoms: Electronically reported diary of symptoms by patients and caregivers, patient-reported outcomes, adverse events, and mood.

Conclusions:

1. Digital technologies are being explored for safety, efficacy, diagnostic, and enrichment biomarker purposes.
2. Dependent upon COU, different evidentiary standards will be required.
3. Continuous monitoring of patient outcomes will likely provide greater ecological validity, and improved statistical power to execute precision medicine.
4. Having open/frequent dialogue with regulators is critical to shape the development, validation, and clinical relevance of this research.

Institutional Information

**Research Summaries and Key Personnel
from Each Participating Institution**

ARIZONA STATE UNIVERSITY

Institutional Abstract

Arizona State University (ASU) is invested in creating novel ways of solving challenges to have an intense positive global impact. In fact, ASU has recently been ranked number one in U.S. News & World Report on its "Most Innovative Schools" list. Over the past decade, ASU has committed to the model of the New American University. It has focused on academic excellence, inclusiveness to a broad demographic, and maximum societal impact. With Alzheimer's disease (AD) affecting approximately one in nine people 65 years old and older, and one in three people 85 years old and older, research on Alzheimer's disease exemplifies the type of endeavor that ASU seeks to promote. In line with this, ASU has committed to the development of a neurodegenerative research center, including dedicating space, a cutting-edge neuroscientist to lead it, and approximately 20 research laboratories. This will be one of the largest and most productive basic science programs in the scientific fight against AD and other neurodegenerative diseases.

For the Arizona Alzheimer's Consortium, ASU provides the leadership for the Data Management and Statistics Core, as well as the Outreach and Recruitment Core and support for the Neuropathology Core, serving researchers throughout the state as part of the Consortium's NIA-sponsored Arizona Alzheimer's Disease Core Center. The ASU team includes leaders in the development of antibody and novel compound strategies for the treatment of AD and other neurodegenerative diseases (Sierks, Hecht, and Johnson laboratories), 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 of mice as a model for odor learning and discrimination to understand pathologies and novel markers of neurodegenerative disease (Smith 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), 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 (led by David Coon). In the last year, we are thrilled that the Oddo and Brafman laboratories have joined the ASU Arizona Alzheimer's Consortium team. Dr. Oddo's cutting edge research focuses on understanding the molecular mechanisms underlying mnemonic deficits in Alzheimer's disease. Using preclinical models, his laboratory is studying signaling pathway dysfunction and relations to the cognitive deterioration associated with Alzheimer's disease. The exciting work being pursued in the Brafman laboratory uses interdisciplinary approaches, including work with stem cells, to determine the mechanisms of, and design targeted therapies to treat, Alzheimer's and other diseases. Moreover, ASU has numerous scientific research domains that are being further developed and strengthened to additionally bolster the impact on Alzheimer's disease and aging research, with a focus on collaboration, discovery, and action to move forward for trajectories, diagnosis, and treatment. 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 varied 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, and momentum is building to move even further in coming years. Moreover, it is noteworthy that the strengths in the research programs at ASU within the Arizona Alzheimer's Consortium represent a range of colleges and institutes across ASU.

Training, mentoring, and education are prodigious strengths at ASU. ASU offers graduate degrees in Statistics and Biomedical Informatics, the Behavioral Neuroscience Program within the Department of Psychology, as well as the Interdisciplinary Graduate Program in Neuroscience. The latter two programs emphasize approaches that integrate several levels of analysis using a systems approach – cellular, behavioral, and cognitive – to investigate preclinical, clinical, and translational questions about brain and behavior relationships. Importantly, the laboratories at ASU that are involved with the Arizona Alzheimer’s Consortium work to engage and train future generations of scientists, including high school students, undergraduate students, graduate students, and postdoctoral fellows. The approach is hands-on, multifaceted, interdisciplinary, and dimensional, with the goal to engage future exemplary scientists in goal-driven aging and neurodegenerative research to yield maximal impact on research discovery at ASU.

ARIZONA STATE UNIVERSITY

Key Personnel

Name (Last, First)	Degree	Role on Project
Petuskey, William	ScD	Institutional PI
Bimonte-Nelson, Heather	PhD	PI
Brafman, David	PhD	PI
Chen, Grace	PhD	PI
Coon, David Wayne	PhD	PI
Gonzalez, Graciela	PhD	PI
Hecht, Sidney Michael	PhD	PI
Johnston, Stephen	PhD	PI
Marchant, Gary	PhD, JD	PI
Renaut, Rosemary	PhD	PI
Rittmann, Bruce	PhD	PI
Sierks, Michael Richard	PhD	PI
Smith, Brian H.	PhD	PI
Verrelli, Brian	PhD	PI
Wang, Yalin	PhD	PI
West, Steve	PhD	PI
Xue, Guoliang	PhD	Professor
Chen, Yana	PhD	Postdoctoral fellow
He, Ping	PhD	Postdoctoral fellow
Williams, Stephaine	PhD	Postdoctoral fellow
Xin, Wei	PhD	Postdoctoral fellow
Shi, Jie	PhD	Postdoctoral fellow
Zhang, Wen	PhD	Postdoctoral fellow
Liang, Mi	PhD	Postdoctoral fellow
Duyan, Ta	PhD	Postdoctoral fellow
Gerkins, Richard	PhD	Research Assistant Professor
Sinakevitch, Irina	PhD	Research Assistant Professor
Ryoko, Hiroi DuBay Sheri	PhD	Research Assistant Professor
Dunckley, Travis	PhD	Assistant Research Professor
Coleman, Paul	PhD	Research Professor
Mastroeni, Diego	PhD	Assistant Research Professor
Decourt, Boris	PhD	Assistant Research Professor
Lue, Lih-Fen	PhD	Research Professor
Walker, Douglas	PhD	Research Professor
Oddo, Salvatore	PhD	Associate Professor
D'Souza, Gary	PhD	Postdoctoral fellow

Delvaux, Elaine	MS	Research technologist
Nolz, Jennifer		Assistant research technologist

BANNER ALZHEIMER'S INSTITUTE

Institutional Abstract

The Banner Alzheimer's Institute (BAI) has three goals: To end 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. It is intended to promote the evaluation of promising investigational AD treatments and accelerate the identification of treatments to postpone, reduce or completely prevent the clinical onset of AD as quickly as possible. It is intended to leverage its brain imaging resources and expertise to advance the scientific study, early detection, tracking, diagnosis, treatment and prevention of AD and related disorders. It is intended to address both the medical and non-medical needs of patients 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 institutional 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. The Memory Center provides a range of services for patients and family caregivers, helping to address their medical and non-medical needs throughout the patient's illness. It provides educational, outreach and research enrollment programs for Arizona's Native American and Latino communities, it evaluates and follows Native Americans in the NIA-sponsored Arizona AD Center's Clinical Core, and it oversees an Annual Conference on AD and Dementia in Native Americans. It conducts numerous clinical trials of investigational treatments, and helps to support programs in the Alzheimer's Prevention Initiative (API) and Banner Dementia Care Initiative (DCI).

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 APOE $\epsilon 4$ 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 $\epsilon 4$ 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, BAI's Alzheimer's Prevention Initiative (API) has helped to launch a new era in AD prevention research. In its partnership with the University of Antioquia, Genentech and the NIH, the API Autosomal Dominant AD (ADAD) trial is evaluating a passive amyloid- β ($A\beta$) immunotherapy in 300 cognitively unimpaired 30-60 year-old PSEN1 E280A mutation carriers and non-carriers in the world's largest ADAD kindred, located in Antioquia Colombia. In its partnership with

Novartis and the NIH, the international API APOE4 (“Generation”) trial will evaluate an active A β immunotherapy and BACE-1 inhibitor in >1,300 60-75 year-old APOE ϵ 4 homozygotes. The 5-year trials are intended to evaluate the investigational treatments in potentially license-enabling prevention trials; to provide a better test of the amyloid hypothesis than trials in the later preclinical or clinical stages of AD; establish the extent to which a treatment’s different biomarker effects are associated with a clinical benefit and provide evidence to support their use as reasonably likely surrogate endpoints in future 24-month prevention trials; provide a shared resource of data and biological fluids for the research community after the trial is over; complement, support and providing a foundation for other prevention trials; to help clarify the benefits, risks and role of APOE genetic test disclosure in the era of Alzheimer’s prevention trials; support the advancement of Alzheimer’s prevention research in the Collaboration for Alzheimer’s Prevention; 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 nearly 5,000 members of the PSEN1 E280A mutation kindred, including >1,000 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 >210,000 people and continues to grow rapidly; our GeneMatch Program (www.endALZnow.org/genematch) was recently launched and will roll out further in the coming months to support APOE genotyping in many thousands of people 55-75 years of age, match interested participants to relevant prevention trials, including but not limited the extremely large number of APOE ϵ 4 homozygotes in the Generation Trial, and to begin to clarify what it means to learn about one’s APOE test results; and these programs continue to grow.

During the past year, we and our colleagues received an outstanding priority score for the Arizona ADCC Renewal Grant, Notifications of Award to participate in NINDS’s longitudinal multi-center study of chronic traumatic encephalopathy and NIA’s longitudinal study of Down Syndrome (and provide a further foundation for prevention trials in that at risk group). An administrative supplement was submitted to add tau PET to the Arizona APOE Cohort Study and a new grant for the API ADAD Trial will be submitted in June, including but not limited to the addition of tau PET and further development of our post-trial data sharing activities. In July 2015, we proposed what it will take to find and support the approval of effective AD prevention therapies in a wide range of individuals at risk for AD by 2025, and we are exploring new API prevention trials to support that effort.

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, and advance the complementary research goals of our partners inside and outside Arizona.

7. To provide a care model that more fully address the needs of patients and families and BAI, and to develop and test the cost-effectiveness of a dementia care program that better addresses the needs of patients and family caregivers in the Banner Health Accountable Care Organization in the Banner Dementia Care Initiative.
8. To support the clinical research and Native American outreach, education and enrollment goals of the Arizona ADCC.
9. To promote the further development, productivity, and close working relationships of research programs involved in the fight against AD and related disorders.

BANNER ALZHEIMER'S INSTITUTE

Key Personnel

Name (Last, First)	Degree	Role on project
Reiman, Eric	MD	Executive Director, Banner Alzheimer's Institute (BAI); PI API; Director, Arizona Alzheimer's Consortium (AAC); Director, Arizona ADCC
Tariot, Pierre	MD	Director, BAI; PI, API
Anderson, Darin	MBA, MHSA	Research Administrative Director
Bandy, Dan	MS, CNMT	PET Technical Director and Sr. Scientist
Batchuluun, Dawn	BA	Clinical Research Coordinator
Brand, Helle	PA	Physician Assistant, Memory Disorders Center
Burke, Anna	MD	Dementia Specialist
Burke, Bill	MD	Director, Stead Family Memory Center
Chen, Kewei	PhD	Director, Computational Brain Imaging Program Biomathematician
Dougherty, Jan	RN, MS	Director, Family & Community Services
Hall, Geri	PhD, ARNT, CS, FAAN	Clinical Nurse Specialist, Family & Community Services
Goradia, Dhruvan	PhD	Associate Scientist
High, Nellie	MS	Research Project Coordinator
Jakimovich, Laura	RN	Multi-Center Clinical Trials Manager
Langbaum, Jessica	PhD	Principal Scientist, Associate Director, Alzheimer's Prevention Initiative
Langlois, Carolyn	MA	Clinical Research Program Manager
Lee, Wendy	MS	Bioinformatics Manager, Computational Brain Imaging
Lomay, Nicole		Native American Outreach Representative
Lopez, Ashley	MS	Clinical Trials Operations Director
Perrin, Allison	MD	Physician Dementia Specialist
Protas, Hillary	PhD	Associate Scientist
Savage, Cary	PhD	Senior Scientist, Brain Imaging Center
Seward, James	PhD	Neuropsychologist
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; b) a world-class Brain and Body Donation Program (BBDP) for the study of AD, PD, related disorders 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, which includes 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) a cardiac stem cell research program; f) 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 g) close working relationships with researchers throughout Arizona and around the world. From July 2001 to June 2016, BSHRI has served as the applicant organization for the Arizona ADCC on behalf of the organizations in the Arizona Alzheimer's Consortium.

Directed by Dr. Thomas Beach, the BBDP includes more than 800 clinically characterized and longitudinally assessed participants, including patients with AD, PD, and related disorders, and older adults who are cognitively and neurologically unimpaired at the time of their enrollment, all of whom have consented to donate their brains after they die. It is internationally recognized for: a) its unusually rapid autopsy program, with a median 3-hour post-mortem interval for the ~1,500 expired brain donors, comprehensive neuropathological assessments, and the unusually high tissue quality needed to support certain kinds of post-mortem studies; 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 400 expired donors since 2005, and the opportunity to relate brain pathology to biological features of other body organs; and d) an extraordinary number of annual tissue distributions to advance research in Arizona and around the world. The BBDP includes many research participants in the Arizona ADCC's Clinical and Ancillary BBDP Cores, the ADCC's Neuropathology Core, and the NINDS's National Brain and Tissue Resource for PD and Related Disorders (NBTR-PD, in partnership with Mayo Clinic Arizona and BNI). 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.

This year has marked a period of significant change, as BSHRI and its organizational partners have sought to provide a foundation for dramatic growth of Arizona's AD, PD, related

disorders, and aging programs. These changes include the following: a) 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) recruitment of 6 new dementia and movement disorder clinicians and clinical trials researchers (2 pending), including Drs. Edward Zamrini (Memory Center Director) and Dr. David Shprecher (Movement Disorders Program Director); c) relocation of Drs. Sabbagh and Shill to BNI (to lead and further develop BNI's respective AD and PD clinical and clinical research programs and foster new research collaborations); d) establishment of the Banner-ASU Neuroscience Alliance, including relocation of the 5 (Coleman/Mastroeni, Decourt, Lue, Oddo, and Walker) basic science laboratories to ASU, creation of the ASU-Banner Neurodegenerative Disease Research Center (NDRC), a commitment from ASU to establish 20 basic/translational research laboratories, the recently started construction of state-of-the-art laboratory space for NDRC researchers at ASU's Biodesign Institute, the ongoing recruitment of an international leader to direct what is intended to become the largest basic/translational research programs in the fight against neurodegenerative diseases, 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.

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
Davis, Kathryn	BA, CSP, CRC	Clinical Core Coordinator
Liu, Ming-Jai	MD, PharmD	Neurologist, Movement Disorder Neurologist
Powell, Jessica	PsyD	Neuropsychologist
O' Connor, Kathy	MS	Outreach Program Manager/Longevity Program Coordinator
Schmitt, Andrea	BS, CRA	ADCC Administrative Director
Serrano, Geidy	PhD	Anatomist, BBDP
Sue, Lucia	BS	Coordinator, Neuropathology Core, BBDP
Shprecher, David R	DO, MD	Movement Disorders Program Director, Movement Disorders Neurologist
Taylor, Peter J.	DO, MA	Geriatric Psychiatrist, Memory Center
Zamrini, Edward	MD	Director, 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

The Barrow Neurological Institute focuses on human and animal research that can translate to clinical care. The BNI focus in Alzheimer's Disease and aging is in prevention, early detection and defining mechanisms of AD. On the cellular level, the Cellular Metabolism laboratory (Dr. Jiong Shi) studies the role of energy metabolism and, more specifically, mitochondrial function, in brain aging and age-related neurological disorders, primarily Alzheimer's disease. Dr. Elliot Mufson has an internationally known molecular neuroanatomy program in the area of dementia in the aged and diseased brain, and is one of the hundred most cited authors in the ISI Web of Knowledge. His focus is on gene expression patterns in Alzheimer's disease and has conducted a study this year examining tau protein in the nucleus basalis of Meynert in autopsy brains. Dr. Sabbagh joins the faculty in the department of neurology at the Barrow Neurological Institute as Director of the Alzheimer's and Memory Disorders Division after 15 years at the Banner Sun Health Research Institute. His focus is development of the clinical trials program which will include prevention, MCI, and treatment trials as well as imaging and biomarker studies. His research interest is longitudinal assessment of adults with Down Syndrome to detect AD changes which occur prior to the onset of cognitive decline. Dr. Leslie Baxter studies longitudinal cognitive and brain changes in aging in Autistic Spectrum Disorders (ASD), one of the first studies of the interaction of aging and ASD.

Alzheimer's and Memory Disorders Program:

With the recruitment of Dr. Marwan Sabbagh as our Director of the Alzheimer's and Memory Disorders Division in the Department of Neurology, Dr. Sabbagh is expanding the flow of the clinic and our clinical trial footprint in AD. We are capitalizing on the strengths of the Behavioral Neurology team in clinical trials and the state-of-the-art imaging platforms at the BNI to expand our work in AD, imaging and prevention. We are an active contributor to the Arizona Alzheimer's Disease Core Center study, and with our expansion, will increase our inclusion of Hispanics in the Phoenix area. We have 1 full-time bilingual/bicultural staff member who participates in the ADCC to recruit and assess Hispanic patients. We continue to partner with the Latino community through a Promotore program and outreach activities. About one third of the BNI's ADCC participants are Hispanic, with Hispanics enrolled for as long as 12 epochs.

Alzheimer's disease biomarker studies in the Cellular Metabolism Laboratory:

The focus of the laboratory is to study and identify biomarkers in brain aging and age-related neurological disorders, primarily Alzheimer's disease. Presently, our efforts are aimed at understanding the role of the PACAP-AMPK-Sirtuin3 pathway in the pathogenesis of Alzheimer's disease, at characterizing the neuroprotective properties and at identifying underlying molecular mediators that will be amenable to pharmacological intervention. We rely on a variety of techniques, including cognitive testing, recording of electrical brain activity, anatomy and microscopy studies, magnetic resonance imaging, biochemical energy measurements and genetic manipulations using specialized viruses to introduce desired DNA into neurons.

Alzheimer's Disease Research Laboratory:

The focus of Dr. Mufson's Alzheimer's Disease Research Laboratory is to study the mechanisms underlying the selective vulnerability of neuronal populations which degenerate in people with mild cognitive impairment, Alzheimer's disease and Parkinson's disease.

Human Brain Mapping Laboratory:

The Human Brain Mapping Lab utilizes both cognitive and neuroimaging data to study brain and behavioral changes associated with normal and pathological aging. In the current year, we continue our focus on an under-studied area of aging research: age-related changes in Autistic Spectrum Disorder. We are currently obtaining cognitive and structural, resting-state and task-based functional MRI data on a group of high-functioning older ASD as well as a sample of younger ASD adults and controls. We are testing the model that aging and ASD may interact, altering the anterior-posterior gradient of brain changes associated with aging.

BARROW NEUROLOGICAL INSTITUTE
at St. Joseph's Hospital and Medical Center
Key Personnel

Name (Last, First)	Degree	Role on Project
Baxter, Leslie	PhD	Principal Investigator
Sabbagh, Marwan	MD	Neurologist; Director, Alzheimer's and Memory Disorders Program
Shi, Jiong	MD, PhD	Neurologist
Mufson, Elliot	PhD	Neuroscientist
Wu, Jie	MD, PhD	Neuroscientist
Braden, Blair	PhD	Post-Doctoral Fellow
Yin, Junxiang	PhD	Post-Doctoral Fellow
Han, Pengcheng	PhD	Post-Doctoral Fellow
Mendoza, Perla	MS	Clinical Coordinator
Zhuang, Ninging	BS	Lab technician
Rowcliffe, Stacey	BS	Psychometrist
Martinez Lujan, Lazaro	BS	Study Coordinator
Chacon, Bianca	BS	Study Coordinator
Pipe, James	PhD	Director, Keller Center for Imaging Innovation
Debbins, Josef	PhD	MR Engineer, Keller Center for Imaging Innovation

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.

During the initial phase of our program, data were analyzed in cross sectional correlations between APOE genetic status, physical and psychological stressors, cognition, and brain imaging measures. Since then, the bulk of our efforts have been dedicated to longitudinal analyses, and we have shown the neuropsychologically defined onset of Alzheimer's disease begins during our 50's in APOE e4 carriers, it 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 missing from this preclinical profile is any indication of depression as a preclinical harbinger.

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 Parro 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. Complete a pilot project of whole exome sequencing and bioinformatics analysis of a 55 gene panel in a clinical cohort of patients with biomarker supported young onset Alzheimer's disease (or frontotemporal dementia)
3. Publish our analyses of personality factors' influence on age-related cognitive trajectories
4. Continue data analysis within our large cross sectional study of multiple MRI-based structural, physiological, and vascular measures across the entire adult lifespan (20's-90's), and their correlation with neuropsychological test scores
5. Completion of a study evaluating a cognitive "stress test" based upon TOMM40 genotype to further test the proposal that TOMM40 is another genetic risk factor for AD
6. Exploration of plasma eosinophil products in patients with vascular contributions to dementia
7. Collaboration to establish lymphocyte derived iPS cells and differentiated in vitro cortical neurons to explore intraneuronal pathophysiology related to Alzheimer's disease.
8. Exploration of a partnership with Mountain Park Health Center to address disparities in dementia care and research opportunities in a large Latino population.

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

MAYO CLINIC ARIZONA

Key Personnel

Name (Last, First)	Degree	Role on Project
Caselli, Richard	MD	Principal Investigator, Clinical Core Director, Associate Director, Behavioral Neurologist
Woodruff, Bryan	MD	Co Investigator, Behavioral Neurologist
Locke, Dona	PhD	Co Investigator, Neuropsychologist
Stonnington, Cynthia	MD	Co Investigator, Psychiatrist
Geda, Yonas	MD	Co Investigator, Psychiatrist
Hoffman-Snyder, Charlene	DNP	Nurse Practitioner
Henslin, Bruce	BA	Study Coordinator
Johnson, Travis	BA	Study Coordinator
Adler, Charles	MD	PI, Chronic Traumatic Encephalopathy Project
Dodick, David	MD	Co-PI, Chronic Traumatic Encephalopathy Project
Wethe, Jennifer	PhD	Co Investigator, Neuropsychologist, Chronic Traumatic Encephalopathy project
Duffy, Amy	BA	Study Coordinator, Chronic Traumatic Encephalopathy Project

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 several research Divisions including: Cancer and Cell Biology, Clinical Translational Research, Computational Biology, Genetic Basis of Human Disease, Integrated Cancer Genomics, Neurogenomics, and Pathogen Genomics. The Neurogenomics Division is the home of Alzheimer's disease (AD) and aging research 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.

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

Key Personnel

Name (Last, First)	Degree	Role on project
Adkins, Jonathan	BS	Research Associate
Bleul, Christiane	MS	Research Associate
Courtright, Amanda	BS	Research Associate
Craig, David	PhD	Director and Professor, Neurogenomics
Cuyugan, Lori	MS	Research Associate
Piras, Ignazio	PhD	Bioinformatician
Henderson-Smith, Adrienne	BS	Research Associate
Huentelman, Matthew	PhD	Principal Investigator
Jespen, Wayne	BS	Research Associate
Lechuga, Cynthia	MBA,CRA	Sr. Grants & Contract Administrator, Neurogenomics
Liang, Winnie	PhD	Co-Investigator
Malencia, Ivana	BS	Bioinformatician
Reiman, Eric	MD	Consultant
Van Keuren-Jensen, Kendall	PhD	Co-Investigator
Siniard, Ashley	BS	Research Associate
Schrauwen, Isabelle	PhD	Research assistant professor
Sekar, Shobana	MS	Graduate Student
Turk, Mari	BS	Graduate Student
Wolfe, Amanda	BS	Research Associate
Yeri, Ashish	PhD	Postdoctoral Fellow

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 substrate, and ways to delay or prevent cognitive aging and dementia. To accomplish these goals, UA investigators representing 11 departments and institutes, including researchers in the fields of neuroimaging, cognitive and behavioral neuroscience, neuropsychology, neurology, 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, including studies that translate findings across species with humans and non-human animal models of aging and age-related disease. A major component of this research uses advanced magnetic resonance imaging (MRI) as a cross-cutting methodology to measure brain function, structure, and connectivity in aging and age-related, neurodegenerative disease.

A translational approach to research is undertaken that spans multiple laboratories and methodologies to address clinical and basic research aims concerning the effects of healthy and pathological aging, including 1) to investigate the neural systems and associated cognitive processes that are altered in the context of aging and age-related disease, 2) to track brain changes and cognitive abilities during aging, 3) to evaluate how genetic and other health risk factors influence brain aging and cognitive decline, 4) to develop and test new imaging methods to aid early detection and the tracking of brain changes due to aging and disease, 5) to develop and test strategies to improve cognitive function during aging, and 6) to provide information to the community to advance understanding about aging, cognitive decline, and age-related neurodegenerative disease.

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

1. Imaging methods development. Our researchers are developing and implementing new magnetic resonance imaging techniques and statistical analysis methods that may prove useful in examining brain structure, function, connectivity, and pathology in both human and non-human animal models of aging and age-related disease. Methods are developed with high resolution MRI for quantitative, non-invasive measurements in humans, non-human primates, and wild-type and transgenic rodents.

2. fMRI studies of memory and aging. These studies utilize functional MRI in order 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.

3. Early detection of healthy and pathological aging. The application of several MR methods including high-resolution anatomical imaging, diffusion MRI, perfusion MRI, and MRI measures of functional connectivity for the early detection, diagnosis, and treatment of cognitive and psychological impairments associated with cognitive aging and Alzheimer's disease (AD). The projects focus on identifying early neurocognitive and biological markers that may signal the early effects of AD prior to the onset of cognitive symptoms. MR methods are also being applied to understand factors that increase risk for AD, including genetics, familial risk, health factors such as hypertension, head injury, and obesity, and those that may decrease risk for AD, such as exercise, education, and the use of anti-inflammatory drugs.

A noteworthy accomplishment this year is the successful recruitment of Dr. Roberta Diaz Brinton, who will join the UA in May 2016 as the inaugural Director of the University of Arizona Health Sciences Center for Innovation in Brain Science. Dr. Brinton is an internationally renowned neuroscientist who has made seminal contributions in the field of

Alzheimer's. As Director of the new Center for Innovation in Brain Science, Dr. Brinton will provide leadership for accelerating the advancement of interdisciplinary research programs that integrate with existing University strengths in cognitive aging in health and disease, chronic pain, traumatic brain and spinal cord injury, stroke and aphasia, as well as the emerging area of brain and cognitive development.

This program of research is complemented by interactions with other UA investigators and programs. Other complementary areas of activity at the UA include research on the underlying biological mechanisms of normal age-related alterations in memory as part of the Arizona Evelyn F. McKnight Brain Institute, studying the longitudinal effects of aging on memory processes in older adults with and without increased risk for AD, investigating the cognitive effects of Down syndrome as a cohort with increased genetic risk for the development of AD pathology, and the development of novel radiotracer imaging methods to detect pathology in transgenic animal models of AD. 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, Evelyn F. McKnight Brain Institute
Alexander, Gene	PhD	Investigator; Psychology, Neuroscience & Physiological Sciences Programs, Evelyn F. McKnight Brain Institute
Bhattacharjee, Sandipan	PhD	Investigator; Pharmacy Practice and Science
Barnes, Carol	PhD	Investigator; Psychology, Neurology, Neuroscience & Physiological Sciences Programs, Evelyn F. McKnight Brain Institute
Beeson, Pagie	PhD	Investigator; Speech and Hearing Sciences
Billheimer, Dean	PhD	Investigator; Biometry, Statistics Program
Edgin, Jamie	PhD	Investigator; Psychology
Erickson, Robert	MD	Investigator; Pediatrics
Furenlid, Lars	PhD	Investigator; Medical Imaging
Glisky, Elizabeth	PhD	Investigator; Psychology, Evelyn F. McKnight Brain Institute
Hay, Meredith	PhD	Investigator; Physiology, Evelyn F. McKnight Brain Institute
Hishaw, G. Alex	MD	Investigator; Neurology
Konhilis, John	PhD	Investigator; Physiology
Koshy, Anita	MD	Investigator; Neurology and Immunobiology
Liang, Ron	PhD	Investigator; Optical Sciences
Matsunaga, Terry	PhD	Investigator; Medical Imaging
Nadel, Lynn	PhD	Investigator; Psychology, Neuroscience Program, Evelyn F. McKnight Brain Institute
Peterson, Mary	PhD	Investigator; Psychology
Raichlen, David	PhD	Investigator; Anthropology
Rapcsak, Steven	MD	Investigator; Neurology, Psychology, Evelyn F. McKnight Brain Institute
Romanowski, Marek	PhD	Investigator; Biomedical Engineering
Ryan, Lee	PhD	Investigator; Psychology, Neurology, Neuroscience Program, Evelyn F. McKnight Brain Institute
Serio, Tricia	PhD	Investigator; Molecular and Cellular Biology
Sweitzer, Nancy	MD, PhD	Investigator; Cardiology
Trouard, Theodore	PhD	Investigator; Biomedical Engineering, Evelyn F. McKnight Brain Institute
Utzinger, Urs	PhD	Investigator; Biomedical Engineering
Wilson, Stephen	PhD	Investigator; Speech and Hearing Sciences
Witte, Russ	PhD	Investigator; Medical Imaging
Zarnescu, Daniela	PhD	Investigator; Molecular and Cellular Biology

Project Progress Reports

Project Progress Reports

Arizona State University

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Pulses of estrogen as a transient hormone therapy in young versus old age. Heather Bimonte-Nelson, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aim: The specific aim of this study is to evaluate age differences in responsiveness to cyclic pulses of estrogen for cognitive efficacy.

Background and Significance: It is estimated that by the year 2050 there will be 88.5 million people in the United States over the age of 65; over half of these individuals will be postmenopausal women (U.S. Census Bureau, 2010). The onset of menopause has been associated with symptoms that affect quality of life, and hormone therapy is given to attenuate menopause-induced symptoms (Curtis & Martins, 2006; Sherwin, 1988). A NIA-sponsored workshop was held in 2010 to elucidate the impact of the menopause transition on cognition and mood (Maki et al., 2010). Outcomes were several-fold, including that "identifying a cognitively neutral or beneficial combination therapy for the treatment of menopausal symptoms in naturally menopausal women is an important goal for future research" (Maki et al., 2010, p2). A critical step toward this goal is defining the hormone regimens to be used in hormone therapy treatments during menopause. This is important now more than ever given recent controversies driving many new hypotheses regarding personalization of hormone therapy, and finding hormone therapies that provide the health benefits without the risks.

We have shown that estrogens have beneficial effects when given tonically in young adulthood or middle age (Bimonte and Denenberg, 1998; Bimonte-Nelson et al., 2006; Talboom et al. 2008). However, we showed that in old age estrogen was no longer beneficial when given tonically (Talboom et al., 2008). Recent evidence from our laboratory has shown profound benefits of estrogens in middle age when given cyclically via a daily injection, in a pulsatile manner (unpublished observations). These findings build on our prior work showing similar beneficial effects with estrogen injections given every other week during middle age (Bimonte-Nelson et al., 2006). Based on data evaluating estrogen receptor recycling in cyclic versus tonic treatments (Bimonte-Nelson et al., 2010; Blaustein, 1993; Kassis and Girski, 1981), we anticipate that cyclic injections in old age could yield beneficial effects. In fact, cyclic estrogen treatment could provide many benefits of hormone therapy, but with less overall exposure, thereby potentially attenuating some of the risks associated with hormone treatments. The current study will directly evaluate the impact of cyclic, pulsed estrogen treatment on memory performance in young versus aged animals.

Experimental Design and Methods: Rats will be young or aged at study initiation. Fisher-344CDF rats born and raised at the National Institute on Aging colony will be used. All procedures are approved by the Arizona State University Institutional Animal Care and Use committee and adhere to National Institutes of Health standards. All rats will receive surgery to remove ovaries (Ovx). The E2 dose per injection will be based on previous studies used in our laboratory, resulting in levels within the range of what circulates endogenously (Bimonte-Nelson et al., 2010). Rats will be randomly assigned to treatment group, and a battery of maze tests will be given.

Proposed One-Year and Long-Term Outcomes: Our long-term overarching goal is to understand how ovarian hormone loss and replacement affects cognitive and brain aging in the

rat model. The ultimate goal is to translate effects to humans so that we can optimize women's health during aging. The one-year outcome will be a manuscript submitted for publication by the end of the year of funding. These data will also allow considerations for future hormone mechanism and/or pharmaceutical studies. We anticipate that these data will be incorporated into a larger RO1 application.

Progress to Date: The experiment is ongoing and final data will be analyzed within the next few months. Manuscript write-up and submission will follow shortly thereafter.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Using bioengineering approaches to generate a three-dimensional (3-D) human induced pluripotent stem cell (hiPSC)-based model of Alzheimer's disease (AD). David Brafman, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Background and Significance: Alzheimer's Disease (AD) affects over 5 million individuals in the U.S. and has a direct cost estimated in excess of \$170 billion/year¹⁻³. There are two forms of AD—early-onset, familial AD (FAD) and late-onset-sporadic AD (SAD). Both forms of AD are characterized by axonal transport defects, synaptic loss, and selective neuronal death. Nonetheless, the mechanisms that cause AD are unknown, thereby making it difficult to design effective therapies⁴. This proposal is significant to human health as it seeks develop an *in vitro* model that mimics the cellular, biochemical and genetic changes associated with AD. In the future, such models can be used to dissect disease mechanisms and develop novel AD therapies.

Specific Aims: Animal models that overexpress specific AD-related proteins or have FAD-related mutations introduced into the animal genome have provided important insights into AD. Nonetheless, these animal models do not display important AD-related pathologies and have not been useful in modeling the complex genetics associated with SAD. The use of AD human induced pluripotent stem cell (hiPSC)-derived neurons have provided new opportunities to study this disease in a simplified and accessible system. However, current studies using AD hiPSCs have been limited by the use of two dimensional (2-D) culture systems that do not mimic the three-dimensional (3-D) architecture of *in vivo* neural tissue. As such, neurons generated from these hiPSC showed some, but not all, of the early molecular and cellular hallmarks associated with the disease. Moreover, neurons generated from only some SAD patients showed phenotypes similar to neurons generated from the FAD lines. Additionally, phenotypes associated with late onset in humans, such as amyloid- β plaques and neurofibrillary tangles, were not observed in these studies. To that end we propose the following specific aims:

Specific Aim 1: Establish a 3-D hiPSC-based neuronal cell culture model. In this aim, we will use engineering methods developed in our laboratory to generate a 3-D cell neuronal cell culture model from hiPSCs. Gene and protein expression as well as electrophysiological analysis will be used to determine the extent of neuronal maturation in the 3-D cultures. To characterize the electrophysiological properties of neurons generated in the 3-D cultures, whole-cell perforated patch recordings will be performed. Cells will be tested for their ability to generate functional Na⁺ and K⁺ currents as well as their capacity to fire spontaneous tetrodotoxin-sensitive action potentials.

Specific Aim 2: Examine the effects of 3-D culture on the induction of AD-related phenotypes in hiPSC-derived neurons. We will use biochemical, cellular, and genetic methods to determine if 3-D culture of AD iPSC-derived neurons induces the manifestation or augmentation of AD-related phenotypes. In particular, we will be interested in determining if 3-D cultures leads to the induction of AD-related phenotypes in SAD hiPSC lines where no phenotypes were previously observed.

Progress Summary: We have developed a robust protocol that allows for the generation of 3-D cultures of neurons from hiPSCs. These neuronal cultures express high levels of mature pan-

neuronal markers (e.g. MAP2, β 3T) and neural transmitter subtype specific markers (e.g. GABA, GABRA1, ChAT). Finally, electrophysiological analysis demonstrates that these neurons have Na⁺ and K⁺ currents as well as the ability to fire action potentials when depolarized with current. Importantly, we have developed differentiation conditions that lead to the generation of near homogenous neuronal populations that express forebrain and cortical related markers such as FOXG1, SATB2, CTIP2, EMX1, CUX1, and TBR1. Because the cognitive decline of AD is directly related to the loss of synapses and neurons in the forebrain and cortex, our ability to generate pure neuronal cultures of cortical identify is critical in using hiPSCs-derived neurons to model and elucidate the molecular underpinnings of AD. More recently, we have developed synthetic polymer- and peptide-based biomaterials that allow for the generation and culture of hiPSC-derived neurons. The advantage of these synthetic culture systems over traditional extracellular matrix protein (ECMP)-based systems is that their physicochemical properties can be precisely controlled. As such, we can now generate 3-D cultures of hiPSC-derived neurons that implement this synthetic substrates to mimic the architecture, composition, and mechanical properties of native brain tissue.

In parallel with these studies, we have generated 3-D cultures of neurons from hiPSC lines derived from patients with SAD and FAD. We are currently performing biochemical, cellular, and genetic analysis for the manifestation of AD-related phenotypes. In the future, these 3-D culture systems will serve as the basis for more mechanistic studies to elucidate the molecular underpinnings of AD. The data and models that we have developed as part of this research has led to the generation of several publications as well as several successful grant applications.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Piloting an evidence-based intervention for LTC family caregivers of ADRD residents.
David W. Coon, PhD. Arizona State University; Arizona Alzheimer's Consortium.

*Note: In January 2016, the project received approval to revise its aims and reallocate a portion of its budget. The revision reallocated funding from the LTC pilot to the development of another intervention for Caregivers of People with ADRD and Down syndrome or another Intellectual Disability (ID). The request was motivated by several activities in Arizona that helped foster the Down Syndrome/ID intervention's development (e.g., the ADRD and Down Syndrome Conference in April, ADRD State Plan components encompassing Down Syndrome/ID, and activities with the Desert Southwest Chapter of the Alzheimer's Association and the Arizona Development Disabilities Planning Council). Thus, the project title is somewhat misleading as the project now involves the development of two separate interventions.

Specific Aims:

Adapt CarePRO for Caregivers of People with ADRD in Long-Term Care Settings

- a) Analyze data collected in prior years from focus groups with staff in LTC and family caregivers of individuals placed into LTC to develop an intervention to assist those family caregivers (and potentially the LTC staff as well).
- b) Build an intervention protocol drawing from focus group feedback and experience with REACH trials, CarePRO translation, and EPIC innovations.
- c) Work toward building screening and interview protocols that draw from the focus group data mentioned in "a" as well as from the PI's experiences in NIH clinical trials (e.g., REACH and REACH II), ADSSP translation projects (e.g., CarePRO), and ADSSP innovation projects (EPIC).
- d) Disseminate project work through presentations at national conferences such as the Gerontological Society of America and the American Society on Aging and through publications.

Adapt CarePRO for Family Caregivers of People with Down Syndrome/Intellectual Disability (ID) and ADRD

- a) Partner with the Desert Southwest Chapter of the Alzheimer's Association and the Disabilities Planning Council to analyze preliminary data from town halls and workshops with families and providers that will assist people with ADRD and Down syndrome or other ID.
- b) Build an intervention protocol drawing from this feedback and experience with the CarePRO translation project and EPIC innovations.
- c) Work toward building screening and interview protocols that draw from the focus group data mentioned in "a" as well as from the PI's experiences in NIH clinical trials (e.g., REACH and REACH II), ADSSP translation projects (e.g., CarePRO), and ADSSP innovation projects (EPIC).
- d) Disseminate project work through presentations at national conferences such as the Gerontological Society of America and the American Society on Aging and through the development of publications.

Background and Significance: Over 85% of all help provided to older adults in the US is from family members. In 2014, family caregivers provided an estimated 17.9 billion hours of

informal (unpaid) care. This care has an impact, including increased depression and other mood disorders, exacerbated health conditions, wage losses, and increased health care utilization. Caregivers who place their loved ones in a long-term care (LTC) setting typically do so after providing many years of direct care. Evidence from the NIH funded REACH and REACH II trials demonstrates that family caregiver distress does not end with placement of the care recipient into an LTC (assisted living, nursing home, dementia care unit, etc.). In fact, family caregivers of people with Alzheimer's disease and related dementias (ADRD) reported similar levels of both depression and anxiety before and after placement. Several factors were found to be associated with sustained levels of distress, including (a) being a spousal caregiver and (b) visiting the facility more often. Thus, placement comes with a new set of issues and concerns that are not simply extensions of the concerns faced by caregivers of community-dwelling ADRD individuals.

Another underserved group of family caregivers impacted by ADRD are those who assist adults with Down syndrome or another Intellectual Disability (ID). Approximately, 6% of adults with any type of ID will be affected by dementia after age 60, with the proportion increasing with age. For those with Down syndrome, there is a genetic propensity to develop early onset AD. 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, may create "double jeopardy" for these caregivers, and no evidence-based interventions have been identified to help them manage changes in care, associated stressors, and related distress.

Preliminary Data and Plan: LTC Family Caregiver Project: Very little is known about how to promote family and formal caregiver partnerships in LTC that will help positively impact quality of life for both family caregivers and their loved ones with advanced dementia. To address these issues and concerns, the proposed intervention project will build on data already collected by my lab through focus groups conducted across the Valley with LTC staff and family members who have placed their loved ones with dementia in LTC. Key themes from them suggest that family caregivers need reassurance and permission to place ("this is not your grandma's nursing home"); family members still experience high levels of stress and distress; and poor communication skills between staff and family caregivers as well as among family members themselves are a consistent concern. Preliminary findings suggest potential intervention targets and strategies; however, additional analyses and feedback from key informants is needed to help guide intervention development. In the LTC Caregiver Project we (1) conducted additional analyses on data from focus groups with LTC staff and family caregivers of LTC residents with dementia; (2) used analyses in "1" to develop the intervention components for a future pilot study of skills-training intervention for family caregivers of people with dementia in an LTC facility; (3) used analyses in "1" to develop recruitment, screening, and interview tools to help implement the future pilot study described in "2"; and (4) plan to disseminate findings at national meetings such as the Gerontological Society of America and submit results of the intervention study to recognized peer-reviewed journals such as *The Gerontologist*.

ADRD and Down Syndrome/ID Family Caregiver Project: Gathered in conjunction with the Alzheimer's Association, we have analyzed preliminary feedback from community members who assist people with Down syndrome or other ID that suggest key components of CarePRO are very useful with high ratings of satisfaction. However, additional tailoring of the intervention through scenarios/role plays/examples specifically addressing issues relevant to this population, specific content addressing differences in these families, and the like is warranted. In this ADRD and Down Syndrome Family Caregiver Project we (1) participated in analyses of data and feedback on family caregiving concerns and needs as well as preliminary exposure to

CarePRO intervention components; (2) used analyses in “1” to develop the intervention components for a future pilot study of skills-training intervention for family caregivers of people ADRD and Down Syndrome/ID; (3) used analyses in “1” to develop recruitment, screening, and interview tools to help implement the future pilot study described in “2”; and (4) plan to disseminate findings at national meetings such as the Gerontological Society of America and submit results of the intervention study to recognized peer-reviewed journals such as *The Gerontologist*.

Proposed One-Year and Long-Term Outcomes: The proposed short-term outcomes are described as outputs in the Methods section. In addition, the data analyses would yield both professional presentations at meetings like 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*. Subsequently, the PI and his community partners would pilot both of these interventions to gather preliminary data to support a future R21 or an R01 submission in 2017, depending on the pilot projects’ findings.

Year-End Progress Summary: For the LTC Family Caregiver Project, critical analyses of the focus group data are complete and extend many of the initial findings, including the need for (a) information/education on ADRD and related LTC facility programs should be the norm rather than the exception, recognizing that orientation and education should be for both staff and families; (b) public awareness campaigns about LTC and dementia care; (c) tools to change negative public perceptions about LTC; (d) referrals that effectively connect families with community-based resources beyond any offerings for their loved ones at an LTC facility; (e) training in communication skills for both family and LTC staff to enhance communication with their loved ones with ADRD, to deal effectively with difficult family members and/or mediate between family members, and to foster communication between staff and family about changes, issues, or problems with their loved ones. These findings have been used to help develop screening tools and create a new intervention for pilot testing as a next phase. Preliminary feedback from key informants has been very positive. For the ADRD and Down Syndrome/ID Family Caregiver Project, we worked with partners in the Desert Southwest Chapter of the Alzheimer’s Association and the Disabilities Planning Council to interpret preliminary data that have been used to adapt CarePRO for the Down Syndrome/ID community. This data, combined with feedback from key informants, will also help to guide related recruitment, screening, and interview tools for piloting of the intervention.

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ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Protein variants as blood based biomarkers for neurodegenerative disease. Michael Sierks, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Project Description: 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. 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. While CSF A β 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 and tau 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 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 and more recently in other neurodegenerative diseases including AD and traumatic brain injury. TDP-43 is also prone to misfold and form aggregate species, where disease associated TDP-43 mutations similar to A β and a-syn aggregate more readily. 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.

Quantification of serum levels of the actual toxic protein species involved in disease onset and progression should provide a much more sensitive and powerful set of biomarkers for early detection and staging of neurodegenerative diseases such as AD. Detection of different toxic variants of A β , tau, a-syn and TDP-43 in serum should provide a powerful tool to facilitate early diagnose of different neurodegenerative diseases, for example presence of toxic oligomeric A β aggregates could be indicative of early AD, oligomeric A β and tau aggregates could indicate a later stage AD, only oligomeric tau could indicate a tauopathy such as Frontal Temporal Dementia, oligomeric a-syn could indicate PD, and oligomeric A β and a-syn could indicate

DLB. While detection of these specific protein aggregate species has great promise, such studies have not been feasible due to the low concentrations of the target aggregate species in sera samples and the poor specificity of reagents for the different aggregated species. To overcome this problem, 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. Here we will utilize 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 to demonstrate that the presence of specific toxic aggregate proteins species in serum are very selective biomarkers for distinguishing AD from other dementias.

Progress to Date:

Aim 1. Grow and purify nanobodies to disease related variants of A β , tau and a-syn for use in a sandwich ELISA. We have grown and purified nanobodies against several disease variants of A β , tau and a-syn.

Aim 2. Assay postmortem sera samples from AD, PD and age matched control samples for the presence of the disease specific protein variants using the sandwich ELISA. We analyzed sera samples from post-mortem AD, PD and age matched controls for the presence of selected A β and a-syn variants. The AD samples had high levels of oligomeric A β , the PD samples had high levels of oligomeric a-syn, while the control samples did not have any oligomeric protein variants. We are continuing analysis with additional sera and plasma samples taken at different time points from living patients.

Proposals:

I submitted proposals to DOD to develop biomarkers for traumatic brain injury and for developing novel therapeutics for treating ALS. I also submitted proposals to NIH (both R01 and R21) to develop biomarkers for neurodegenerative diseases including AD, PD and MSA. To date none of these proposals have been funded.

Commercialization potential:

We have started a company, Neurodiagnostix, LLC. to use our nanobodies as potential diagnostics and therapeutics for neurodegenerative diseases. Along with Brian Spencer, neuroscientist (UCSD), and Pat Mallon (CEO) we are developing a business plan. In addition, we have initiated a collaboration with Denali Inc. to study the potential therapeutic value of our antibodies against oligomeric tau variants for treating AD.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Dissecting the role of tau in the adult mouse brain. Salvatore Oddo, PhD, Heather Bimonte-Nelson, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Project Description: Tau is microtubule-binding protein that plays a key role in several neurodegenerative disorders, known as tauopathies. Among these are Alzheimer's disease (AD), frontotemporal dementia, Pick's disease, and corticobasal degeneration. Whether tau leads to neurodegeneration by a toxic gain-of-function mechanisms (e.g., accumulation of toxic NFTs) or by a loss-of-function mechanisms (e.g., alterations in microtubule stability and axonal transport) is highly debated. We have generated conditional tau knockout mice, which will allow us to selectively remove tau from the adult brain. Here we will test the hypothesis that tau is necessary for learning and memory in the adult brain.

Specific Aims: Determining the effects of removing tau from adult brains on cognitive function.

Progress to date: Using an extensive cross-breeding strategy, we have removed the Neomycin cassette from the mice, thus generating pure MAPT floxed mice. The preliminary data obtained were used to submit a R21 grant application to the NIH. Currently, we are aging the mice in order to perform the experiments described in the application.

Project Progress Reports
Banner Alzheimer's Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Native American Outreach Program. Dawn Batchuluun, CCRP, Anna Burke, MD, Jan Dougherty, RN, MS, Nicole Lomay, Richard Caselli, MD, Marwan Sabbagh, MD, Eric 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: 1) To forge a close working relationship with members of our Native American Community in the awareness, care, and scientific understanding of AD through educational and service-related outreach activities. 2) To support the participation of interested Native Americans in the ADCC clinical core and research studies of interest to them without detracting from our other outreach and partnership-development goals. 3) To work with our Native American partners to identify and begin to prepare for one or more research studies that advance the understanding of AD and/or service to patients and families from this understudied, underserved population.

Background and Significance: Native Americans facing the problem of Alzheimer's disease (AD) 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 Arizona Alzheimer's Disease Core Center (ADCC) Clinical Core.

Preliminary Data and Plan: To date, 47 Native Americans have been followed through the ADCC and whose clinical findings are reported in a national database. As of January 2016, there are 46 are active participants, 5 have withdrawn, and 1 died. Over the past year, we have connected with 2,574 Native American individuals that include 960 professionals and 1,624 community members. These contacts include professional and lay education, memory screening, tribal caregiver conferences, nursing home training and memory screening. We are very proud of executing the first National Conference on Alzheimer's disease in Native Americans in October 2015. We had 175 professionals represented from 48 tribal communities from across the U.S. The evaluations were outstanding and we are now working with a national committee to determine next steps in order to educate health care providers about Alzheimer's disease/related dementias. We secured a number of radio interviews about this work that included highlighting the disparities that Native caregivers face in a piece that ran on both Arizona and National NPR. We have established a consistent and solid working relationship with many urban and tribal communities to continue on with these efforts. We presented a poster session. "Cultural bias in memory screening in American Indian individuals in Arizona" at University of Arizona College of Medicine Scholarly Project and at the Inaugural National Conference.

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 46 Native American cohorts in the ADCC trial in the next 12-months with a goal of recruiting 14 new participants.
3. Refine methods to reach more Native Americans from youth to elders to educate using the Native American Brain Health program.

Funds will be used in a way that complement but do not overlap with funding provided by the National Institute on Aging (NIA, which supports some of our outreach and clinical core enrollment activities), the Ottens Foundation (which provides partial support for our Annual Conference), and funds from Tohono O'odham Nation and Gila River Indian Community to support development of culturally sensitive memory screening/brain health programs.

Year End Progress Summary:

Aim 1: A variety of education/outreach programs reached 1,624 community participants and another 960 professional staff. These efforts also include successful completion of the “Inaugural Conference on Alzheimer’s disease/dementia in Native American Communities: Issues, Impact and Next Steps” drawing 175 professionals.

Aim 2: A total number of assessments have been completed: 29 in total including 9 new visits. 1 participant died and 5 participants have withdrawn after repeated attempts to call without response back. The goal is to recruit/enroll another 8 participants in the coming year.

Aim 3: We have finalized a brain health program, including a painting that incorporates Native traditions that promote brain health from children through elders. We have been successful at presenting this information to lay communities and select elder groups. We will continue to develop relationships with schools and youth groups to also educate about lifestyle factors and brain health unique to Natives.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Alzheimer's Prevention Initiative. Eric M. Reiman, MD, Pierre N. Tariot, MD, Jessica B. Langbaum, PhD, Kewei Chen, PhD. Banner Alzheimer's 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 ϵ 4 homozygotes ages 60-75.

Aim 3: 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 4: To continue to develop registries to support future preclinical treatment trials.

Aim 5: To continue to conduct biomarker studies of ADAD mutation carriers to assist in designing future preclinical treatment trial programs/surrogate marker development programs.

Background and Significance: The Alzheimer's Prevention Initiative (API) is a multi-partner, multi-institutional collaborative program established and directed by Drs. Reiman and Tariot at the Banner Alzheimer's Institute. The API was created to help advance a new era in Alzheimer's disease (AD) prevention research; evaluate promising investigational preclinical AD treatments in people who, based on their genetic background and age, are at high imminent risk of clinical progression; and further develop the biomarker and cognitive endpoints and accelerated regulatory approval pathway needed to rapidly evaluate the range of putative treatments(1-3). (We define preclinical AD treatments as those intended to postpone, reduce the risk of or completely prevent progression to clinical stages of AD.) It currently consists of two complementary preclinical treatment trial programs/surrogate marker development programs in cognitively normal individuals who are (1) autosomal dominant AD (ADAD) mutation carriers within 15 years of their estimated age at clinical onset, and (2) apolipoprotein E (APOE) ϵ 4 homozygotes close to their estimated median age at clinical onset. The current project will help to lay the foundation for these and other prevention treatment trials/surrogate marker development trials, including refining trial design and outcome measures.

Progress Summary: 1) API's first prevention treatment trial in cognitively unimpaired autosomal dominant AD mutation carriers continued to meet its stated goals (Clinicaltrials.gov Identifier: NCT01998841). This trial, which includes \$15.3 million in NIH funding, \$15 million in philanthropic funding; and about \$100 million in cash and in-kind funding from Genentech, has several aims: It will evaluate the amyloid antibody agent crenezumab in the prevention of AD and (based on public statements by regulatory officials) could provide the evidence to support its use in the prevention of autosomal dominant AD. It will provide a better test of the amyloid hypothesis than trials in clinically affected patients, either supporting the use of anti-amyloid agents in the prevention of AD or providing a compelling reason for drug discovery efforts to target other elements of the disease. It will help to establish whether a treatment's 2-year effects on biomarkers predict a clinical benefit in order to determine whether the biomarkers could be used to evaluate promising therapies in 2-year label-enabling trials. We secured an unprecedented agreement from Genentech to release the trial data and biological samples to the research community after the trial is over to help in the preclinical study of AD and the

development new, faster methods for evaluating therapies. We are working with other groups to provide a foundation for the conduct of future prevention trials. It has empowered family members at the highest risk in the fight against AD. 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 in approximately 1,300 individuals. The Accelerating Medicines Partnership (AMP) will provide several million dollars in additional funding (the exact dollars to be determined) to incorporate a promising new imaging technique called tau PET into this trial. As with our first trial, we are contributing \$15 million in philanthropic funding. The trial will take place at over 60 sites in North America, Europe, and Australia. 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) We continue to refine our work developing composite cognitive test scores that are sensitive to detecting and tracking the preclinical stages of AD, anticipate clinical onset, and can be used to evaluate preclinical AD treatments. 4) 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. We are honored to have leaders in the field serve on the Registry's executive committee. The Registry has over 210,000 enrollees. The Registry recently launched a program, GeneMatch, 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. This will be one of the primary recruitment sources in the United States for the API APOE4 Trial. To date, over 1,500 people have joined. 5) We exceeded our ambitious goals for the Colombian API Registry, to date having enrolled over 4,900 autosomal dominant kindred members, including 1,095 mutation carriers and several new families. Registry expansion will continue throughout 2016. 6) We completed a two-year longitudinal follow-up MRI, FDG PET, amyloid PET, CSF and plasma biomarker data from a subset of 24 young adult mutation carriers and non-carriers (individuals who would not be eligible for our prevention trial) as well as clinically affected carriers. These findings have already had a major impact on the field's understanding of the earliest biological and cognitive changes associated with the risk of AD. Data is currently being analyzed and manuscript preparation is underway. We are partnering with Dr. Yakeel Quiroz to collect tau PET data in a subset of kindred members.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Advanced image analysis techniques for the detection and tracking of Alzheimer's disease and its prevention. Kewei Chen, PhD, Hillary Protas, PhD, Wendy Lee, MS, Eric M. Reiman, MD. Banner Alzheimer's Institute, Arizona Alzheimer's Consortium.

Specific Aims:

1. To further develop, test and apply voxel-based image analysis techniques for the early detection, tracking, and differential diagnosis of AD and the evaluation of AD-modifying treatments in the symptomatic and presymptomatic stages of the disorder. During the funding period, to extend our multi-modal partial least squares (MMPLS) algorithm to support the analysis of resting state functional connectivity MRI (fcMRI) data; to characterize functional connectivity using multiple region-of-interest (ROI) seeds; to extend our hypometabolic convergence index (HCI) strategy to the analysis of longitudinal FDG PET data; to begin to extend our "convergence index" strategy to summarize the magnitude and spatial extent of tau burden in a person's AV-1451 PET image; and to modify other image-analysis techniques as needed to support our AD-related research projects.

2. To make our data analysis algorithms available to research laboratories inside and outside Arizona, including a format that is relatively easy for the investigators to use.

3. To develop a comprehensive, user friendly, and HIPPA compliant platform for the sharing of anonymized data from APOE4 cohort with the international research community.

Background and Significance: We and our colleagues continue to develop, test, and apply PET and MRI image analysis methods with improved power to detect and track the brain changes in the preclinical and early clinical stages of AD and contribute to the scientific understanding, early detection, diagnosis, treatment, and prevention of AD. Examples include our HCI method to characterize the magnitude and spatial extent of AD-related hypometabolism in a single measurement; our statistical ROI (sROI) method to track the longitudinal AD-related declines in cerebral glucose metabolism with improved power and freedom from the Type I error associated with multiple regional comparisons; our fully automated iterative principal component analysis (IPCA) method for the computation of whole brain shrinkage from sequential MRIs; our multi-modal partial least squares (MMPLS) algorithm to characterize the linkage between covarying patterns in FDG PET and volumetric MRI images from the same research participants; and our cerebral white matter reference region to track longitudinal increases in fibrillar amyloid burden from sequential amyloid PET scans and evaluate amyloid-modifying treatments with improved power. Some of our methods have had a major impact on the field. In this project, we intend to further develop and test these algorithms, help demonstrate their added value to the field, and increase their availability to and use by other laboratories. We also propose to further develop our data management software for the Arizona APOE Cohort Study, increasing the availability of this precious dataset for the study of preclinical AD.

Research Plan: The proposed project will capitalize on FDG PET, amyloid PET, fcMRI, and volumetric MRI data from patients with probable AD dementia, mild cognitive impairment (MCI), and normal control subjects from the AD Neuroimaging Initiative (ADNI), cognitively unimpaired APOE4 homozygotes, heterozygotes, and non-carriers from the Arizona APOE Cohort, and PSEN1 E280A mutation carriers and non-carriers from the world's largest autosomal dominant AD (ADAD) kindred in the Alzheimer's Prevention Initiative (API)

Biomarker Study, and collaborative research projects in China. These data will be used to help refine these image analysis techniques, demonstrate their improved power to detect and track AD, develop other image analysis techniques as the opportunities arise, and share our algorithms with other research laboratories. During the funding period, we will continue to refine our HCI for the longitudinal analysis of FDG PET images and compare it to our sROI method in terms of its power to track AD-related CMRgl declines and evaluate investigational disease-modifying treatments in the clinical and preclinical stages of AD; we will extend our MMPLS algorithm to investigate the linkage between co-varying patterns in complementary fcMRI and florbetapir (amyloid) PET data sets; we will further refine our method for the analysis of longitudinal florbetapir PET images (e.g., using a person's co-registered MRI to define cerebral and reference ROIs and use of a voxel-based algorithm to correct for the combined effects of longitudinal brain shrinkage and partial-volume averaging); and we will begin to develop a tau convergence index to characterize the magnitude and spatial extent of AV-1451 standard value uptake ratio (SUVR) elevations in a single measurement. We will continue to make our image analysis algorithms available to the research community and provide a core resource to support the analysis of brain imaging data from other studies. We will begin to establish a user-friendly graphical interface for sharing of brain imaging of other data from the Arizona APOE Cohort.

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, provide a foundation for their potential use in the future analysis of data from our API trials, and begin to summarize our findings in research abstracts and manuscripts. Meantime, we will continue to collaborate with colleagues inside and outside Arizona, helping our colleagues use our data and methods in support of our shared goals.

Progress (July 1, 2015-March 31, 2016):

Aim 1: We have continued to refine and test our white matter reference ROI method for the analysis of longitudinal florbetapir PET data, demonstrated improved power to track changes and evaluate amyloid-modifying treatments, published findings from our laboratory and our ADNI colleagues (Chen et al, J Nucl Med 2015; Landau et al, J Nucl Med 2015), helped other researchers implement and confirm the value of our method for the analysis of florbetapir SUVRs in comparison with other reference ROI methods (e.g., Villemagne et al, Hum Amyloid Imaging Conf 2016), presented resulting findings from a Phase 2 trial of crenezumab in patients with the clinical diagnosis of mild AD dementia. We have successfully incorporated the software pipeline needed to assess the impact of different reference ROIs and partial-volume correction methods on our ability to track longitudinal changes in florbetapir SUVRs, and our results are pending. We demonstrated the promise of our longitudinal HCI method to track AD-related decline in cerebral glucose metabolism with improved power (Chen et al, Hum Amyloid Imaging Conf 2016), but still need to clarify the extent to which it is specific for the preclinical stage of AD. We have implemented methods for the analysis of diffusion tensor imaging (DTI) data, continued to refine our approach to the analysis of fcMRI data, and implemented pipelines to support these and other voxel-based analyses. We have provided data and support for researchers inside and outside of Arizona, contributing to several abstracts, conference proceedings, and manuscripts, including researchers like Yalin Wang and his colleagues, who have been developing innovative approaches to the assessment of volumetric MRI data. We are finalizing a manuscript that supports the comparability of PiB PET perfusion imaging to FDG PET in the cross-sectional detection of AD but not in the longitudinal tracking of AD. Other methods continue to be developed as noted above.

Aim 2: We have provided expertise, effort and algorithms to support the analysis of PET and MRI data from several laboratories, inside and outside Arizona (e.g., several organizations in the Arizona Alzheimer's Consortium, Stanford, Yale, Harvard, Brown, and Washington University, a clinical research organization involved in the analysis of data from clinical trials, and two pharmaceutical companies), and we continue to share data and support whenever we can.

Aim 3: We have shared data and samples with more than a dozen research groups, helping to generate new methods and findings, support the analysis of clinical trial data, and provide a further foundation for AD prevention trials. We have selected the XNAT data management platform, are modifying our server, and are recruiting a data manager who take the lead role to optimize data management, security, and sharing with qualified researchers.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Alzheimer's Prevention Registry. Jessica B. Langbaum, PhD, Eric Reiman, MD, Pierre Tariot, MD. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

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

Aim 2: To continue to develop collaborations with academic and non-academic partners to increase enrollment into the Registry.

Aim 3: To demonstrate that the Registry accelerates recruitment into AD prevention studies, such as the Takeda/Zinfandel trial TOMMORROW study, the ADCS "A4" trial, and the Alzheimer's Prevention Initiative APOE4 trial.

Background and Significance: A growing number of investigational agents, repurposed medications, dietary supplements and lifestyle interventions have been suggested but not yet proven to reduce the risk of progressing to the clinical stages of Alzheimer's disease (AD). Therapeutic trials of investigational AD-modifying agents in clinically affected people have begun to provide critical safety data and some of the other information needed to support their evaluation in cognitively unimpaired at-risk persons. It has been suggested that some of these interventions may need to be started before the clinical onset of AD, when there is already extensive neuropathology, in order to exert their most profound effects—and that therapeutic trials of investigational amyloid-modifying agents in cognitively unimpaired at-risk persons would provide a better test of the amyloid hypothesis than trials in clinically affected individuals (1;2). If a treatment could delay the clinical onset by even a few years, it would have an enormous public health benefit(3). Despite the exciting breakthroughs, recruitment of study participants remains one of the biggest obstacles that researchers face. It has been estimated that 80% of all research studies fail to meet their enrollment goals, which results in increased study costs and delayed findings. Moreover, there is a concerted effort amongst researchers to recruit and enroll participants to ensure racial and ethnic diversity. As an example, the Alzheimer's disease Cooperative Study (ADCS) "A4" trial requires that one in four participants screened be from a underrepresented group. The Banner Alzheimer's Institute launched the web-based Alzheimer's Prevention Registry (www.endALZnow.org) in 2012 as a mechanism to keep the general public informed about the latest news in Alzheimer's prevention research and notify them as study opportunities become available in their communities. The Registry is intended to be a resource to the entire scientific community, helping researchers quickly and efficiently enroll participants into Alzheimer's prevention related studies.

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, the Registry had over 210,000 enrollees. During this funding period, we refreshed the website (www.endALZnow.org) based on the results from the A/B and usability testing conducted in 2014-2015.

Aim 1) We are working to increase minority group enrollment into the Registry. Based on user feedback, we are launching a communication campaign to existing Registry members

encouraging them to update their profile with their race/ethnicity information since this is an optional demographic question enrollees are asked at the time of signup and over 75% elect not to provide this information. We are also updating the website to include information about why we ask that enrollees share their race/ethnicity and reinforce the privacy measures of the Registry.

Aim 2) The Registry Executive Committee (Drs. Paul Aisen, Marilyn Albert, Jeffrey Cummings, Jessica Langbaum, Jennifer Manly, Ronald Petersen, Eric Reiman, Reisa Sperling, Pierre Tariot, Michael Weiner, Ms. Meryl Comer, and Ms. Gabrielle Strobel) meets on a quarterly basis to ensure that the Registry is a valuable resource to the academic community. We continue to work with our Banner PR colleagues, our national PR firm GYMR, our website design partners Provo, Banner Alzheimer's Foundation, and other stakeholders help promote the Registry through national and local communications as well as at invited speaking engagements. Based on her experience directing the Registry, Dr. Langbaum co-chaired a AAIC 2015 pre-conference Registries workshop, was an invited attendee at the E.U / U.S - CTAD TASK FORCE ON ALZHEIMER'S TRIALS: Registries and Cohorts to Accelerate Early Intervention Trials; Appropriate Guidelines for Clinical Trial Centers in November 2015, is a co-chair of the Alzheimer's & Dementia Patient/Caregiver-Powered Research Network (AD-PCPRN) Advisory Council for Registries/Clinical Trials, and is a member of the FTD Registries Scientific Advisory Board. The APR is serving as a model template for other registries, including the FTD Registries and the Butler Hospital Alzheimer's Registry.

Aim 3) The TOMMORROW study closed enrollment in summer 2015, but we have actively promoted over 25 other studies, including the A4 trial, helping sponsors and study sites meet their enrollment goals. In July 2016 we will launch a secure portal allowing registry members to authorize sharing their contact information and other PHI as required with enrolling studies. This portal will provide the Registry with important metrics tracking its success at helping studies accelerate their enrollment goals. In late 2015 we launched an IRB-approved genetic testing program of the Registry, GeneMatch, open to adults age 55-75 residing in the US and without a diagnosis of a cognitive impairment. After electronically signing the ICF, individuals are provided a cheek swab kit by mail for at-home collection of DNA. The sample is returned to a CLIA-certified lab for APOE genotyping. The genetic results are used in part to help match people to research studies. The API APOE4 Trial will be the first study to use GeneMatch as its primary recruitment tactic in the US. GeneMatch does not disclose genetic results to participants, and all invitations to participate in a study must be done so as to not inadvertently disclose test results. To date, 1,500 people have joined.

Project Progress Reports
Banner Sun Health Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Establishing an *in-vivo* blood biomarker repository with post-mortem diagnosis confirmation. Thomas G. Beach, MD, PhD, Douglas G. Walker, PhD. Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Project Description: Blood is the most accessible and repeatable sampling source of specimens for disease biomarkers; ample efforts have been made to search for blood based biomarkers of neurodegenerative diseases, especially Alzheimer's Disease (AD) (for review see¹). However, many studies that have utilized blood based biomarkers to categorize individuals based on clinical diagnosis have been inconclusive. This may be due to the low clinical diagnostic accuracy for AD, which creates a major roadblock in finding and monitoring new therapeutic agents.^{2, 3} Having banked *in-vivo* blood on patients who will eventually have an autopsy confirmed diagnosis will aid in these categorizations, as well as provide the potential to assess other items related to disease etiology. The brain and body donation program (BBDP) at the Banner Sun Health Research Institute is an autopsy-based, research-devoted brain bank, biobank, and biospecimen bank that derives its human donors from the Arizona Study of Aging and Neurodegenerative Disease (AZSAND), a longitudinal clinicopathological study of the health and diseases of elderly volunteers living in Maricopa county and metropolitan Phoenix, Arizona. We study their function during life and their organs and tissue after death. To date, we have concentrated our studies on AD, Parkinson's disease, heart disease, and cancer. We also share the banked tissue, biomaterials, and biospecimens with qualified researchers worldwide. Currently the BBDP only collects postmortem serum; collecting blood specimens during life would provide a resource for discovering biomarkers that could be used to monitor disease progression. We propose to perform annual blood draws on 200 current living BBDP individuals. This proposal will lay the foundation for future prospective studies involving interventional and *in-vivo* biological measures with an overall goal of disease prediction and monitoring.

Specific Aim 1. Support and expand the BBDP's longitudinal clinicopathologic study, through inclusion of *in-vivo* blood collection with the goal of generating predictive algorithms and biomarkers for monitoring AD pathological and clinical progression. This award will allow a significant expansion of the Program's capabilities, ultimately allowing the development of predictive algorithms for neuropathology utilizing blood based biomarkers. This aim will produce a resource to be shared at a statewide as well as national level.

Background and Significance: To better understand the etiology of AD, this proposal will provide a foundational series for *in-vivo* blood biomarkers. This study seeks to maximize a pre-existing cohort (the BBDP), through incorporation of *in-vivo* annual blood draws. This will provide critical in-life biological data, which we will be able to correlate to biological processes through tissues obtained after death. We have been very successful with our BBDP generating extensive extramural funding, and numerous peer reviewed scientific papers, while establishing an exceptional global scientific presence.^{4, 5} Expanding the BBDP through collection of *in-vivo* biological materials will allow for greater utilization while providing an additional cohort that can be utilized for separate interventional and *in-vivo* biological studies. There is no place in the world that has the existing resources to perform such studies with rapid autopsies with which to understand the etiology and pathology of neurodegenerative disease as well as healthy aging.

Knowledge gained from this study will have a great impact on our understanding of the continual AD disease spectrum.

Preliminary Data: The BBDP at the Banner Sun Health Research Institute is a multifaceted program, enrolling normal, AD and Parkinson’s disease subjects for over 20 years, who have had longitudinal annual clinical evaluations from enrollment until death at which time a brain ± other organ autopsy is performed.⁵⁻⁹ The BBDP has generated numerous breakthroughs and collaborative efforts internationally and across Arizona, many of which are evident in awarded grant funding and scholarly publications (over 300 publications, and 30 million dollars in funding since its inception).

We have established outstanding recruitment efforts having over 800 active participants within the BBDP. Of these, a large majority are considered cognitively normal (see Table 1). The current BBDP focus has been post-mortem research on banked brain and body biospecimens. We seek to expand and enhance the current resource through *in-vivo* collections of biological materials (blood). The current proposal aims to fill this void, with a focus on normal individuals, probable AD, and other dementias (as a dementia control) given the dire need of understanding the etiology of AD progression and monitoring. The below table represents a subset of BBDP cases that we have targeted for blood draws for this project, including those clinically diagnosed with AD and non-AD dementias as well as normal control subjects.

Table 1. Total number of living participants actively enrolled in the BBDP by decade of age, and clinical classification. Abbreviations: AD= Alzheimer’s disease, MCI= mild cognitive impairment, VaD= Vascular dementia, DLB= dementia with Lewy bodies, PDD= Parkinson’s disease dementia, FTD= Frontotemporal dementia.

Participants by Age Group							
Clinical classification	60’s	70’s	80 – 84	85 – 89	90 – 94	95+	Totals
Cognitively Normal individuals	31	137	99	107	56	21	456
Probable AD		10	9	3	13	3	38
Other Dementias (VaD, DLB, PDD, FTD, etc.)	6	10	13	9	9	8	55

Experimental Designs and Methods:

Inclusion Criteria

- 1) Subjects currently enrolled within the BBDP
- 2) Receiving annual clinical assessments at BSHRI
- 3) Individuals over the age of 65 at the time of consent
- 4) Agree to have blood draw

Exclusion Criteria

- 1) Individuals with a dangerous active infectious disease (examples: active Hepatitis B, Hepatitis C or HIV)
- 2) Individuals with known or suspect Creutzfeldt-Jakob disease or other prion encephalopathy
- 3) Subjects with major systemic diseases that possibly affect cognitive function such as cardiopulmonary failure, hepatic or renal failure, poorly controlled diabetes (HbA1C >8.5), head injury, or stroke

The cohort will consist of 125 cognitively normal individuals, 40 probable AD, and 35 other dementias (as a dementia control)- for a total of 200 individuals. Last year we enrolled 62 new participants, so we anticipate having additional individuals enrolled by the end of the study period.

Informed Consent: Subjects already enrolled within the BBDP have given consent for blood draws. The recruitment and scheduling process will be conducted by qualified personnel (Kathryn Davis, Kathy Long, Lisa Gale, and Lisa Nicholson) in the Cleo Roberts Center for Clinical Research. The subjects who participate in this study will be scheduled for an appointment to collect blood by an experienced phlebotomist (Amy Rangel).

Whole blood specimen collection and processing: Blood draws will be conducted in accordance with recently published guidelines for the standardization of pre-analytic variables for blood-based biomarker studies in AD research.¹ All blood draws will be done in a fasting state at least 8 hours since last meal (time since last meal will be recorded) and will be performed by venipuncture (21 g needle) by a designated phlebotomist. 10mL of whole blood will be collected into a Red Top Tube and 20mL of whole blood will be collected in an EDTA blood collection tube (two K3 EDTA, lavender-top tubes). Sample tubes will be assigned with a serial number and picked up within 15 mins by a pathology technician within the BBDP after collection. All processing will be conducted no more than 2 hours after draw. For serum (red top tubes), samples will be centrifuged at 2000 rpm for 10 minutes in collection tube and the supernatant will be placed, in 0.5 ml aliquots, into 1.5 ml polypropylene (sterile) microcentrifuge tubes and then stored at -80°C. Whole blood (lavender-top tubes) will be centrifuged at 2,500xg for 15 minutes at room temperature. Plasma samples will be carefully taken out and aliquoted immediately in 0.5 ml aliquots, into 1.5 ml sterile polypropylene microcentrifuge tubes and frozen at -80°C. White blood cell layers will be collected and further spun to obtain pellets. White blood cell layers will be purified by Histopaque centrifugation; cell pellets will be stored at -80°C for ApoE genotyping and determination of other AD-related mutations. The procedures will be standardized to those being used within other projects underway within our consortium including “Long Term Consequences of Repetitive Brain Injury and Athletes: A Longitudinal Study with Eventual Brain Donation” and “Arizona Alzheimer’s Disease Center Biorepository for Plasma and Serum” as well as blood biobanks such as the Alzheimer’s Disease NeuroImaging Initiative¹⁰ and the Parkinson’s Progression Markers Initiative.¹¹ This will allow for multiple comparisons across cohorts given methodology similarities.

Proposed one-year and long-term outcomes:

One Year- We will perform blood draws on 200 BBDP subjects

A detailed timeline is located below.

<u>Timeline:</u>	month				
	0	3	6	9	12
Staff training and IRB approvals	xxx				
Recruitment		xxxxxxxxxxxxxxxxxxxxxxxx			
Blood draws		xxxxxxxxxxxxxxxxxxxxxxxx			
Grant submission				xxxx	

Long-term outcomes- Developing a strong in-vivo blood biobank will complement and enhance the current BBDP program. As with the current BBDP program, all samples will serve as a core

resource for investigators supporting biomarker discovery and related research. This one year grant will provide the preliminary evidence and data to further implement *in-vivo* blood collections can complement and expand the dataset. During the subsequent years, we intend to a) conduct grant funded *in-vivo* fluid biomarker studies in patients with autopsy diagnosis of dementia due to Alzheimer's disease (AD) and cognitively normal control subjects b) begin to clarify similarities and differences between AD blood biomarker features and c) provide preliminary data in support of competitive research grants to help sustain the BBDP in future years. Given the extent of this critical resource, we hope to generate research grants, philanthropic funds, and blood sample cost-recovery fees needed to sustain this program and provide a critically important core resource of participants, data and samples for the study of AD, age-related cognitive disorders, and other disorders, and to provide new insights into factors that may predict disease progression. Due to the current success of the BBDP, the expectation is to create the most valuable combined pre-mortem and post-mortem clinical and biospecimen resource for the study of neurodegenerative diseases and healthy aging in the world and to ultimately utilize the population to conduct focused intervention studies.

Year End Progress Summary: Over the last year we were able to add significant value to the Brain and Body Donation Program (BBDP) as we started collecting plasma and peripheral mononuclear blood cells from living subjects. The first phase of this project was to implement the blood processing protocol in our laboratory as we had not previously done this protocol. Then we needed to train laboratory staff to perform the procedure in a consistent manner. Once the laboratory staff was fully trained, the clinical staff started contacting and scheduling patients during the month of November. Collection of samples started in December 2015 and since then we have been collecting specimens from approximately six to eight subjects each week. The number of specimens collected per week depends on the willingness of patients to donate their blood as although this is part of our informed consent, each subject has the opportunity to refuse. To date we have collected blood samples from 49 non demented controls, 14 subjects with mild cognitive impairment and 7 subjects with a clinical diagnosis of Alzheimer's disease. We will increase our weekly collection to 10 subjects per week and therefore anticipate meeting our target of having 200 total subjects sampled by June 30th. Biobanking of plasma and white blood cells from these donors is a big milestone for our program, as it will help us with the development of predictive algorithms for neuropathology utilizing blood based biomarkers.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Validation of submandibular gland tau species to determine Braak NFT staging. Brittany N. Dugger, PhD, Thomas G. Beach, MD, PhD, Douglas G. Walker, PhD, Travis Dunckley PhD. Banner Sun Health Research Institute; Banner Sun Health Research Institute; Translational Genomics; Arizona Alzheimer's Consortium.

Project Description: The brain is connected to the body, yet many studies on Alzheimer's disease (AD) focus solely on the brain. One of the main components of the pathology within AD brains is abnormal deposits of the tau protein. Within the brain, these abnormal aggregates have a pathological progression that is indicative of disease stage, termed Braak neurofibrillary tangle (NFT) stage. Determining the extent and type of tau in more readily accessible peripheral areas that are typically screened and probed in a health care setting, will not only provide new insights into the extent of the histopathological spread of the AD but will lay groundwork for a minimally invasive, inexpensive way to monitor disease progression, leading to better case selection for clinical trials, and a potential way to monitor interventions. We have generated preliminary evidence that tau is present within certain peripheral tissues; the highest levels being found within the submandibular gland (Fig. 1). Furthermore, and of more importance, these levels relate to brain Braak NFT stage (Fig. 2). The next step towards the possibility of a submandibular biopsy site is to thoroughly evaluate and validate these findings. To validate and confirm these preliminary findings we will: 1) add control peptides to the primary antiserum that contains the specific epitope recognized by each tau antibody, and 2) use alkaline phosphatases (to dephosphorylated tau *in situ*) in order to address whether the phosphorylated tau labeling is specific in immunohistochemistry (IHC) and western blots. We will also perform additional enzyme-linked immunosorbent assays (ELISA). If a particular tau form or a combination of tau forms consistently predicts Braak NFT stage, biopsy of submandibular gland could allow, for the first time, pathologically-based staging of AD as well as clinical monitoring of tauopathy progression. If pathological tau found in the PNS does not correlate to disease states, the molecular differences between CNS and PNS tau may provide additional insights into disease mechanisms. Our long term overarching goal is to provide an integrated picture of peripheral vulnerability in AD and to incorporate this understanding into the etiopathogenesis of the disease.

Specific Aim: Aim 1: To confirm and validate preliminary findings of the correlation of submandibular glands tau species to Braak NFT staging.

Background and Significance: Physicians currently lack reliable tools to monitor the pathological progression of AD. As with cancer treatment, it is likely that drug response may depend on disease stage. Although amyloid imaging will improve diagnostic accuracy, it does not indicate Braak NFT stage, the main pathological staging scheme of AD, which correlates very well with cognitive status.¹⁻³ The only current way to determine Braak NFT stage is through postmortem examination. There are recent developments in in-vivo human tau imaging, but these have yet to have neuropathological confirmation.⁴ Cerebrospinal fluid and blood have been extensively examined for tau, but results are variable and it is likely that any central nervous system (CNS) injury will elevate tau levels in these fluids.⁵ There is an urgent need to develop biomarkers to detect the extent of AD pathological manifestations, not just a global neurodegenerative state, that are minimally invasive, simple to perform, and inexpensive.

Biopsies of readily accessible peripheral tissues typically screened in a health care setting could fulfill these needs. We recently conducted a comprehensive examination of the distribution of aggregated phosphorylated tau in human spinal cords of non-demented control (NC) and AD cases and revealed aggregated tau to be present in over 95% of AD subjects and 50% of ND subjects.⁶ Furthermore, we observed a strong correlation between spinal cord tau deposits and Braak NFT stage. The spinal cord innervates all peripheral organs through autonomic and somatosensory nerve fibers, and these anatomic connectivity's may demonstrate alterations as well.

In the peripheral nervous system, rodent work has demonstrated the main tau isoform has an additional 4a exon with a molecular weight of 110kDa, as opposed to the 45 to 65kDa species found in human brain, giving it the name "big tau".^{7, 8} In the adult rat CNS, nearly all neurons that extend processes into the periphery express big tau.⁹ Rat skeletal muscle, heart, testis, lung and kidney also contained relatively high levels of tau mRNA.¹⁰ Despite extensive rodent work, only a handful of studies have examined peripheral tau species in humans.¹¹⁻¹⁸ Determining the extent and type of peripheral tau may provide crucial insights into AD-related tauopathy. We have preliminary evidence of tau deposition within the submandibular gland and our analogous investigations have indicated that submandibular gland biopsy holds promise as a diagnostic and progression biomarker for Parkinson's disease.¹⁹⁻²¹ The connectivity of the submandibular gland does situate it as a prime candidate given parasympathetic innervation of the submandibular gland is through the chorda tympani branch of the facial nerve and the fibers later run with the lingual branch of the trigeminal nerve while the preganglionic and postganglionic sympathetic innervations originate from the thoracic spinal cord and cervical sympathetic ganglia, respectively.^{22, 23}

	NC (n=2)	AD (n=16)
M:F	1:1	8:8
age at death	88 ± 3.5	84 ± 5.4
PMI	7.4 ± 6.93	3.4± 1.44
Total tau brain levels	7941 ± 237	7881 ± 2944
Subman. Gland (% brain)	1.72%	1.67%
Ab. Skin (% brain)	0.26%	0.34%
Scalp (% brain)	0.23%	0.18%
Colon (% brain)	0.26%	0.33%
Liver (% brain)	0.24%	0.16%
S396 tau brain levels	14.5 ± 9.92	229.2 ± 256.1
Subman. Gland (% brain)	6.23%	3.37%
Ab. Skin (% brain)	2.88%	1.39%
Scalp (% brain)	4.56%	0.44%
Colon (% brain)	0.76%	0.32%
Liver (% brain)	n/a	n/a

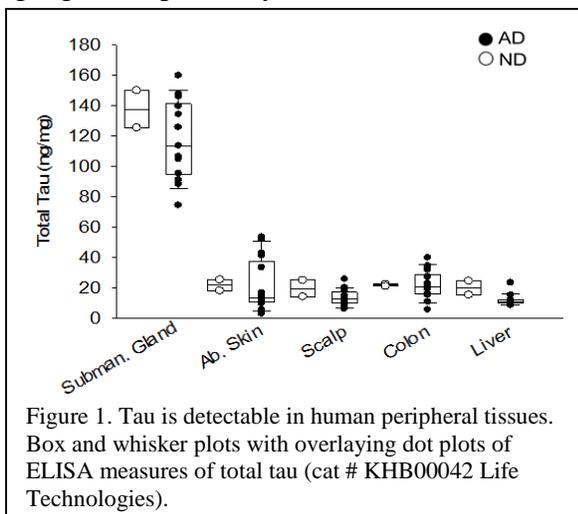
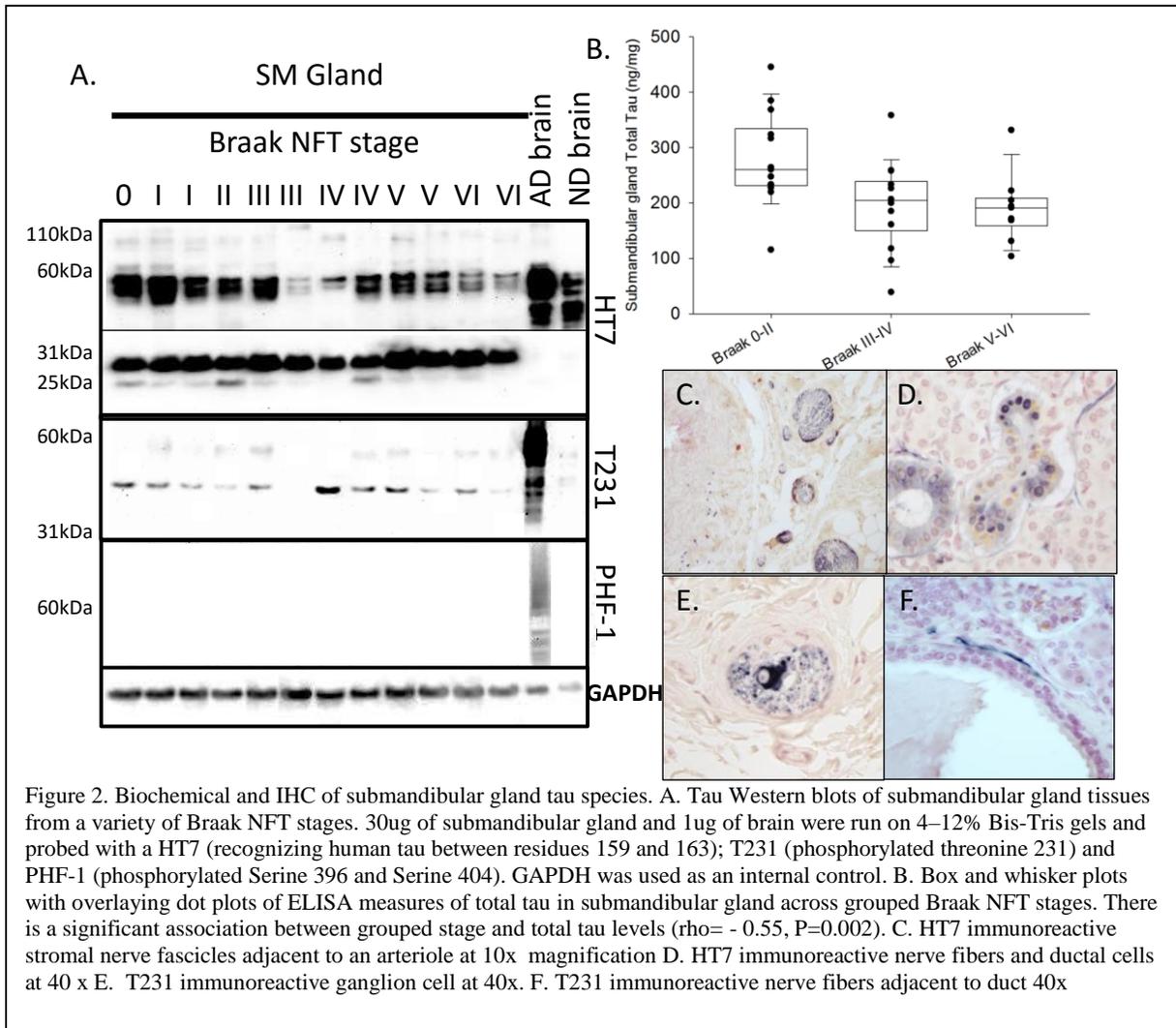


Figure 1. Tau is detectable in human peripheral tissues. Box and whisker plots with overlaid dot plots of ELISA measures of total tau (cat # KHB00042 Life Technologies).

Our Brain and Body Donation Program (BBDP)²⁴ is the only repository that we know of that has adequate samples of peripheral tissues from autopsy-confirmed AD and control subjects and therefore we are unique in our ability to perform such studies. If tau in the PNS can consistently predict Braak NFT stage, low-risk biopsies of accessible tissue sites might be used as a diagnostic and disease progression biomarker. If tau is not predictive, this might be due to molecular differences between CNS and PNS tau and will provide further insights into selective vulnerability. Either way, these results will provide a significant paradigm shift into the

understanding of AD pathogenesis.



Preliminary Data: We recently demonstrated a significant correlation between Braak NFT stages and the presence of spinal cord tau deposits ($\rho=0.49, P<0.001$).⁶ Using these published cases containing frequent tau deposits through the extent of their spinal cord,⁶ we investigated tau concentrations in several peripheral sites accessible to biopsy including abdominal skin, liver, scalp, colon, and submandibular gland. We found using ELISA analysis, the highest levels of total tau to be within the submandibular gland (Fig. 1). Levels of a phosphorylated form of tau (S396) were variable and only a fraction of the total tau levels (range of 0-2ng/mg; data not shown). Furthermore, peripheral total tau was only a fraction of that found in the middle frontal gyrus of the same individuals (0.16% to 1.7%) as well as S396 tau (0.32% to 7.2%) (Table 1). Additional submandibular glands from a second set of subjects, having a variety of Braak NFT stage, showed a significant association between grouped Braak NFT stage and total tau levels ($\rho = -0.55, P=0.002$) (Fig. 2). Although lower total tau levels in AD submandibular glands seem at first to be counterintuitive, it may be that the presence of pathological forms of tau may be causing a regressive neuropathy that lowers axonal density and hence total tau levels. Further study is necessary to validate and confirm these findings as well as understand the anatomic deposition of tau and its different forms within the submandibular gland.

Experimental Designs and Methods: Given antibodies can have non-specific binding to off-target molecules, in the current study to validate and confirm our preliminary results we will use two tau control peptides containing each of the epitopes recognized by the HT7 and T231 antibodies. Further, we will use alkaline phosphatases (to dephosphorylated tau *in situ*) in order to address whether the T231 labeling seen in the preliminary result for is specific. Brain samples of cases with no known NFT will be used as negative controls, while cases with high NFT densities will be used as positive controls. This will be carried out for western blots as well as IHC experiments. We will also perform additional ELISAs, to further confirm data on total Tau (cat # KHB00042 Life Technologies) as well as detect and quantify the level of the tau phosphorylated at Threonine residue 181 (cat # KHO0631, Life Technologies). Using commercially available ELISAs will provide a means for others to replicate our work in a straightforward manner; this will be critical if results will progress to in-vivo studies. These methods will allow for confirmation and validation of preliminary findings of the correlation of certain submandibular glands tau species to Braak NFT staging. We have expertise in these methods, as demonstrated through our preliminary data and previous publications.^{6, 25-28} All samples will be from our BBDP.²⁴ We have on hand 176 autopsy confirmed AD cases and 89 ND cases with submandibular gland tissue; breakdown of demographics and Braak NFT stages are listed in Table 2. Methods will be adapted from similar approaches used to identify a peripheral biopsy site for PD;¹⁹ results were very fruitful, generating a confirmatory publication²¹ and the phase I clinical trial has been published.²⁰

Table 2. Demographics of available AD and ND cases with submandibular tissues.

	AD	ND
N	176	89
M:F	101:75	54:35
age at death	83±7.9	84±11.2
PMI	3.8±3.93	4.5±7.69
Braak NFT stage, N (%)		
Stage 0	0	2 (2%)
Stage I	0	10 (11%)
Stage II	5 (3%)	7 (8%)
Stage III	11 (6%)	26 (29%)
Stage IV	39 (22%)	42 (47%)
Stage V	55 (31%)	1 (1%)
Stage VI	66 (38%)	1 (1%)

Data Analysis: Data from our BBDP (Table 1) demonstrate the frequencies of each Braak NFT stage in subjects with submandibular gland availability. Since certain Braak NFT stages are present at low frequencies, we will divide groups based on low, intermediate, and high Braak stages, instead of analyzing individual Braak NFT stages. This will also allow for larger group sizes thus boosting the statistical power (as done in our preliminary data, Fig 2). All data will be adjusted for age, PMI, and gender ratios across groups. Correlation and multiple regression analyzes will be performed comparing tau species across grouped Braak NFT stages as well as to note any further demographic correlations. We have statistical expertise within our Arizona AD consortium to aid with these endeavors.

Proposed One-Year and Long-Term Outcomes: Data and findings from this project will be submitted for presentation at relevant scientific conferences and in peer-reviewed manuscripts. Tau in the periphery has been hypothesized to have different forms based on rodent work,^{7, 9} and in humans different forms of tau correlate with severity of neuronal cytopathology (pre, intracellular, and extracellular tangles).²⁹ Hence, these confirmatory results will be used to as data in a larger NIH grant application which will investigate other tau species, given there are over 70 different phosphorylation sites for brain tau.

Year End Progress Summary: As of February 2016, proper validation experiments have been completed; a manuscript submitted and accepted. These works demonstrated certain phosphorylated forms of tau to be inversely related Braak NFT stage (as more tau deposits were found in the brain, there was less within submandibular gland). This groundbreaking work

suggests that tau appears to have distinct compositions and relationships to Braak NFT stage and AD based on location (central nervous system vs. periphery). All work was submitted to the Journal of Alzheimer's Disease and accepted for publication in December of 2015 and slighted for publication in March 2016, volume 51, issue 2. To pursue these concepts further, we are in the process of an R21 (National Institutes of Health Federal Grant) submission for the Feb 16, 2016 deadline. The R21 seeks to delve further into understanding peripheral tau with the following questions 1) is the tau found within the submandibular gland derived from the gland itself and does its peripheral expression relate to disease; and 2) what are the associations of the biochemical states of submandibular gland tau compared brain in AD and non-demented elderly individuals. The best models, therapies, and biomarkers are those based on knowledge of the human disease itself. Fundamental descriptions generated from these projects have provided a foundation for further understanding of the pathophysiology of tau on a systems level, with ultimate goals of better model systems of disease and understanding the pathophysiology of the disease for biomarker and therapy development.

2015 Publications and Manuscripts

1. Dugger BN, Whiteside CM, Maarouf CL, Beach TG, Dunckley T, Meechoovet B, Roher AE. Feasibility of peripheral tau detection to determine Braak neurofibrillary tangle stage. *91st Annual Meeting of the American Association of Neuropathologists 2015. abstract*
2. Dugger BN, Whiteside CM, Maarouf CL, Beach TG, Dunckley T, Meechoovet B, Roher AE. Feasibility of peripheral tau detection to determine Braak neurofibrillary tangle stage. *AD/PD International conference 2015. abstract*

2016 Publications and Manuscripts

1. Dugger BN, Whiteside CM, Maarouf CL, Beach TG, Sue LI, Garcia A, Dunckley T, Meechoovet B, Reiman EM, and Roher AE. The Presence of Select Tau Species in Human Peripheral Tissues and Their Relation to Alzheimer's Disease. *Journal of Alzheimer's disease*. Accepted. Schedule for print in scheduled for Volume 51, issue 2 (March 2016)

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Development of an enhanced “Longevity Study” in older and oldest old adults. Edward Zamrini, MD, Brittany N. Dugger, PhD, Kathy O’Connor, MS, Sharon Schofield, Paul D. Coleman, PhD, Thomas G. Beach, MD, PhD, David W. Coon, PhD, Bijan Najafi, PhD, Jane Mohler, NP-C PhD, Matthew Huentelman, PhD, David A. Bennett, MD, Charles Adler, Richard Caselli, MD, Eric M. Reiman, MD. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Translational Genomics Reserach Institute; Rush University; Mayo Clinic; Banner Alzheimer’s Institute; Arizona Alzheimer’s Consortium.

Project Description: The BSHRI Center for Health Aging’s Longevity Study has been performing annual clinical and cognitive assessments in more than 850 residents from the greater Sun City area, including >575 “older” adults in their 70s and 80s, and nearly 200 “oldest old” adults” in their 90s and 100s—by proportion, the nation’s fastest growing and least well studied age group. During the next year, we propose to invite these and other older and oldest old adults to participate in a modified longitudinal research study that includes a) a more complete, standardized battery of annual in-home clinical and cognitive assessments and b) enrollment in a brain and body donation program that complements and enhances BSHRI’s world-renowned Brain and Body Donation Program (BBDP). We also propose to c) develop and maintain a relational database for researchers to conduct studies of aging and age-related disorders involving interested participants, their data, and/or their biological samples. This proposal will lay the foundation for future prospective studies involving interventional and *in-vivo* biological measures with an overall goal of better health for elderly individuals. During the following year, we intend to create a foundational infrastructure for clinical and pathological data with a state of the art database that parallels that of other centers within Arizona as well as across the wider United States.

The infrastructure of the new and enhanced “Longevity Cohort Study” will serve to address the following long term goals:

- 1) Provide a core resource of research participants, data and brain and body tissue samples from longitudinally assessed, clinically and pathologically well-characterized older and oldest old adults for the study of aging and age-related diseases.
- 2) Provide new information about the cognitive and physical changes associated with aging, age-related cognitive disorders, and other age-related disorders in older and oldest old adults;
- 3) Clarify similarities and differences between the cognitive, brain imaging, other biomarker, and pathological changes associated with AD and other forms of cognitive impairment in the oldest old;
- 4) Clarify the genetic and non-genetic risk factors and biological processes associated with resilience to AD, other forms of cognitive impairment and other age-related disorders in the oldest old;
- 5) Continue to educate our senior citizen community about ways in which to promote healthy aging, cope with age-related disorders, and participate in our research studies.

Background and Significance: The fastest growing segment of the United States population are persons aged 85 and older. By 2050 it is projected that over 19 million persons will fall within this age group, this is more than four times as many people than there is now.¹ These

individuals have the highest rates of dementia, as well as other multifactorial health problems, leading to increased number of physician visits and increased health care costs. Despite the large economic impact these individuals will have in the upcoming years, little is known about the etiology of aging past the age of 85. To better understand etiology of aging in older and oldest old adults, this proposal will provide a foundational series for *in-vivo* biomarker and interventional investigations. This study seeks to maximize a pre-existing cohort (The Longevity Study), through implementation of whole body donation and a foundational clinical dataset, incorporating a streamlined database that parallels other centers within Arizona and the United States and allows for optimal recording of information. We will not only continue to gain insightful in-life data, but through addition of whole body donation/autopsy, we will be able to correlate these data to biological processes through tissues obtained after death. We have been very successful with our Brain and Body Donation Program (BBDP) generating extensive extramural funding, and numerous peer reviewed scientific papers, while establishing an exceptional global scientific presence. Emulating certain aspects of the BBDP with the Longevity Study will allow for greater utilization while providing an additional cohort that can be utilized for separate interventional and *in-vivo* biological studies. There are very few places in the world with such a high density of individuals over the age of 90, and there is no place in the world that has the existing resources to perform rapid whole body autopsies with which to understand the etiology and pathology of advanced age. As more people live to advanced old age it is critical to gain a greater understanding of their health status and functional trajectory in relation to aging as a whole. Knowledge gained from this study will have a great impact on our understanding of the continual aging spectrum.

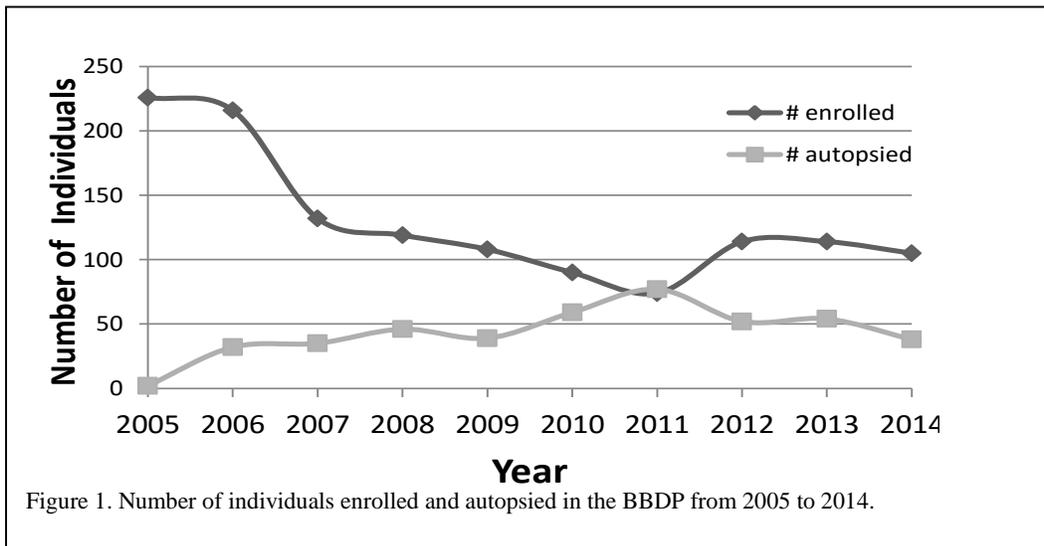
Preliminary Data: We have established outstanding recruitment efforts having nearly 200 individuals currently in the program over the age of 90 (see Table 1). The current study has developed a local reputation that will continue to allow growth through its' collaborations with senior living communities throughout the state and especially through participants already in the study. The Mayo Clinic Arizona, Banner Alzheimer's Institute, and Banner Sun Health Research Institute have been collaborating for the past 20 years in the BBDP. This multifaceted

Participants by Age Group									
Age Group	50's	60's	70's	80 - 84	85 - 89	90 - 94	95 - 99	100+	Totals
Currently Active Longevity Study	10	89	288	133	155	115	43	29	862

program has been enrolling normal, Alzheimer's disease and Parkinson's disease subjects

who have had longitudinal annual clinical evaluations from enrollment until death at which time a brain ± other organ autopsy is performed. However, the current BBDP is a case-control endeavor with the focus being post-mortem research on banked brain and body biospecimens. There is no opportunity for prospective interventional studies or prospective *in-vivo* collections of biological materials (such as blood, cerebrospinal fluid, and/or imaging data). The current proposal aims to fill this void, with a focus on individuals over the age of 90, given the dire need of understanding the etiology of aging in these individuals.

To understand the trajectory of potential enrollment and autopsies within the BBDP for the Longevity Study- Figure 1, illustrates the number of individuals who consented to the BBDP- since the inception of the whole body donation program in 2005. Given the focus of the grant is



infrastructure and the one year time frame, we anticipate enrolling 75 individuals over the age of 70, conducting a total of 25 assessments on individuals 90 years or older, and performing 2 autopsies.

Experimental Designs and Methods:

Infrastructure for Longevity 2.0:

Inclusion Criteria

- 1) Individuals over the age of 70 at the time of consent
- 2) Agree to brain and body donation
- 3) Agree to all annual procedures
- 4) Agree to in home/residence assessment
- 5) Willing to have an informant respond to questionnaires

Exclusion Criteria

- 1) Individuals with a dangerous active infectious disease (examples: active Hepatitis B, Hepatitis C or HIV)
- 2) Individuals with known or suspect Creutzfeldt-Jakob disease or other prion encephalopathy

Variables to be Measured. A guiding principle in the selection of all measurements is the sharing of data with other investigators, either through the entry of data into larger shared datasets, such as the National Alzheimer's Coordinating Center (NACC)¹², or by outside investigators directly accessing our database. Within the first months, we will seek guidance to determine the optimal and most cost effective measures. This will include but not limited to all current stakeholders: Brittany N. Dugger, PhD, Kathy O'Connor, MS, Sharon Schofield, Paul D. Coleman, PhD, and Thomas G. Beach, MD, PhD, - Banner Sun Health Research Institute; David W. Coon, PhD- Arizona State University; Bijan Najafi, PhD and Jane Mohler, RN, MPH, PhD - University of Arizona; Matthew Huentelman, PhD- Translational Genomics Research Institute; Charles H. Adler, MD, PhD, Richard Caselli, MD- Mayo Clinic David A. Bennett, MD- Rush University, Eric M. Reiman, MD- Banner Alzheimer's Institute, and Arizona Alzheimer's Consortium.

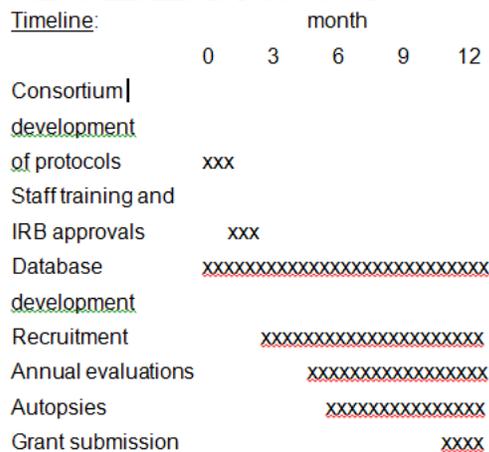
Of note, if a subject is found to have mild cognitive impairment, dementia, and/or parkinsonism during the research evaluation, then the subject will be informed of the findings and will be advised to see their personal physician or seek a clinical neurological assessment outside of this research program.

Autopsy Procedures. Should a subject come to autopsy during this study, procedures as documented in our previous publications^{6,7} will be followed for the autopsy.

Education/Outreach. In addition to the great impact this study will have in the global scientific community, another prong to this proposal is continued efforts within the local older adult communities to increase awareness of healthy aging. To accomplish this, we will provide education and outreach e.g. health fairs, screenings and educational collateral for older adults involved in the program to increase awareness of physical and mental challenges, including increased awareness of Alzheimer’s disease and brain fitness. The Center for Healthy Aging has previously provided Healthy Aging Fairs that are scheduled annually for communities throughout the Phoenix metropolitan area with a focus on screenings for depression, anxiety, and memory. Other health expos for employees of Banner and new members of the community are also staffed by Center for Healthy Aging personnel to better inform them of the ongoing research in Alzheimer's disease and other studies at BSHRI.

Proposed One-Year and Long-Term Outcomes: One Year- We will a) develop and implement a more complete, standardized battery of annual in-home clinical and cognitive assessments as determined through guidance of all current stakeholders and b) enroll subjects in a brain and body donation program that complements and enhances BSHRI’s world-renowned BBDP and c) develop and maintain a relational database for researchers to conduct studies of aging and age-related disorders involving interested participants, their data, and/or their biological samples. Given the focus of the grant is laying a firm infrastructure, and the one year time frame, we anticipate enrolling 200 individuals over the age of 70, conducting a total of 25 complete assessments on individuals 90 years or older, and performing 2 autopsies. Subsequent addition of a Hispanic elder sub-cohort to will be considered in year 2.

A detailed timeline is located below.



Long-term outcomes- Developing a strong infrastructure with this one year grant will provide the preliminary evidence and data to implement in-vivo collections and measurements that can complement and expand the currently proposed dataset. During the subsequent years, we intend to a) conduct grant funded brain imaging and fluid biomarker studies in patients with the clinical diagnosis of dementia due to Alzheimer’s disease (AD) and cognitively normal control subjects from the oldest old and older old age groups, b) begin to clarify similarities and differences between AD biomarker features in the oldest old versus the younger old and c) provide

preliminary data in support of competitive research grants to help sustain the Longevity Cohort Study in future years. Given the extent of this critical resource, we hope to generate research grants, philanthropic funds, and post-mortem tissue sample cost-recovery fees needed to sustain this program and provide a critically important core resource of participants, data and samples for the study of AD, age-related cognitive disorders, and other disorders, and to provide new insights into the factors that contribute to healthy aging. Given the success of our parallel experience with Brain and Body Donation Programs, the expectation is to create the most valuable combined pre-mortem and post-mortem clinical and tissue resource for the study of longevity and healthy aging in the world and to ultimately utilize the population to conduct focused intervention studies.

Year End Progress Summary:

a) All stakeholders were consulted to decide upon the standardized battery of clinical and cognitive assessments to include Claudia Kawas, MD, 90+ study, University of California at Irvine. A comprehensive comparison of various batteries 1) Brain and Body Donation Program (BBDP) assessments, 2) APOE assessments, 3) Memory and Aging Program (MAP) assessments from Rush University was also done. It was decided to utilize the standardized battery UDS Version 3.0 National Alzheimer's Coordinating Center as well as an additional neuropsychological executive component, the STROOP Color and Word test. A detailed plan has been outlined as to who will staff the enrollment/consenting, scheduling, preparation and administration of assessments and follow-ups to include chart review and data entry and storage.

b) 100 participants in the Longevity Study will be enrolled into the BBDP with a priority list of 200 to be invited over the course of the next several years that includes 90 and over and participants that have completed 8 years in the study, half of which are over 90 and the remainder under 90. Our enrollment pace has slowed down due to transfer of the Longevity study to Western IRB to coincide with the BBDP. 1-2 participants will be enrolled and assessed per month to start with 30 percent of participants ready to enroll/enrolled. This will be helpful in recruitment for subsequent substudies to compare young old with old old subjects later this year.

c) A dedicated IT Administrator is being recruited for Banner Research to assist in the management of REDCap. The platform is being designed in Redcap for the assessments for the BBDP enrollees for the Longevity project. When the forms, data fields and field requirements have been well defined, we will map the historical Longevity 1 data into the new system. Aligning of current database in preparation for transition has already begun. Tablet features with REDCap can be explored for those participants that cannot come to BSHRI or when we are ready for direct data entry.

2015 Publications and Manuscripts

BANNER SUN HEALTH RESEARCH INSTITUTE

CENTER FOR HEALTHY AGING LONGEVITY STUDY: LEARNING FROM OUR ELDERLY

1. O'Connor Kathy, Malek-Ahmadi Michael, Dugger Brittany, Schofield Sharon, Coon David W., Nieri Walter · **Description and Cohort Characterization of the Longevity Study: Learning From Our Elders**, *Aging Clinical and Experimental Research*, 2015. doi 10.1007/s40520-015-0488-z
2. Malek-Ahmadi M, Powell J, Belden CM, O'Connor K, Evans L, Coon DW, Nieri W. **Age- and education-adjusted normative data for the Montreal Cognitive Assessment**

- (MoCA) in older adults age 70 to 99. *Aging, Neuropsychology, and Cognition* 2015;22(6):1-7. doi.org/10.1080/13825585.2015.1041449
3. Birch, Kelly, ten Hope, Merritt, Malek-Ahmadi, Michael, O'Connor, Kathleen, Schofield, Sharon, Coon, David, and Nieri, Walter, **Cognitive Function and Physical Activity Interaction on Depression Status in Older Adults**, *Journal of Aging and Physical Activity*, In press.
 4. Michael Malek-Ahmadi, Krishna Kora, Schofield, Sharon, Coon, David, and Nieri, Walter, **Longer self-reported sleep duration is associated with decreased performance on the montreal cognitive assessment in older adults**, *Aging Clinical and Experimental Research*, 2015. doi10.1007/s40520-015-0388-2
 5. Leonard, Brian, O'Connor, Kathleen, Evans, Linda, Nieri, Walter, It's the life in your years, not the years in your life: Commentary on Schafer and Shippee, **Age Identity, Gender, and Perceptions of Decline: Does Feeling Older Lead to Pessimistic Dispositions About Cognitive Aging?** *Journal of Gerontology: Social Sciences*, 2010, 65B (1), 91-96
 6. O'Connor, Kathleen, Leonard, Brian, Nieri, Walter, & Coon, David. Learning from our Elders: **A Longevity Project at the Center for Healthy Aging at the Sun Health Research Institute**, *Arizona Geriatrics Society Journal*, 2009; 14(1), 19-22.

2016 In process:

1. Talmage, Craig, Coon, David, Dugger, Brittany, Knopf, Richard, O'Connor, Kathy Schofield, Sharon **Exploring Differences in Physical Activity Predictors among the Young Old, Middle Old, to Oldest Old: Examining Valuation of Life, Social Leisure Activity, and Physical Attributes**
Draft manuscript for review and publication in *Journal of Aging and Physical Activity*
2. Lin, Ivy, Coon, David, O'Connor, Kathy, Malek-Ahmadi, Michael, Mohler, Jane, **Depression, Life Satisfaction and Life Valuation in a Cohort of Older Community Dwelling Adults**
3. Malek-Ahmadi, Michael, O'Connor, Kathy, Schofield, Sharon, Snyder, Noelle, Zamrini, Edward, Coon, David **Physical Activity Level and Cognitive Function as Predictors of Life Satisfaction in Older Adults Age 80 and Older**
4. Gary, M, Toosizadeh, Nima, Mager, Reine, Veldhuizen, Jaimeson, OConnor, Kathy, Mohler, Jane, Najafi, Bijan, **Upper Extremity Function Testing as an Alternative to Gait Performance Measures in Older Adults**,
5. Veldhuizen, Jaimeson, Mager, Reine Toosizadeh, Nima, Mohler, Jane Reiman, Eric, OConnor, Kathy, Najafi, Bijan, **Association between Cognitive Impairment and Upper Extremity Performance un a dual task condition**,
6. Rana, Harnoor, Coon, David, O'Connor, Kathy, Schofield, Sharon, Nieri, Walter, **What are Nonagenarians and Centenarians' Self-Reported Contributors to Aging Successfully?**

Project Progress Reports
Barrow Neurological Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Alzheimer's disease biomarker studies. Jiong Shi, MD, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

My laboratory is focused on biomarker studies in aging brain and age-related neurological disorders, primarily Alzheimer's disease.

One of our studies is to understand the PACAP-AMPK-Sirtuin3 pathway in the pathogenesis of Alzheimer's disease. We have characterized the neuroprotective properties and are planning to study its therapeutic potentials.

Specific Aims:

Aim 1: We will test if Sirtuin3 levels differ between normal control (NC), Mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects in postmortem brains.

Aim 2: We will test if Sirtuin3 levels correlate with AD pathology.

Aim 3: We will test the specificity of Sirtuin3 in other neurodegenerative conditions.

Aim 4: We will examine the cause-effect relationship of Sirtuin3 and AD pathology in transgenic models of AD.

Background and Significance: Biomarkers in dementia. The growing aging population is facing the challenge of dementia. However, we don't have a reliable biomarker for early diagnosis. Mild cognitive impairment (MCI) describes a syndrome of cognitive impairment beyond age-adjusted norms that is not severe enough to impair daily function or fulfill clinical criteria for dementia (Petersen et al., 1999). Longitudinal studies have shown that 15% of MCI patients progress to AD per year (Ewers et al., 2012; Landau et al., 2010). Amnesic MCI (aMCI) has the highest conversion rate among all subgroups (Fischer et al., 2007). Current therapy provides limited symptomatic benefit in MCI patients, and disease-modifying therapy will likely be most effective when the disease is diagnosed early. Biomarkers that accurately predict disease progression would ameliorate prevailing uncertainties regarding which MCI patients will develop AD and aid in early treatment.

CSF A β and p-tau biomarkers for MCI and AD. CSF A β 42, total tau and phosphorylated tau (p-tau) are most commonly used biomarkers. Many studies have shown that compared to NC, AD patients have lower CSF A β 42 levels and higher total tau and phosphorylated tau (p-tau) levels. As mildly demented AD patients show elevated tau protein levels (Galasko et al., 1997; Riemenschneider et al., 1996) and decreased A β 1-42 levels (Andreasen et al., 1999; Galasko et al., 1998; Motter et al., 1995) in CSF compared to NC, altered CSF tau and A β 1-42 levels have been proposed as putative early diagnostic markers for MCI subjects at high risk of developing AD. Patients who converted from MCI to AD showed significantly higher tau levels at baseline compared to NC (Arai et al., 1997). Moreover, subjects with MCI who later develop AD can be identified by the combination of decreased CSF concentrations of A β 1-42 and increased levels of tau (Andreasen et al., 1999; Riemenschneider et al., 2002), suggesting that CSF tau and A β 1-42 may be valuable to detect the preclinical stages of AD. However, the specificity is relatively low since up to 20% of NC subjects may have abnormal CSF AD biomarkers. Therefore, more specific biomarkers are needed. PACAP is such a potential biomarker. We will determine whether changes in PACAP levels in MCI patients correlate with clinical progression and conversion to AD.

PACAP as a novel biomarker. We have discovered reduced PACAP level in the brains of patients with AD compared to controls (Han et al., 2015; Han et al., 2014). ADCYAP1 (the PACAP gene) expression was significantly reduced in the Middle Temporal Gyrus (MTG), Superior Frontal Gyrus (SFG), and Primary Visual Cortex (PVC), while its protein levels were reduced in all three regions plus the Entorhinal cortex (ENT). PACAP protein levels were correlated with higher CERAD amyloid plaque score in the ENT and SFG but not in the MTG or PVC. In terms of neurofibrillary tangles, PACAP levels were reduced in Braak stage V-VI (all AD cases) than in stage III-IV. Therefore, PACAP expression was inversely associated with both pathological hallmarks of AD. Furthermore, the PACAP level in CSF was correlated with that of the brain and was reduced in AD as compared with CN. This reduction in PACAP is specific for AD since PACAP levels in Parkinson Disease with Dementia (PDD) and in Frontotemporal Lobe Dementia (FTLD) were comparable to that of CN. Hence, downregulation of PACAP may be an early pathogenic factor in AD. Therefore, early detection of reduced PACAP levels in the CSF may be indicative of underlying AD pathology in patients with MCI and in those with an increased risk of developing AD.

Sirtuin3 as a novel biomarker. Sirtuin3 belongs to the Sirtuin family and is localized in mitochondria to have its deacetylation activity. PACAP modulates Sirtuin3 production via AMPK. We have found that Sirtuin3 expression is reduced in AD brains and this reduction is closely related to Tau pathology. The dual measurement of PACAP and Sirtuin3 provides a more robust assessment of AD progression.

Preliminary Work: We showed that Sirtuin3 expression is reduced in AD brains. Sirtuin3 reduction in different brain areas was associated with Braak stage, but not CERAD amyloid plaque burden. In addition, we showed that lower Sirtuin3 was associated with poorer cognitive performance.

Year End Progress Summary:

Aim 1: We have shown that Sirtuin3 levels decreases as the disease progresses from NC to MCI to AD. Sirtuin3 levels in MCI are between its levels in NC and AD. This gradual decrease in Sirtuin3 happens in the frontal and temporal areas that are commonly affected by AD.

Aim 2: We have shown that Sirtuin3 levels correlate well with the Tau pathology of AD. Since the MCI and AD cases we included in our study have definitive AD pathology, this correlation of Sirtuin3 and Tau pathology suggest Sirtuin3 is involved in the early stages of pathogenesis of AD.

Aim 3: Regarding specificity of Sirtuin3, we will collect more cases of non-AD dementia. The pure Tauopathology cases will provide us more information regarding the Sirtuin3 involvement in pathogenesis.

Aim 4: We have established a cellular model of Sirtuin3 knockin and knockdown.

Proposed One-Year and Long-Term Outcomes:

1) We will examine whether Sirtuin3 levels differ between NC, MCI and AD subjects. We will first compare Sirtuin3 from patients with AD (meeting NINCDS-ADRDA criteria, (1997)) to age-matched NC individuals. Since the diagnosis of MCI is applied to individuals who experience cognitive decline but do not meet the clinical criteria of dementia (Petersen et al., 1999), we will determine whether Sirtuin3 levels in MCI patients are of an intermediate level between that of AD and NC individuals. Furthermore, we will use Tau 18F PET image as a gold standard to correlate tauopathy with Sirtuin3 levels in the same population.

2) We will examine whether longitudinal changes in Sirtuin3 levels correlate with conversion from MCI to AD. Because of the need for early diagnosis, we will apply several types of analyses to evaluate longitudinally whether Sirtuin3 levels predict risk of cognitive impairment and progressive decline based on cognitive test scores and/or CDR sum of boxes. Specifically, we will follow subjects > 65 years of age with annual evaluations, and we will investigate whether there is a decrease of Sirtuin3 in NC and MCI subjects that precedes the clinical diagnosis of AD.

3) We will examine the specificity of Sirtuin3 in other neurodegenerative conditions. To test its specificity, we will include cases of Parkinson's disease (without dementia), Amyotrophic Lateral Sclerosis, Frontotemporal Lobe Degeneration and related tauopathies. These neurodegenerative pathologies differ from AD, and so will show whether reduction in Sirtuin3 is specific to AD or universal in neurodegeneration.

4) We will examine the cause-effect relationship of Sirtuin3 and AD pathology in a transgenic model of AD. We have identified Sirtuin3 as a marker of AD, but the cause-effect relationship of Sirtuin3 and A β / p-Tau is unknown. We will use a triple transgenic model of AD to exam the Sirtuin3 levels over a time course of 12-month to delineate its relationship with A β / p-Tau.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Genetic signature of NFT cortical neurons in FAD and sporadic AD. Elliott Mufson, PhD, Bin He, MD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aim: During the second year of funding from the Arizona Alzheimer Consortium, we investigated whether conformational phosphorylation and cleavage events drive the tau protein from a soluble, monomeric state to a relatively insoluble, polymeric state that precipitates the formation of neurofibrillary tangles (NFTs) in the cortical projection neurons located within the magnocellular perikarya of the nucleus basalis of Meynert (NBM) complex of the basal forebrain during the onset of Alzheimer's disease (AD).

Background and Significance: Cholinergic neurons located within the region of the substantia innominata termed the nucleus basalis of Meynert (NBM) degenerate early in Alzheimer's disease (AD). These neurons provide the primary source of acetylcholine to the entire cortical mantle and their degeneration correlates with deficits of memory and attention in AD patients. Several lines of evidence suggest that cholinergic NBM cytopathology begins prior to the onset of mild cognitive impairment (MCI), a putative prodromal stage of AD. NBM neurons are prone to neurofibrillary tangle (NFT) cytopathology, which consist of abnormally phosphorylated aggregates of the microtubule-associated protein tau. Biochemical and neuropathological studies indicate that conformational changes in the tau protein drive this molecule from the soluble, microtubule-bound state to the relatively insoluble polymeric form that precipitates NFT formation within NBM neurons during the progression of AD. However, whether progressive stages of NFT formation are associated with differential gene expression and cellular pathogenic alterations within NBM neurons during the progression of AD remains unknown. In the present study, we quantified gene expression patterns of individual NBM neurons singly immunostained for the pS422 tau epitope, an early phosphorylation event preceding C-terminal truncation of tau at D421, or dual labeled for pS422 and TauC3, a later stage tau neopeptide revealed by tau truncation at D421. Individual NBM neurons were microdissected from tissue sections obtained postmortem from subjects who died with an antemortem clinical diagnosis of no cognitive impairment (NCI), MCI, or AD followed by custom-designed microarray analysis.

Research Plan: Custom-designed microarray analysis of single NBM neurons was performed using tissue obtained postmortem from 28 participants who received yearly clinical testing and agreed to brain autopsy in the Rush Religious Orders Study (RROS). Tissue sections containing the anteromedial NBM subfields were incubated with a mouse monoclonal antibody raised against the tau D421 cleavage neopeptide, TauC3 (1:5,000) overnight at 4 °C, then incubated with biotinylated goat anti-mouse IgG (1:500; Vector Labs), and processed with avidin-biotin complex reagent (ABC; Vector Labs) and Vector SG peroxidase substrate (Vector Labs) to yield a dark blue reaction product labeling TauC3+ neurons. Subsequently, tissue sections were incubated with a rabbit polyclonal antibody directed against the phospho-tau epitope pS422 (1:15,000; Biosource/Invitrogen, Carlsbad, CA). Individual Nissl positive but immunonegative, pS422reactive, dual-labeled pS422/TauC3, and singly TauC3-labeled NBM neurons were accessed. Approximately 50-60 neurons per phenotype were individually analyzed by the custom microarrays. RNA amplification from NBM neurons was performed using terminal continuation (TC) RNA amplification methodology. Radiolabeled TC RNA probes were hybridized to custom-designed microarrays without further purification. Arrays were

hybridized overnight at 42 °C and placed in a phosphor screen for 24 h and developed on a Storm phosphor imager (GE Healthcare, Piscataway, NJ). Expression of TC amplified RNA bound to each linearized cDNA minus background was expressed as a ratio of the total hybridization signal intensity of the array (i.e., global normalization) [36,43]. The data analysis generated expression profiles of relative changes in mRNA levels among the phenotypically distinct NBM neurons dissected from each case within the clinical diagnostic groups. Each neuron was analyzed in triplicate via three independent probe amplifications and array hybridizations using the original neuronal cDNA pool as template.

Progress to date: Conformational phosphorylation and cleavage events drive the tau protein from a soluble, monomeric state to a relatively insoluble, polymeric state that precipitates the formation of neurofibrillary tangles (NFTs) in projection neurons in Alzheimer's disease (AD), including the magnocellular perikarya located in the nucleus basal of Meynert (NBM) complex of the basal forebrain. Whether these structural changes in the tau protein are associated with pathogenic changes at the molecular and cellular level remains undetermined during the onset of AD. Here we examined alterations in gene expression within individual NBM neurons immunostained for pS422, an early tau phosphorylation event, or dual labeled for pS422 and TauC3, a later stage tau neopeptide, from tissue obtained postmortem from subjects who died with an antemortem clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI), or mild/moderate AD. Specifically, pS422-positive pretangles displayed an upregulation of select gene transcripts subserving protein quality control. On the other hand, late stage TauC3-positive NFTs exhibited upregulation of mRNAs involved in protein degradation but also cell survival. Taken together, these results suggest that molecular pathways regulating protein homeostasis are altered during the evolution of NFT pathology in the NBM. These changes likely contribute to the disruption of protein turnover and neuronal survival of these vulnerable NBM neurons during the progression of AD.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Cognitive and neural correlates of aging in autism spectrum disorder. Leslie C. Baxter, PhD, Blair Braden, PhD, Jiong Shi, MD, PhD, Curtis McKnight, MD, Christopher Smith, PhD, Jieping Ye, PhD. Barrow Neurological Institute; 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 [1]. Conversely, ASD individuals often have preserved or enhanced visuospatial skills, such as embedded figure recognition and detail processing [2]. 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 [3, 4]. 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 may 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 y.o.) 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. 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. 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; he will participate in the conceptualization and manuscript preparation of this study. Dr. Caselli, also at MCA, has incorporated measures of ASD in his longitudinal APOE cohort.

In our first year, we recruited 16 ASD and 17 typically developing (TD) Control males, ages 40-60, who are right-handed, and the 12 ASD and 11 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 obtained Department of Defense funding that will enable us to expand the cohort to a total of 70 ASDs/age-matched controls and obtained two data points, two years apart.

Progress to date: Data were collected on the first wave of a longitudinal/cross-sectional cognitive aging study in ASD. 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 and the data obtained from the first cohort's baseline time point. We found that the older ASD group had significantly greater errors on an executive functioning task (WCST) and slower processing speed within the context of otherwise similar functioning. This is consistent with our model that older individuals with ASD may have exacerbated aging effects because the weaknesses they experience are subserved by the frontal lobe. The "anterior-posterior aging gradient" posits that greater brain changes in the anterior portion of the brain. In addition to cognitive differences found for functions subserved by the frontal lobe, we also found decreased integrity of white matter (via the fractional anisotropic (FA) measure of diffusion tensor imaging) and that this weakness in FA integrity in the genu of the corpus callosum also correlated with cognitive functioning on executive measures, indicating a brain-behavior relationship. This and other data from this dataset are being prepared for publication. Comparing our older and younger cohorts, we are finding that there is a greater difference observed between the young-old ASD compared to the TD groups, further reflecting an aging effect for errors on the WCST and FA in white matter.

The literature indicates that ASD individuals have greater rates of comorbid anxiety and depression. In addition to imaging and cognitive data, we collect anxiety and depression self-report at the time of cognitive testing and MRI scanning. These data showed that 88% of the middle-age ASD group reported significant levels of anxiety and 44% reported significant depression, as compared to 45% in the young-adult ASD group for both anxiety and depression. Social network measures did not significantly correlate with mood measures in either middle-age or young-adult ASD, and the report of caregivers was not correlated with the symptom severity reported by the participants (we do not report the TDs in these analyses since they are excluded if they have psychiatric illness or symptoms). Interestingly, anxiety and depression symptoms correlated with several cognitive measures for the young ASD group, but there was no correlation in the older ASD group with cognition. This suggests that the cognitive deficits observed in the older ASD participants are not due to the presence of anxiety and depression but instead anxiety and depression may be independently affected in aging. These findings were submitted for presentation at the International Meeting for Autism Research in May 2016. We also received extramural funding to further investigate emotional status in our older ASD cohorts. Participants will undergo a clinical interview by a psychiatrist and will be assessed

using the Structured Clinical Interview for DSM Disorders (SCID for DSM5) to better understand how individuals with ASD express/self-report anxiety and depression. It is quite possible that ASD individuals have difficulties with integration of the interoceptive and emotional awareness systems. We think research in this area will ultimately provide a clearer understanding of aging in ASD.

Year End Progress Summary:

- Obtained funding from the Department of Defense “Cognitive and Neural Correlates of Aging in Autism Spectrum Disorder” for three years, which will allow us to obtain a larger sample size and two time points, two years apart.
- Obtained funding from the Institute for Mental Health Research to include comprehensive assessments of anxiety and depression in the younger and older ASD groups. Participants will undergo a clinical interview by a psychiatrist and will be assessed using the Structured Clinical Interview for DSM Disorders (SCID for DSM5) to better understand how individuals with ASD express/self-report anxiety and depression.
- Presented preliminary data as an Oral Presentation at the 2015 annual meeting of the International Meeting for Autism Research in May, 2015.
- Joined the Autism Brain Imaging Data Exchange (ABIDE) and will contribute our imaging and demographic findings to the consortium.

Proposed One-Year and Long-Term Outcomes:

- Continue acquiring 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.

Project Progress Reports

Mayo Clinic Arizona

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Normal and pathological aging (preclinical Alzheimer's disease). Richard J. Caselli, MD, Dona E.C. Locke, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Project Description: Cognitively normal individuals age 21-99 (most age 45-70) undergo 1) APOE genotyping to categorize their relative risk for developing Alzheimer's disease; 2) longitudinal neuropsychological and behavioral assessments; and 3) serve to create a biorepository for DNA, serum, plasma, viable frozen lymphocytes, and immortalized cell lines to determine what factors divert individuals from normal to pathological aging/Alzheimer's disease with the intent of identifying optimal timing of treatment and new potential therapeutic targets for preventing this divergence (prevention of Alzheimer's disease). This "APOE Cohort" also serves as a core resource for multiple collaborative projects within our site and for the consortium. Mayo collaborators and their projects supported by this budget include 1) Bryan Woodruff, MD, Correlating APOE genotype with cognitive and behavioral outcomes among adults with an autism spectrum disorder, 2) Yonas Geda, MD, APOE genotypes, Brain Derived Neurotrophic Factor and cognitive function among Hispanics in Phoenix, Arizona, 3) Cynthia Stonnington, MD, Predicting Cognitive Decline in Cognitively Normal Individuals. Separate project descriptions will be included for these three investigators.

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)
- 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 2500 participants from which were selected our study population for further testing. We have completed one or more epochs of neuropsychological testing on 744 individuals including 425 APOE e4

noncarriers, 230 e4 heterozygotes, and 89 e4 homozygotes. Of these, 579 have completed two or more epochs of testing, with an average followup duration of up to 20 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).

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. Complete our analysis of computerized cognitive assessment tools
2. 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 2 specific goals:
 - a. do "minor" genetic variants correlate with young onset dementia (implying their generally accepted nonpathogenic status may vary between individuals so that they are more pathogenic in some), and
 - b. how disclosure of such 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 PS1 mutation offer solace to families concerned about familial transmission)
3. 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 age-related cognitive decline and the risk for incident MCI and dementia alone or in conjunction with APOE e4
4. Support our collaborative projects

Year End Progress Summary: We have completed our 2014-2015 goals:

1. survey public attitudes regarding preclinical genetic and biomarker testing for Alzheimer's disease in the absence of a highly effective therapy to help guide preclinical investigation and intervention that will may entail disclosure of such results to participants (7,8)
2. compare incident MCI with "clinical MCI", that is, the relative cognitive profile and severity of MCI identified during the course of longitudinal testing compared with that seen in patients presenting with symptomatic memory loss to an outpatient Neurology department. (abstract presented at the Alzheimer Association International Conference July 2014 [9])

3. do traditional neuropsychological tests or newer computerized cognitive assessment tools correlate better with neuroimaging-derived AD biomarkers? (abstract presented at the Alzheimer Association International Conference July 2015, and continued analysis ongoing)
4. Whole genome and epigenetic analyses of unexpectedly young onset AD patients: patients recruited, samples collected and analyses underway which have already resulted in the discovery of a novel PS1 mutation in a patient lacking a similarly affected relative (ongoing analysis).
5. examined the effect of sex-based cognitive advantage (e.g., verbal memory is better in women than men) as a proxy for cognitive reserve that is developmentally determined rather than environmentally (in contrast to education, the most frequently utilized proxy) and found that such advantages are maintained but do not mitigate the rate of age-related decline (challenging the cognitive reserve construct and indirectly implying that environmentally based proxies more likely reflect cerebrovascular than neurodegenerative contributions to age related decline and dementia severity) (10)

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ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Predicting cognitive decline in cognitively normal individuals. Cynthia M. Stonnington, MD.
Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

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

Background and Significance: Even at the earliest clinical stages of Alzheimer's disease (AD), amyloid pathology has nearly peaked yet neither symptoms nor brain atrophy correlate well with amyloid burden. Anti-amyloid therapies have all fallen well short of expectations to date, for the generally held reason that they are started too late, and that for a disease modifying agent to be effective it must be started during an earlier, preclinical stage, i.e., before patients develop symptomatic memory loss. Preclinical AD is superficially indistinguishable from normal aging. We therefore plan to develop methods to differentiate normal from pathological aging by combining imaging based biomarkers, neuropsychological, and genetic data to better identify those individuals on the cusp of symptoms and therefore most likely to benefit from treatment.

Preliminary Data:

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

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

2. From our longitudinal APOE data base of cognitively normal individuals, we have identified 21 individuals with baseline FDG PET and MRI and neuropsychological data who subsequently developed incident MCI, along with 180 in the same age cohort who remain cognitively normal also had FDG PET and MRI and neuropsychological data.

3. From our longitudinal APOE data base of 180 cognitively normal individuals with baseline FDG PET and MRI and neuropsychological data, we have identified 18 who show evidence of cognitive decline but have not yet developed MCI or AD.

4. From our longitudinal APOE data base, we identified 14 individuals with amyloid imaging data who also had evidence of cognitive decline but remained cognitively normal and matched by age, sex, APOE status, and education to 14 individuals who did not show any cognitive decline. At $P < .005$ (uncorrected), decliners had significantly greater evidence of fibrillar A β burden in comparison to nondecliners (1).

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.

Firstly, we will examine the statistical power in distinguishing the two groups using Receiver Operating Curve method. Secondly, we will apply machine learned decision trees to various sets of features from brain imaging, genetic, and neuropsychological data. We will then test diagnostic and prognostic performance using different maximum number of features.

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.

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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 to date:

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.
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3. 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. 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. Abstract of this work was accepted to the ISBI conference.
4. 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. 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 nonconverters, those who developed aMCI in approximately 2 years had significant decreases in glucose metabolism, gray matter volume, and cortical thickness in regions known to be affected by AD. The imminent aMCI group also showed relative increased glucose metabolism in the left and right pre and post central gyrus. The best single predictor of aMCI was left hippocampal volume, with 74% sensitivity and 72% specificity. Combining MRI and FDG PET data increased the sensitivity and specificity of the predictive model to 77% and 78%. We will be presenting this data at the American Neuropsychiatric Association annual meeting, March 2016. We will also be submitting an abstract to AAIC demonstrating that APOE partially mediated the effect on left (versus right) hippocampus.

5. Professor Wang's group has recently also developed a patch-based sparse coding method to classify different stages of AD on hippocampal morphometry. An abstract demonstrating the method with ADNI data was submitted to the Human Brain Mapping Conference. The AUC measures were 0.78, 0.75, 0.79, 0.75 and 0.68 for AD vs. cognitively normal (CTL), AD vs. MCI, MCI vs. CTL, MCI-converter vs. MCI-stable and CTL-converter vs. CTL-stable classification studies, respectively. Multivariate morphometry statistics (MMS) produced the best results and the comparison demonstrated that the MMS has good potential for prediction and classification studies.

6. We applied this same method to the APOE cohort and received the following results (will be submitting abstract to AAIC and also writing up results for publication):

a. The experiments were conducted on hippocampus and ventricle. For the comparison purpose, we calculated radial distance (RD) and multivariate tensor-based morphometry (mTBM), respectively. Our Patch Analysis based Sparse-coding System (PASS) used Surface Multivariate Morphometry Statistics (MMS) features. The original MMS features are $30000 * 4$, i.e. $15000 * 4$ on each side of hippocampus of each subject ($30000 * 1$ RD, $30000 * 3$ mTBM). After processing with PASS system, the final features are 2000 for each subject. Similar feature reduction and selection were also processed on ventricular surface features. Here, we used leave-one-out and five-fold cross-validation to do classification with AdaBoost. Five standard measures are used to evaluation: accuracy, sensitivity, specificity, positive predictive value (ppv), negative predictive value (npv). The results demonstrate that PASS performs very well when predicting cognitive decline using MMS features.

In Table 1, we tested whole hippocampus, left hippocampus and right hippocampus on RD, mTBM and MMS, respectively.

In Table 2, we tested whole ventricle, left ventricle and right ventricle on RD, mTBM and MMS, respectively.

To compare with other standard features, we used volume and area, which were computed in MNI standard space. The experimental results are shown in Volume Area sheet. Similarly, we also calculated whole volume, left volume and right volume; whole area, left area and right area. But we used different method instead of PASS because the feature dimension is much lower and cannot adapt sparse learning. The Parzen window classifier with the linear kernel assuming a prevalence of 50% was applied to classify individuals based on volume and area data.

Table 3 shows the experimental result of hippocampal volume and area.

Table 4 shows the experimental result of ventricle volume and area.

<i>Hippocampal</i>	<i>RD</i>	<i>RD_left</i>	<i>RD_right</i>	<i>mTBM</i>	<i>mTBM_left</i>	<i>mTBM_right</i>	<i>MMS</i>	<i>MMS_left</i>	<i>MMS_right</i>
Accuracy	0.77	0.62	0.54	0.92	0.69	0.54	0.96	0.77	0.54
Sensitivity	1.00	0.33	0.20	0.75	0.60	0.25	1.00	0.50	0.33
Specificity	0.75	0.86	0.75	1.00	0.75	0.67	0.95	0.82	0.60
ppv	0.33	0.67	0.33	1.00	0.60	0.25	0.86	0.33	0.20
npv	1.00	0.60	0.60	0.90	0.75	0.67	1.00	0.90	0.75

Table 1. Experiment Result of Hippocampal

<i>Ventricle</i>	<i>RD</i>	<i>RD_left</i>	<i>RD_right</i>	<i>mTBM</i>	<i>mTBM_left</i>	<i>mTBM_right</i>	<i>MMS</i>	<i>MMS_left</i>	<i>MMS_right</i>
Accuracy	0.69	0.69	0.62	0.77	0.54	0.62	A	0.69	0.69
Sensitivity	0.43	0.33	0.33	1.00	0.33	0.50	1.00	0.50	0.67
Specificity	1.00	0.80	0.86	0.70	0.71	0.67	0.83	0.78	0.70
ppv	1.00	0.33	0.67	0.50	0.50	0.40	0.33	0.50	0.40
npv	0.60	0.80	0.60	1.00	0.56	0.75	1.00	0.78	0.88

Table 2. Experiment Result of Ventricle

Accuracy	0.57	0.64	0.34	0.70	0.57	0.66
Sensitivity	0.43	0.33	0.32	1.00	0.14	NaN
Specificity	0.83	0.66	0.50	0.69	0.63	0.66
ppv	0.83	0.06	0.83	0.11	0.06	0.00
npv	0.43	0.94	0.09	1.00	0.83	1.00

Table 3. Experiment result of Hippocampal Volume and Area

<i>Ventricle</i>	<i>Volume</i>	<i>Volume_left</i>	<i>Volume_right</i>	<i>Area</i>	<i>Area_left</i>	<i>Area_right</i>
Accuracy	0.75	0.67	0.67	0.67	0.67	0.58
Sensitivity	0.50	0.33	0.25	0.67	0.50	0.60
Specificity	0.88	0.78	0.88	0.67	0.75	0.57
ppv	0.67	0.33	0.50	0.40	0.50	0.50
npv	0.78	0.78	0.70	0.86	0.75	0.67

Table 4. Experimental results of Ventricle Volume and Area

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Correlating APOE genotype with cognitive and behavioral outcomes among adults with an autism spectrum disorder (ASD). Bryan K. Woodruff, MD, Richard J. Caselli, MD, Amylou C. Dueck, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Project Description: Expand our cohort to include individuals with autism spectrum disorder (ASD), and examine the interaction of APOE genotype on cognitive and behavioral performance

Specific Aims: Perform APOE genotype testing on a cohort of well characterized adults with ASD, and explore possible relationships between APOE genotype, cognitive, behavioral, and functional performance.

Background and Significance: We will begin to examine the relationship of AD-related genetic risk to cognitive, behavioral, and functional performance measures in individuals with ASD. Research from members of the consortium have disclosed that even infants exhibit metabolic alterations that correlate with APOE genotype. We will explore the possibility that ASD individuals may have poorer outcomes that correlate with APOE e4 gene dose prior to the added neurological burden of AD in later life. Alternatively, an over representation of the APOE e2 allele has been described among autistic individuals which we could confirm in our cohort.

Preliminary Data: Dr. Woodruff is working collaboratively with a local autism research group (Southwest Autism Research and Resource Center) as part of an intramurally-funded Mayo career development award and has access to a relatively large ASD adult population.

Experimental Designs and Methods: All data for the projects detailed above were collected as part of the Normal and Pathological Aging longitudinal research project or Dr. Woodruff's intramural award. Statistical analyses will be conducted by the project statistician, Amylou C. Dueck, PhD.

Proposed One-Year and Long-Term Outcomes:

1. Gather cross-sectional neuropsychological and behavioral assessments in a well-characterized cohort of adults on the autism spectrum.
2. Collect data regarding autistic traits utilizing the Autism Spectrum Questionnaire^[6] in our Normal and Pathological Aging cohort as well as collect APOE genotype data in a group of autistic adults who are enrolled in a separate project, "Cognitive, Occupational and Psychosocial Outcomes of Adults on the Autism Spectrum", recognizing that the autism spectrum disorders represent an increasingly prevalent group, and that outcomes among autistics in adulthood are understudied. This knowledge gap in particular applies to late life health outcomes for autistic adults such as the development of dementia.

One-Year Progress: We have successfully recruited 49 subjects (target n = 50) for the cohort of adults on the autism spectrum. Administration of the Autism Spectrum Questionnaire has been conducted in 226 participants in the Normal and Pathological Aging cohort. Comparison of APOE genotype effects on neuropsychological performance and autistic traits in both cohorts will be performed.

2015 Progress Update: Analysis of the Normal and Pathological Aging Cohort failed to demonstrate any correlation between higher AQ scores and APOE genotype. Additionally the age differences between the adult ASD cohort and the Normal and Pathological Aging Cohort make comparisons between the two groups problematic. We anticipate that further effort expended on this project will not yield relevant results.

2016 Progress Update: Though comparison of the Normal and Pathological Aging Cohort and the adult ASD cohort was deemed unfruitful, analysis of the neuropsychological and behavioral data in the Normal and Pathological Aging Cohort with the highest AQ scores (10.8%) identified characteristics common to those reported in individuals with ASD and the broad autism phenotype (BAP). This finding suggests the presence of subthreshold autistic traits in a substantial portion of the general population that may impact multiple lines of research on cognition, behavior and aging.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Apolipoprotein E (APOE) genotypes, brain derived neurotrophic factor (BDNF), and cognitive function among Hispanics in Phoenix, Arizona. Yonas E. Geda, MD, Janina Krell-Roesch, PhD, Richard Caselli, MD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

This project has two complementary parts: 1) To correlate plasma brain derived neurotrophic factor (BDNF) levels with Apolipoprotein E (APOE) genotype on up to 500 Hispanic members of the Sangre Por Salud Biobank, a collaborative project between Mayo Clinic Arizona and Mountain Park Health Center; and 2) To compare cognitive status and APOE genotype between three groups: Sangre Por Salud Cohort members (many of whom are immigrants), Hispanic members of the Arizona APOE Cohort (very few of whom are immigrants), and non-Hispanic members of the Arizona APOE Cohort (very few of whom are immigrants) in order to determine whether these three different levels of naturalization in the U.S. correlate with APOE genotype distribution as well as cognitive status. Proceeding from these specific goals, we hope to build a closer relationship with Mountain Park Health Center that may help to engage more members of this under-served population into our research program.

Specific Aims:

- 1) To determine serum BDNF, and perform BDNF genotyping in a large Hispanic cohort, and to correlate BDNF levels with BDNF and APOE genotypes.
- 2) To compare APOE genotypes, particularly $\epsilon 4$ prevalence in immigrant Hispanic, non-immigrant Hispanic, and non-Hispanic cohorts.
- 3) To correlate the relationship between APOE and cognitive status in each of these three cohorts looking for possible interactions reflecting either genetic, demographic, or social influences.

Background and Significance: APOE $\epsilon 4$ is a major risk factor for Alzheimer's disease whose prevalence varies worldwide, being higher in indigenous populations, lower in Mediterranean and Asian countries, and intermediate in North America (1-3). The prevalence of APOE $\epsilon 4$ among Mexican immigrants to the U.S. is currently unknown, but may significantly impact future health care needs, particularly in members of vulnerable under-served populations whose health care ranges from tenuous to government-subsidized. In addition to APOE, BDNF has also been identified as contributing to dementia risk as well as related aging effects in Caucasian populations (4). However, BDNF levels and genotypes in other populations have been less well studied. Hispanic participation in research trials has been limited by a variety of factors, and immigrant Hispanics in particular remain vastly under-represented.

Preliminary Data: Between 2009 and 2011, Mayo Clinic investigators collaborated with Mountain Park Health Center leadership who serve a large proportion of the Latino community of Phoenix, Arizona (regardless of insurance and other factors that traditionally have been barriers to health care in this population) to assemble a registry of self-identified Latino persons for the purpose of investigating cardiometabolic diseases that are disproportionately more prevalent in the Latino community. As part of their study, they administered a comprehensive health survey and biobanked plasma, DNA, RNA, and immortalized lymphoblastoid cell lines in Mayo Clinic's Arizona biorepository. Accrual continues and is approaching 500 members with banked specimens. Additionally, to date, we have recruited and evaluated 89 Hispanic participants, 27 of whom are APOE $\epsilon 4$ carriers in the Arizona APOE cohort.

Experimental Designs and Methods: We will assemble a cohort of 500 adult Hispanics. We will collect blood specimens in order to perform BDNF assays and genotyping to correlate with APOE genotypes that will be performed with separate funding. Health survey data, BDNF, and APOE results will be entered into a JMP database for statistical analysis and ultimately compared with APOE Cohort data. For direct cognitive measurement of the Mountain Park Health Center cohort we plan to implement CogState, a computer-based test of executive and memory ability that is language and culture neutral, and is also being administered to the Arizona APOE Cohort. The CogState will be done during face-to-face evaluations when participants go to Mountain Park Health Center for other medical- and research-related appointments so that a separate visit will not be needed. The CogState takes 20-30 minutes and will be administered during the 2 hours of down time when they undergo a 2-h glucose tolerance test as part of an unrelated research study being done collaboratively with other Mayo Clinic investigators.

Proposed One-Year and Long-Term Outcomes:

- 1) To analyze the serum BDNF assay and examine its correlation with APOE genotype, physical exercise, and cognitive health data among immigrant Hispanics in Phoenix, Arizona.
- 2) To sequence the BDNF gene and explore whether the BDNF genotype mediates the association between serum BDNF, memory complaints, and physical activity.
- 3) To investigate the association between BDNF plasma levels, BDNF genotype, and APOE genotype.
- 4) To compare APOE ϵ 4 prevalence in three different groups: immigrant Hispanics, non-immigrant Hispanics, and non-immigrant non-Hispanics.
- 5) Based upon the above, to begin developing an estimate of future dementia burden in the immigrant Hispanic population.
- 6) To build upon the current relationship with Mountain Park Health Center in a way that serves their needs and offers participation to this underserved and under-represented population.
- 7) To implement CogState, a computerized language/culture neutral attention and memory task that is also being administered to the Arizona APOE Cohort, for the Mountain Park Health Center cohort.

Funds will be use in a way that complement but do not overlap with funding provided by the National Institute on Aging (which supports some of our outreach and clinical core enrollment activities), the Ottens Foundation (which provides partial support for our annual conference), and the Gila River Indian Community and Tohono O’odham Nation for targeted memory screening/brain health programs.

Year-End Progress Summary:

- 1) In 2015, we were funded a supplement to P30 grant to launch the study involving Latinos in Mountain Park Hospital (“Research Supplements for Aging Research on Health Disparities Link: <http://grants.nih.gov/grants/guide/pa-files/PA-14-256.html>”. Principal investigator of the parent grant (# 5P30 AG019610-10) is Dr. Eric Reiman. The co-principal investigator is Dr. Richard Caselli. The site principal investigator for the supplement is Dr. Yonas Geda.
- 2) The following steps were completed in 2015: a. We completed a 2-month process of getting approval from the biobank oversight committee of the Mayo Clinic in order to launch the study involving Latinos that receive medical care at Mountain Park Hospital in Phoenix, Arizona.
b. The Institutional Review Board agreement from Mountain Park Hospital is still pending.
c. We translated the consent, telephone script, and follow-up information into Spanish. It is now undergoing the final proof and approval process by Mountain Park Hospital.

- d. We hired a Spanish speaking study coordinator who has a well-established record of working with the Latino population.
 - e. We recruited 41 adult Latinos aged 40 and above to measure cogstate and MMSE.
 - f. We modified the protocol in December of 2015, to conduct a pilot study to measure Resting Energy Expenditure and activity induced energy expenditure by using Breezing and Actigraph technologies respectively. In December of 2015 and January of 2016, we have so far administered the 2 technologies to 7 study participants..
- 3) We conducted a preliminary analysis of the data on APOE ϵ 4 (Principal Investigator – Dr. Richard Caselli) acquired from the Latino population in the past. The post-doctoral fellow (Dr. Janina Krell-Roesch) won a travel award to present the results at the Kogod Aging Center at Mayo Clinic in Rochester, Minnesota.

Project Progress Reports
Translational Genomics Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Functional characterization of genetic variants identified in exceptional dementia cases.
Matthew Huentelman, PhD, Christiane Bleul, Wayne Jepsen, Amanda Wolfe, Ashley Siniard.
Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Project Description: In collaboration with Arizona researchers at the Mayo Clinic and Banner Alzheimer's Institute we performed genome sequencing and analysis in a selection of dementia patients who exhibited unique or exceptional characteristics. These included early onset of Alzheimer's dementia in the absence of family history and an autopsy confirmed cohort of AD dementia/low amyloid patients with a primary tauopathy diagnosis. Our analysis has yielded several rare genetic variants that exist in genes already associated with Alzheimer's disease in general or amyloid/tau biology specifically. Our proposal is to use three dimensional neuronal cell cultures to investigate the possible functional role of these variants and therefore provide further evidence for their importance in the development of disease.

We will characterize six different genetic mutations in three dimensional cell cultures. Each genetic mutation will be introduced into neural stem cells that were previously engineered to over-express human variants in PSEN and APP (over-expression of these variants results in the formation of plaques and tangles after approximately 8 weeks of culture). These cells will then be introduced into our three dimensional culture set-up and allowed to differentiate for two months. At the end of two months we will assess the amyloid and tau pathology present in the modified lines as well as in control lines. Evidence of an alteration in these characteristic AD pathologies will suggest a putative functional role for our identified genetic variants.

Year End Progress Summary: We successfully optimized the conditions for production of the 3D cell cultures. This included variables related to media composition, cell density / seeding level, ratio to extracellular matrix, and incubation conditions. Additionally we reduced to practice a toolbox approach for rapidly introducing new genes into the neuronal stem cell line that makes up the 3D cultures. The approach uses a transposon-based insertion system that allows the user to add a new gene to the genome rapidly and also includes the ability to perform drug selection for the transposon integration. Using that approach we have created several stable cell lines from the neural stem cells including PSEN, APP, and MAPT mutant lines as well as a line that directly mimics the 5XFAD mouse model mutations. Additionally we have introduced mutant or wild type versions of several new candidates that we expect might alter amyloid production, deposition or tau tangle formation. Currently these cultures are differentiating under 3D conditions and we plan to measure a-beta 1-42, plaque, and tangle levels.

Additionally, we have started to explore adding microglia cells into the 3D culture model. Microglia are not neural in origin therefore the stem cells that seed the 3D cultures do not produce microglia, however, the microglia are a major cell type in the brain and are believed to be important in amyloid plaque metabolism. We feel that the 3D model may be inadequate without the inclusion of these cells. To address this we are utilizing an immortal human microglia cell line and are spiking it into the 3D cultures at various times during differentiation as well as at varying amounts.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Identification of piRNA and PIWI protein in serum and CSF of healthy control subjects, patients with Alzheimer's disease, and patients with Parkinson's disease. Ivana Malencia, Amanda Courtright, Ashish Yeri, PhD, Kendall Van Keuren-Jensen, PhD. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Project description: We recently examined the miRNA content of CSF and serum in postmortem subjects with Alzheimer's disease, Parkinson's disease, or normal healthy controls (Burgos et al., 2014). We wanted to determine whether or not we could detect changes in other extracellular small RNAs associated with disease. In addition to miRNA, small RNAs, such as piRNA, are of particular interest. Until recently, piRNA were thought to be expressed only in germ line cells. However, we were able to detect piRNA sequences in cerebrospinal fluid, which caused us to consider where these piRNA might be coming from and if they had a regulatory role in aging (Li et al., 2013) or disease.

While DNA transposons are not active in humans, retrotransposons are active and make up almost half of the genome. Retrotransposons have been found to be active in neural progenitor cells in the adult brain (Muorti et al., 2005). Retrotransposon insertions are one potential way to contribute to somatic variation in the brain. But they may be responsible for much more. Phenotypic and behavioral differences between isogenic animals may be a result of somatic neuronal variation (Singer et al., 2010). It is also possible that retrotransposon insertions that accumulate over a lifetime, might contribute to the heterogeneity of Alzheimer's disease and modulation of risk. Environmental factors, such as stress, may also alter the rate of retrotransposon insertion. Currently, the rate of LINE1 insertion is not known, nor if there are specific brain regions that are more affected (Evrony et al., 2012; Erwin et al., 2014). LINE1 retrotransposon insertions are increased in patients with schizophrenia (Bundo et al., 2014) and in Rett Syndrome (Muotri et al., 2010). piRNA typically work to repress retrotransposon activity in germ line cells. The goal of our study is to examine piRNA expression in the CSF and serum from patients with Alzheimer's disease and controls.

Year End Progress Summary: We sequenced the small RNA species in CSF and serum samples from normal controls and Alzheimer's patients. We found that the analysis was difficult to interpret for piRNA. The piRNA databases are redundant and not well curated. They have many overlapping sequence fragments with tRNA. For example, if we align the small RNA reads hierarchically from rRNA, to miRNA, tRNA and then piRNA, there are very few piRNA detected. But if we align rRNA, miRNA, piRNA, and then tRNA, there appears to be many piRNA (Figure 1). Thus, there is a problem with alignment and overlap between the sequences in the tRNA and piRNA databases. We changed our analysis to be much more stringent in what was included as piRNA sequences and excluded many sequences. When we did this, we still detected more piRNA sequences in CSF than serum, and two that were differentially expressed in Alzheimer's CSF compared with control samples.

One piece of evidence that would boost our confidence that these sequences are piRNA, would be to detect the PIWI protein in CSF. PIWI proteins are members of the Argonaute family, and like AGO2 binds to miRNA, PIWI binds piRNA. We immunoprecipitated PIWI from CSF samples and sent the pulled-down protein to mass spectrometry for identification. We should have information regarding the presence or absence of PIWI in CSF. We will also confirm the piRNA sequences that are differentially expressed by custom Taq assays.

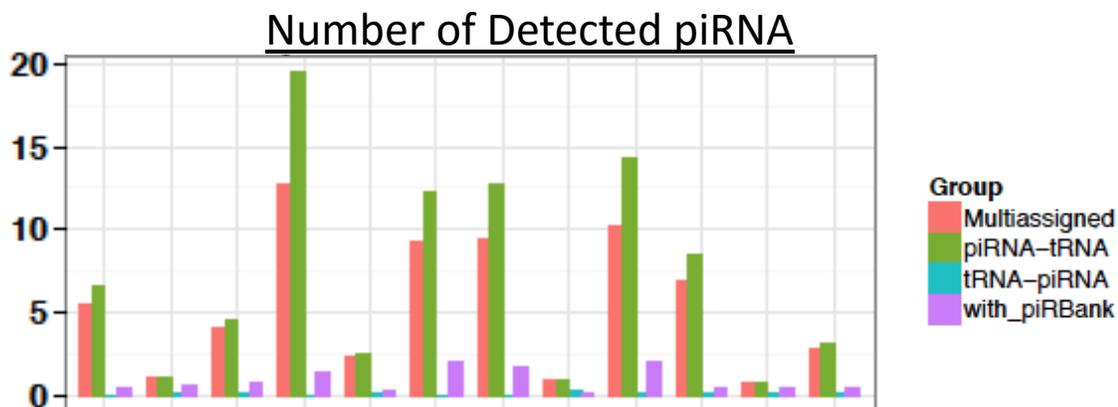


Figure 1. Hierarchical clustering of small RNA databases changes the detection of piRNA. The category ‘multi-mapped’ represents the sequences that map to piRNA but that also map to more than one database or location on the genome. The green bar represents mapping with the piRBase database before mapping to tRNA, and you get more reads mapped to piRNA. The blue bar represents the number of reads that map to piRNA after first mapping to tRNA – there are very few sequences that remain. The purple bar are the number of detected piRNA when we use a different database, piRBank.

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ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Identification of circular RNAs in Alzheimer's disease. Shobana Sekar, MS, Lori Cuyugan, MS, Winnie S. Liang, PhD. Translational Genomics 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.

Preliminary Data and Plan: Using previously generated RNA sequencing (RNAseq) data of astrocytes laser capture microdissected from the posterior cingulate of late-onset Alzheimer's disease (LOAD) subjects (n=10) and healthy elderly controls (n=10), we tested and applied analyses and workflows for identifying circRNAs from the whole transcriptome sequencing data set. The raw fastq files generated were aligned (hg19) using either bwa or Bowtie2 and run through two circular RNA detection algorithms - Circular RNA Identifier (CIRI, v2) and find_circ. CIRI takes the bwa-aligned sequence alignment files (SAM) to look for segments of a read that align to the genome in chiasitic order. Paired end mapping and GT-AG splicing signals are used as filtering criteria to reduce the false positive rate. Find_circ first filters out reads that align contiguously and full length to the genome, since such reads are representative of linear splicing. From the remaining reads, 20-mers are extracted from both ends and aligned individually to the reference to find unique anchor positions within spliced exons. Anchors aligning in the reverse orientation indicate circular splicing and are picked up by the tool. Using Cytoscape, we also performed gene ontology enrichment analysis on the genes from which the identified circRNAs arise.

Following circRNA detection, find_circ identified 1335 circRNAs that were unique to the AD samples and 1705 circRNAs unique to the control tissues. On the same dataset, CIRI was able to identify 1459 circRNAs unique to the disease affected tissues and 1454 circRNAs unique to the controls. GO enrichment analysis of the circRNAs identified in the AD samples revealed significant enrichment of ontology terms such as regulation of neuron differentiation, nervous system development, neuron projection development/morphogenesis and synaptic vesicle cycle.

Year End Progress Summary: We are currently evaluating additional circRNA detection analyses and also plan to evaluate differences in circRNAs in RNase R (ribonuclease R) in treated and untreated samples as RNase R enriches for circRNAs by degrading linear transcripts. Following optimization of our analytical workflows, we will also extend these analyses to RNAseq data generated from whole posterior cingulate sections in LOAD subjects and controls to determine if there is an enrichment of specific circRNAs in astrocytes.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

TREM2 agonism: A new approach for Alzheimer's disease therapy. Isabelle Schrauwen, PhD, Chris Sereduk, Holly Yin, PhD, Matthew Huentelman, PhD. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: AIM 1 is to identify novel TREM2/TYROBP agonists using high throughput screening in a TREM2 *Luciferase* reporter cell line. In AIM 2, we will validate positive hits by potency estimations (EC₅₀) and confirm TREM2 agonism in a counter screening cell line.

Background and Significance: The global prevalence of dementia is projected to increase in the coming decades as the population ages. Alzheimer's disease (AD) is a leading cause of dementia, and current FDA-approved drugs for AD do not prevent or reverse the disease, and provide only modest symptomatic benefits. Alterations in both astrocytes and microglia, reflecting underlying changes in innate immune activation within the brain, are invariant pathological features of AD as well as other neurodegenerative disorders.

Preliminary Data and Plan: Several studies have demonstrated that genetic variants in triggering receptor expressed on myeloid cells 2 (TREM2), a known regulator of microglial activation and phagocytosis, confer substantial risk to several forms of dementia and neurodegenerative disease. This evidence is further strengthened by the first report of a nonsense mutation we recently identified in a family with behavioral variant frontotemporal lobar degeneration (bvFTLD). TREM2 function may affect AD pathology through the phagocytosis of amyloid plaque deposits and other debris, and recent studies overexpressing TREM2 in vitro and in vivo support this hypothesis. We hypothesize that agonists of TREM2 could increase the clearance of amyloid- β , apoptotic neurons and other debris in the brain and may therefore act to prevent or to slow disease progression when administered during the optimal timeframe.

We have developed a reporter cell line that can detect the activation of TREM2 to identify compounds that can stimulate TREM2 in high throughput. The luciferase reporter cell-line stably expresses TREM2, TYROBP and NFAT Luciferase. We screened 2,400 compounds from the well characterized libraries. This includes the Prestwick Chemical Library® (PCL, Prestwick Chemical, Illirick, France), a collection of 1,200 compounds, all of which are marketed off patent FDA-approved drugs and that have been selected for their high chemical and pharmacological diversity, for their known bioavailabilities, and for their safety in humans. The collection has a significant ion-channel and CNS component, notably ~20% of the compounds are CNS drugs with well annotated mechanisms of action. The PCL will be complemented with an equally sized second tier of compounds from the 1,280-compound LOPAC library (Sigma-Aldrich, St. Louis, MO). This collection contains pharmacologically active compounds, it also has a significant ion-channel and neurotransmission component.

Proposed One-Year and Long-Term Outcomes: Our primary screen lead to several positive hits that will be investigated further for specificity and potency. This cell-based high throughput assay for TREM2/TYROBP dependent signaling and agonist discovery program are aimed at laying the foundation for the detection of potent and selective compounds for future in vitro and in vivo development to prevent/halt AD progression and other forms of dementia. The experiments performed in this pilot study is anticipated to be the basis for several additional research studies, including: 1) *In vitro* and *in vivo* testing to confirm an increased A β clearance

and neurodegeneration associated with these agonists 2) Further HTS 3) Identified agonists may provide structural lead molecules for the development of new therapeutics. 4) Further blood-brain barrier passage profiling.

Overall, efficient targeting of the TREM2/TYROBP signaling pathway is expected to have application for improved clinical management across a broad range of neurodegenerative disorders. These studies will be the foundation for an R21 or R01 application that can focus on further compound screening/development and/or *in vitro* or *in vivo* assaying of promising compounds.

Year End Progress Summary:

Aim 1: We ran a primary screening at an assay concentration of 5 μ M for each of the 2,400 compounds [final 0.05% or 0.1% DMSO (v/v)] with two replicate screens with internal replicates. The reporter cell line was seeded in 384-well plates in DMEM and incubated at 37°C in a 5% CO₂ humidified atmosphere overnight, followed by compound treatment (together with positive control of 0.5 μ M Ionomycin and 10ng/ml Phorbol myristate acetate (PMA) and negative control of DMSO) for 8 h. Subsequently, *Luciferase* activity was measured using Bright-Glo™ (Promega, Madison, WI). Initial hits from the primary screen were defined as compounds that increase luciferase by 2-fold compared to the vehicle control (DMSO). This resulted in 27 compounds that can be defined as initial hits.

Aim 2: In addition to the reporter cell line, a BW-NFAT-Luc cell line has also been developed with the same MOI as the reporter (MOI = 20), but without expression of TREM2 or TYROBP. By induction of the NFAT-Luc cell line with the initial hits (27 compounds from AIM1), we can eliminate false positive compounds that directly stimulate NFAT signaling. Compounds that exhibit an EC₅₀ in the control cell line at least 10 times greater than the EC₅₀ of respective compounds on TREM2/TYROBP cells will be selected for further study. This suggests that these compounds have 10 times or more specific targeting to the TREM2/TYROBP signaling.

Project Progress Reports

University of Arizona

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Patient recruitment and outreach for Alzheimer's disease and related-disorders. Geoffrey Ahern, MD, 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 AD, 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 [see Literature Cited for selected recent publications (1-15,17)]. Geoffrey Ahern, M.D., Ph.D., 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, M.D. 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 past year's ACoSA meeting was Successful Aging: Reducing your Risk for Alzheimer's disease, and planning for the next conference is underway. Similarly, Dr. Rapcsak has given several lectures on Alzheimer's disease and related dementias at various community centers in the Tucson area.

Year End Progress Report: We have met our recruitment goals by 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 several individuals on the waiting list to join the study. We have continued with our outreach efforts to neurological colleagues, including the Neuromuscular Division at the University of Arizona in order to recruit individuals with FTD/ALS. Dr. Rapcsak has given 8 lectures on the topic of AD and dementia, including presentations at educational events sponsored by the Arizona Alzheimer's Association, Pima Council on Aging, Western Area Council of Governments/Yuma, Tucson VA Medical Center, Departments of Medicine/Family Practice University of Arizona, and an interview for NPR. Dr. Ahern gave invited lectures on "Dementia: Diagnosis and Treatment Options" at the 2015 Update on Psychiatry (2/18/2015) sponsored by the UA Department of Psychiatry. Our plans to project conclusion are to increase activities in all the areas listed above.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Risk factors for brain aging & preclinical Alzheimer's disease. Gene Alexander, PhD, G. Alex Hishaw, MD, Matthew Huentelman, PhD, David Raichlen, PhD, Ted Trouard, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims: This proposal requests support to conduct a multi-disciplinary research project with the goal of advancing our understanding of how common health-related factors in the elderly impact brain aging and the preclinical risk for Alzheimer's disease (AD). To accomplish this goal, we have a multi-disciplinary collaborative team of Arizona Alzheimer's Consortium (AAC) investigators, including researchers in the fields of neuropsychology, neurology, neuroimaging, neuroscience, genetics, biomedical engineering, and biological anthropology. This hypothesis-driven, research proposal will use "state-of-the-art" methods for testing human cognition, imaging of brain structure, function, and connectivity, genetics, and behavioral measures of lifestyle, physical activity, and sleep quality. This integrative approach will support efforts to investigate health-related factors, including hypertension and cerebrovascular risk, exercise/physical activity and sleep quality, and traumatic brain injury (TBI) on the neural systems supporting cognitive function during aging and their impact on the preclinical risk for AD. Our overall hypothesis is that the common health risk factors of hypertension and mild TBI, as well as the beneficial effects of exercise/physical activity and sleep influence brain aging and the preclinical 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. Further, we expect that these health factors will be affected by genetic variation related to the preclinical risk for AD.

In our proposed study, we plan to address the following primary specific aims: 1) to investigate how the health factors of hypertension, mild TBI, exercise/physical activity, and sleep quality affect brain structure, function, and connectivity in the elderly and 2) to determine how the effects of hypertension, mild TBI, exercise/physical activity, and sleep quality influence cognitive performance on measures sensitive to the early effects of cognitive aging and preclinical AD (i.e., memory, executive function, and processing speed).

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 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 preclinical 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 and increases the risk for cerebrovascular disease and AD. The occurrence of TBI represents another important health risk

factor in the elderly. Approximately 1.4 million people in the United States sustain a TBI annually and a large proportion of these patients are elderly, with 70% of TBIs being mild in severity. Importantly, the cognitive changes typically associated with aging reflect those cognitive domains that are often affected in mild TBI. Identifying the regional pattern of brain changes associated with cerebrovascular risk due to hypertension and mild TBI during brain aging represents an essential step toward distinguishing the effects of these risk factors from those of healthy cognitive aging and for developing interventions to enhance function and reduce risks for AD. In contrast to these health risks, exercise may help mitigate or improve cognition and brain function during the lifespan. Studies have shown that aerobic exercise can improve cognition during aging and may 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. In addition, the importance of sleep quality is an emerging area that may reflect an important factor influencing healthy aging and the risk for AD.

Preliminary Data: We previously reported patterns of MRI gray matter volume associated with healthy aging [Alexander et al., 2006, 2008; Bergfield et al., 2010] using a multivariate model of regional covariance, the scaled subprofile model (SSM) [Alexander and Moeller, 1994]. We found a pattern of gray matter related to APOE $\epsilon 4$ in young to early middle aged adults, suggesting longstanding brain morphological differences related to this genetic risk for AD [Alexander et al., 2012]. Preliminary results from 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 the brain. Using Freesurfer to measure cortical volume, thickness, and area, we found a pattern of gray matter reduction associated with increasing age (Monte Carlo corrected, $p < 0.05$). Further, we recently found that, after controlling for age, greater regional gray matter volume and area, but not thickness was related to higher levels of aerobic fitness in healthy older adults (Monte Carlo corrected, $p < 0.05$). Together, these findings support the use of MRI to evaluate health and genetic risk factors for preclinical AD. In addition, we proposed a new hypothesis that was featured on the cover of Trends in Neurosciences, suggesting demands for physical activity supported the evolution of the human lifespan and healthy brain aging [Raichlen and Alexander, 2014], helping to show how exercise may prevent AD and cognitive aging.

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 hypertension and exercise/physical activity on brain structure, function, and connectivity, as well as associations with cognitive performance. In addition, this work will be leveraged to support a complementary effort to investigate the effects of TBI on brain structure, function, and connectivity. These studies reflect collaborations focused on developing externally funded grant proposals to investigate how cerebrovascular risk factors, differing levels of aerobic fitness, and TBI impact brain aging and the preclinical risk for AD. The proposed research will provide novel and rich datasets with which to publish findings that will advance our understanding of the brain changes associated with multiple health-related factors that may either enhance or diminish the risk for dementia and age-related cognitive decline. It is expected that this dataset will provide essential pilot data to support new applications for external funding to NIH, NSF, and other funding sources. Specifically, this project will provide key data and methodological developments to support pending and planned grant applications by the project investigators, including

applications to investigate the effects of differences in exercise/physical activity and sleep quality on brain aging and cognitive function, and to evaluate how hypertension and other cerebrovascular risk factors interact with genetic risk for preclinical AD to affect brain aging and cognitive decline. In addition, we plan to continue our ACoSA and SAHAR to provide for enhanced community outreach, education, and subject recruitment in support of 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: Over the past year, we have made significant progress in our studies on the influence of individual differences in risk factors and lifestyle characteristics for brain aging and preclinical AD. Analysis from our healthy aging cohort investigated the relation of mild subjective memory complaints in older adults, 70 to 89 years of age to hypertension status. In this study, an interaction was observed with poorer memory performance in those with mild complaints and hypertension compared to non-complaining hypertensives. Importantly, among non-hypertensive elderly in the cohort, no relationship with mild memory complaints was found. Together, these findings suggest that in the context of treated hypertension, even mild memory concerns may be an important indicator of cognitive differences and risk for decline during aging. A manuscript from this work has been published (Nguyen et al., 2015). In addition, a study of ambulatory blood pressure in this healthy elderly cohort revealed that those not showing the typical 10-15% nocturnal dip in blood pressure demonstrate greater cognitive difficulties and that the combination of hypertension with nocturnal non-dipping blood pressure was associated with poorer cognitive performance than the other groups. This finding suggests that nocturnal variation in blood pressure may be an important factor influencing cognitive decline during aging. A manuscript of these findings is under review for publication (Haws et al., invited revision). To evaluate the effects of hypertension and its associated risk for cognitive decline to brain structure, we have begun to implement and test automated methods to measure volumes of white matter lesions in MRI. Currently, there are no widely used or accepted methods to evaluate this important brain biomarker of vascular disease. Work currently underway in this project shows promise in the use of automated lesion segmentation methods optimized for our healthy aging cohort to measure the volume of MRI white matter hyperintensities in comparison to those measured using manual segmentation with consensus by an expert rater. Preliminary results of this work was presented at Society for Neuroscience meeting and a manuscript is being prepared for submission (Bharadwaj et al., in preparation). Further, we have begun to apply this approach to our entire older adult cohort to evaluate its relation to tests of cognition and other brain markers to white matter lesions in aging. The human hypertension studies have been extended to a translational research study with a transgenic rodent model of hypertension in a funded NIH R01 grant (Multiple PIs: Alexander, Barnes, Coleman). This five-year study with AAC collaborators, which is now underway, will use “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. In support of this work, a manuscript showing the first demonstration of a regional network gray matter covariance pattern in rodent brain MRI at 7.0T was submitted (Alexander et al., submitted), supporting the use of such 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 study is currently underway and reflects ongoing collaborations between the University of Arizona, the University of Florida, the

University of Alabama, and the University of Miami. We have now expanded this multi-site effort with a new proposal that was funded this year 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). In addition, this work has led to a new collaborative NIH R01 grant that was submitted this year by the University of Florida, University of Miami, and the University of Arizona to evaluate ways to enhance the benefits of cognitive training in older adults (PIs: Cohen, Woods, Wright, Alexander). Efforts continue by Dr. Hishaw (Co-I) in the recruitment of older adults with mild traumatic brain injury from the University of Arizona Emergency Department. This work will focus on comparing participants with our healthy older adults cohort to evaluate the effects brain injury in the context of healthy aging.

During this past year, Drs. Alexander and Raichlen further developed and refined a novel exercise training method for applications in cognitive aging and the risk for AD. With expanded complementary support from both a Bio5 Fellowship grant (Multiple PIs: Alexander, Raichlen) and a Tech Launch Arizona Wheelhouse Proof of Concept grant (Multiple PIs: Alexander, Raichlen), we have launched an initial intervention study, which is underway. We plan to submit new NIH and NSF grant proposals to expand on our very encouraging findings with exercise and brain aging during the coming months. In addition, Dr. Alexander established an ongoing collaboration with Dr. Phil Kuo in Medical Imaging at the University of Arizona, serving as a co-investigator on a funded NIH R42 grant (PI: Zubal, UA Subcontract PI: Kuo) to help develop and test an automated method for the analysis and detection of amyloid deposition using positron emission tomography (PET). A new collaborative NIH R42 grant with Drs. Kuo, Zubal, and Alexander to extend this work has been submitted. This collaborative work has led to a new NIH R42 grant proposal that has been submitted this year to apply this and related methods for the analysis of PET amyloid imaging (PI: Zubal, UA Subcontract: Kuo, Alexander). Dr. Alexander also established a new collaboration with Dr. Judith Su in the Departments of Optical Sciences and Chemistry and Biochemistry at the University of Arizona to apply a new technology developed by Dr. Su to evaluate AD-related blood and cerebrospinal fluid biomarkers. This work includes a collaboration with Dr. Beach of Arizona ADC Pathology Core and a new NIH R03 grant on this work has been submitted (PI: Su; Co-Is: Alexander, Beach).

Drs. Alexander and Ryan continued to lead the implementation of our Annual Conference on Successful Aging (ACoSA), providing members of the Tucson-metro area community with up to date information and new research findings on ways to enhance and support cognitive functions as we age. Our fourth annual conference occurred in March, 2016 with the topic of “How Technology is Changing the Face of Aging”. The conference for this year was very successful and plans for our next year’s conference are currently underway.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Memory, executive function, and prospective memory training. Elizabeth Glisky, PhD, Gene Alexander, PhD, AJ Figuerdo, PhD, Meredith Hay, PhD, Lee Ryan, PhD, Nancy Sweitzer, MD, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Project Description: This project involves three different sub-projects each of which has involved or will involve the collection and analysis of neurocognitive data from three different groups of older adults. The first project involves longitudinal data that have tracked cognitive changes in memory and executive function over several years and several time points in normally-aging older adults. The second project involves cross-sectional data, comparing older and younger adults on a battery of executive function tests. The data for these two projects have been largely collected, and so the work will involve a series of statistical analyses, including factor analysis, regression analyses, hierarchical growth curve analyses, etc. The third project, in collaboration with Ryan, Hay, and Sweitzer (described in a separate proposal), involves prospective memory training in older adults with heart failure. This project will also involve data collection of pre- and post-intervention measures of memory and executive function.

Specific Aim1: To document and account for individual differences in memory and executive function in older adults and in the changes that occur over time, and to identify variables that are associated with abnormal aging, normal aging, and super aging.

Specific Aim 2: To validate an executive function battery in older adults consisting of 6 different tests, two from each of 3 different executive functions—shifting, updating, and inhibition—and compare to young adults.

Specific Aim 3: To determine the effectiveness of prospective memory training in heart failure patients following the administration of Angiotensin 1-7.

Background and Significance:

Aim 1. Recent theoretical views, bolstered by fMRI findings, suggest that memory is determined jointly by processes associated with frontal and medial temporal brain regions. There are as yet few studies, however, that have looked at changes in these two neurocognitive functions together in a longitudinal study of older adults. We have collected longitudinal data on 311 participants over the age of 65, tracking two independent composite measures of executive and memory function over time. At the same time we have collected data on several other variables that might moderate or mediate change trajectories, including all of the standard demographic variables, as well as APOE status and DTI imaging on a subset of these individuals. Although static cognitive measurements have for the most part not been able to discriminate between normally-aging individuals and those who may be in the prodromal phases of MCI or AD, changes in cognitive function over time may be more sensitive and could provide an early indicator of AD.

Aim 2. We have also been collecting data from both young and older adults on three different components of executive function: shifting, updating, and inhibition. It is now apparent that executive function is not a unitary construct and that different aspects of executive function may be differentially sensitive to normal and/or pathological aging. Factor analysis and structural equation modeling have suggested that these three executive functions are independent although

correlated in young adults (Miyake et al., 2000). Using a subset of the tests proposed by Miyake, we have collected data on 200 older adults along with a sample of young adults, with the intention of validating a small battery of executive function tests that may be differentially sensitive to decline in older adults.

Aim 3. Cognitive impairment, particularly in memory, is a common complaint in heart failure patients, and may be a significant contributor to medication non-compliance and repeated hospitalizations. Remembering to take medications requires prospective memory, i.e., remembering to do things in the future, and there have been relatively few intervention studies that have focused on improving prospective memory in memory-impaired populations, and none in heart failure patients.

Preliminary Data: In the longitudinal study, we have data on 311 older adults with at least two time points, and 162 older adults with three or more time points for a total of 887 observations on each of the composite measures of memory and executive function. For the executive function battery, we have data on 200 older adults over the age of 60, and will also have 100 younger adults.

Proposed One-Year and Long-Term Outcomes: The one-year goals for the first two projects are to get the data analyzed and papers written and submitted for publication. The goal for the third project is to gather sufficient pilot data to support submission of a federal grant.

Year End Progress Report:

Aim 1. The data from the longitudinal study have been cleaned, collated, and organized and preliminary analyses have begun, and will continue. We hope to have those analyses completed within the spring semester.

Aim 2. Executive function data from three labs have been merged and cleaned, yielding a complete data sample for 152 older adults and 100 young adults. Confirmatory factor analyses have been completed, yielding a pattern not completely consistent with the Miyake findings in young people, and with interesting differences between younger and older adults. These findings will be written up for publication this spring.

Aim 3. The prospective memory training protocol for heart failure patients is still in development stages. The protocol will be part of a larger grant proposal for a clinical trial looking at the combined effects on cardiac function of Angiotensin 1-7 targeting inflammation and the prospective memory training targeting medication compliance. The prospective memory training will be piloted in a small group of heart failure patients starting this spring. An R21 grant proposal has been submitted to support this pilot study.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Angiotensin (1-7) treatment to improve cognitive functioning in heart failure patients. Lee Ryan, PhD, Meredith Hay, PhD, Elizabeth Glisky, PhD, Nancy Sweitzer, MD, PhD, John Konhilas, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Project Description: Heart failure (HF) is the major cardiovascular disease that continues to grow in prevalence, largely due to aging of the population. Cognitive impairment is common in HF patients, with age-adjusted performance in spatial and memory tasks particularly impaired. Cognitive impairment is associated with medication non-compliance, poor self-care, recurrent hospitalization, poor physical recovery after medical events, higher mortality, and a significantly increased risk of developing dementia, particularly Alzheimer's disease. In the few studies to date that have examined brain function in HF patients, multiple mechanisms have been implicated, including cerebral blood flow, microembolization, and inflammation. Using a cohort of stable older HF patients with moderate HF, we propose a randomized, placebo-controlled 2X2 factorial trial of 2 interventions designed to improve cognitive performance in a group of HF patients: a memory training intervention shown to improve prospective memory performance in healthy older adults, and Angiotensin (1-7) (Ang 1-7) treatment that targets the inflammatory cascades that impair cognitive performance in animal models of HF. Recent work by our group has shown that Ang 1-7 can inhibit production of reactive oxygen species, increase nitric oxide synthase production and reduce inflammatory cytokines in the brain, microvasculature and peripheral tissue via activation of the Mas receptor. Because the Mas receptor is found in high quantities within the hippocampus and perirhinal cortex, Ang 1-7 may be particularly effective in targeting memory impairments associated with heart failure or other disorders that result in damage to medial temporal lobe structures.

Data obtained from this project will be used to support submission of an RO1 proposal for a larger randomized, placebo-controlled study to determine the efficacy of Ang 1-7 in patients with heart failure as well as healthy older adults.

Specific Aims:

Aim 1: To conduct a pilot study to evaluate the safety and efficacy of Ang 1-7 to enhance cognitive function in participants with mild to moderate heart failure.

Aim 2: To determine the impact of Ang 1-7 on inflammatory markers and neuroimaging measures in participants with mild to moderate heart failure.

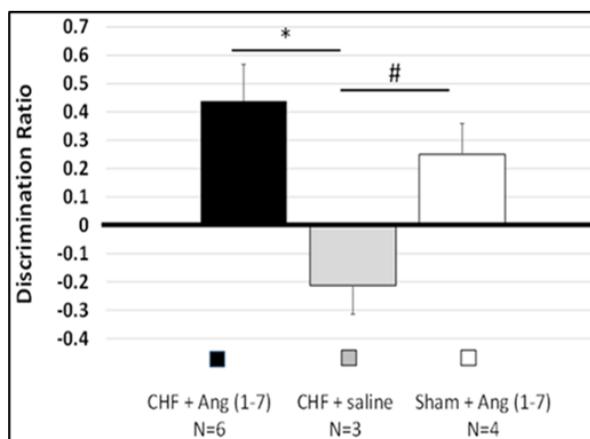
Background and Significance: Heart failure (HF) is a chronic, progressive disease associated with gradual increases in disability and ultimately death in most cases. HF disproportionately occurs in older adults.¹⁰ The pharmacologic regimen prescribed to most patients is complex, involves significant polypharmacy, and is challenging for even the most sophisticated patients. It is not surprising, then, that cognitive impairment, a common comorbidity among HF patients, impacts disease course.⁵ It is estimated that 25-85% of people with HF experience more cognitive impairment than healthy persons of similar age, with variation related to differences in factors between studies such as age and the severity of cardiac dysfunction.^{11,12} Cognitive impairment is associated with poor clinical outcomes in HF patients.¹³ Patients with HF and cognitive impairment show decreased ability to monitor symptoms and carry out self-care activities essential to management of their disease, leading to worsening clinical symptoms, more hospitalizations, higher mortality rates, and poorer medication adherence. In older adults (ages

60 or older) with HF, cognitive impairment is more prominent compared to age-matched controls, and these individuals experience faster age-related memory decline. Mechanisms thought to contribute to CI in patients with HF include changes in cerebral blood flow (CBF), altered cerebrovascular autoregulation, microembolism⁸, and inflammation. There is substantial evidence linking increases in systemic inflammation to impairment in cognitive function. Studies in patients have shown that increases in inflammatory factors such as IL-1 and IL-6 following surgery are strongly correlated with a decrease in cognitive performance

Thus, there is an important clinical need for a safe and effective therapy for the treatment of cognitive impairment in patients with heart failure. The peptide *Angiotensin-(1-7)* is known to decrease brain ROS production and inflammation in pre-clinical models²¹ and is known to be safe in preliminary studies in humans²². Ang-(1-7) is an endogenous peptide hormone of the renin-angiotensin system with endogenous receptors known to be located in brain regions involved in memory. The renin angiotensin system involves two separate enzymatic pathways that provide a physiological counterbalance of two related peptides acting at distinct receptors. The well described Angiotensin converting enzyme (ACE) -AngII-Angiotensin receptor, Type 1(AT1R) system is thought to be physiologically opposed and balanced by the ACE2-Ang-(1-7)-Mas receptor system. In the brain and other tissues, Ang II activation of AT1 receptors increases ROS and inflammation while Ang-(1-7) and Mas receptor activation decrease ROS and inflammation.

Medication compliance requires a particular kind of memory ability referred to as prospective memory — remembering to do things in the future. Despite its importance in everyday life and its role in medication adherence, there are relatively few intervention studies focused on improving prospective memory in individuals with memory impairment,²⁶ and no studies have been conducted with HF patients. The memory training intervention proposed here utilizes a self-imagination strategy that successfully improves memory for words, word pairs and sentences in memory impaired individuals.²⁷⁻²⁹

Preliminary Data: Studies in our laboratories have shown that Ang 1-7 reverses HF-induced memory impairment in an animal model of heart failure. In these studies, myocardial infarction (MI) was induced in male C57Bl/6J mice by ligation of the left main coronary artery (HF group). A sham control group (n=4) had similar surgery but no coronary ligation. At 8 weeks post MI, a subgroup from the HF group and the sham group were given 1.2 mg/kg/day Ang 1-7 (n=6) or saline (n=3) subcutaneously for 4 weeks. Following 3 weeks of treatment with Ang 1-7, HF mice performed similarly to sham control animals on a novel object recognition task, and significantly better than the HF mice treated with saline (see graph above).



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 support submission of an RO1 to fund a large-scale clinical trial of Ang 1-7 in heart failure patients and healthy older adults.

Year End Progress Report: We have made good progress towards completing several key steps that will allow us to carry out a larger treatment trial. Drug stability testing, a requirement for FDA approval, has been completed to 7 days and 30 days. The IND for Ang1-7 was approved by the FDA in August 2015 to treat cognitive impairment in cardiac bypass surgery

patients (IND 125320). The FDA has agreed that this IND can be amended to include MCI in patients with and without heart failure, based on work completed during this project. By June 30th, we anticipate collection of full data from 5 HF patients and 10 age-matched control participants. Neuropsychological testing and inflammatory biomarkers will be available from an additional 10 HF patients.

Preliminary data from the project has already resulted in two major donations from the Gooter Foundation (\$25,000) and an anonymous donor (\$15,000), which has significantly enhanced our ability to complete the proposed study. We intend to submit an RO1 for a larger randomized, placebo-controlled study to determine the efficacy of Ang 1-7 in patients with heart failure as well as healthy older adults in September 2016.

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Enhanced delivery of therapy to the brain in mice. Ted Trouard, PhD, Marek Romanowski, PhD, Terry Matsunaga, PhD, Robert Erickson, MD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: The ability to deliver therapeutic drugs to the brain is often hindered by the blood brain barrier (BBB) and, because of this, therapies that work in cell cultures often do not provide benefit in humans. A relatively new technology that uses focused ultrasound (FUS) in conjunction with magnetic resonance imaging (MRI) guidance (referred to as **Magnetic Resonance-guided Focused Ultrasound, MRgFUS**), has potential to address this problem. When used in conjunction with FDA-approved **microbubble (μB)** ultrasound contrast agents, MRgFUS has been shown to be able temporarily make the BBB permeable to drugs in the vascular system. In this one-year project, we propose to refine the method of delivering drugs to the brains of mice to establish the safety and efficacy of the technique. We will also continue development of a new nanoparticle drug delivery system that should allow more efficient delivery of drugs to the brain while minimizing their exposure to peripheral organs.

Aim 1. Develop and evaluate MRgFUS for the delivery of drug in mice. We will optimize techniques to locally, temporarily, and reliably open the BBB in mice using MRgFUS. MRI will be used to evaluate the BBB opening to contrast agents. High resolution computed tomography (CT) and single photon emission computed tomography (SPECT) will be used, as well as fluorescence microscopy of labeled molecules.

Aim 2. Synthesize and evaluate liposome- μB nanoparticles for enhancing the delivery of therapy to the brain. Liposomes that can be internally loaded with therapeutics, e.g. cyclodextrin, will be conjugated to the lipid monolayer of μBs . These liposome- μB nanoparticles will then be used in the MRgFUS experiments to deliver therapy to the brain.

Background and Significance: The effectiveness of drugs for treating neurological diseases is continually hindered by the inability of drugs to cross the blood brain barrier (BBB) and unless significant advancements are made to safely deliver drugs to the brain, drug development for neurological disease will remain limited [1,2]. Existing techniques for circumventing the BBB have had limited success. Intraventricular infusion is a poor method of delivering drugs to the brain because it requires skull penetration and introduces the risk of infection. In addition, drugs are rapidly cleared by the CSF and diffusion of drugs into tissue can be minimal [4]. MRgFUS techniques use focused ultrasound (FUS) in combination with FDA-approved intravascular microbubble (μB) contrast agents to locally and temporarily open the BBB to intravenous drugs [5]. In combination with magnetic resonance imaging (MRI), local regions of FUS delivery can be accurately determined so that drug delivery to specific brain regions can be achieved.

Preliminary Data: Over the last year, we have developed the capability to carry out MRgFUS in mice to deliver drugs to the brain. We have designed and built an MRI compatible FUS system in collaboration with Synergy Electronics (Tempe, AZ) that fits within the bore of our 7T small-animal MRI magnet and will allow targeting and monitoring of the delivery of FUS and the opening of the BBB. Bench top experiments have been carried out that demonstrate the ability of the FUS system and the MRgFUS technique to safely and consistently open the BBB in mice

and monitor the opening to MRI contrast agent. We have also miniaturized the system to work within the 7T magnet.

We have also initiated development of more efficient drug delivery systems to be used in MRgFUS. In our initial work in this area, we have developed the facilities and techniques necessary to fabricate liposome- μ B nanoparticles. Their structure has been verified by microscopy and we have utilized them in preliminary MRgFUS experiments in mice.

An R01 grant was submitted in February of 2015 and will be reviewed in June of 2015. The work in this proposal will serve to support this application.

Proposed One-Year and Long-Term Outcomes: The μ B-liposome complexes as well as the in vivo SPECT imaging of the kinetics and distribution of drugs delivered to the brain are very novel and innovative and will be the focus of at least one manuscript. A grant has been submitted to the NIH and we expect that the data obtained from this project will support a potential resubmission

Year End Progress Summary:

Aim 1: All of the FUS parameters involved in successful BBB opening in the mice have been determined and are included as preliminary data in an NIH R01 grant submission on this research. We have also characterized the opening of the BBB to different molecular weight contrast agents, in preparation for the therapeutic studies that are included in the R01. The SPECT systems that we planned to use in this aim were not operational and we therefore switch to fluorescence microscopy to determine the distribution of delivered drugs into the brain. This work is also being written up for publication.

Aim 2: We have made great progress on development of a new nanoparticle for drug delivery using FUS. We have shown that the lipobubble is successful in opening the BBB and are in the process of characterizing the drug delivery through this new particle. In addition to the proposed lipobubble agent, we have designed and generated a novel lipodroplet, which has a smaller size and is more stable in the vasculature. We submitted an invention disclosure for this new particle (UA 15-034) and the University of Arizona is pursuing a patent on it (62/257,986, filing date 11/20/2015).

ARIZONA ALZHEIMER'S CONSORTIUM

2015-2016 Scientific Progress Report

Validity and reproducibility of functional maps derived from naturalistic audiovisual stimuli. Stephen M. Wilson, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims: The specific aim of this project is to evaluate the validity and reproducibility of a naturalistic functional MRI protocol for rapid mapping of multiple functional areas in individual human subjects.

Background and Significance: Functional magnetic resonance imaging (fMRI) is widely used to evaluate the functionality of cortical and subcortical brain regions in numerous clinical populations (e.g. neurodegenerative disease, stroke, multiple sclerosis, etc.) as well as in healthy volunteers. There are two predominant approaches to experimental design. In one approach—task-based fMRI—patients are asked to perform a task (e.g. name pictures), and neural responses related to the task are identified. In the other approach—resting state fMRI—patients are asked to lie at rest, and the functional connectivity between different brain regions is investigated by identifying correlated patterns of activity. Recently a third approach has been developed, which we will refer to as naturalistic fMRI (Hasson et al., 2004; Bartels and Zeki, 2005; Wilson et al., 2008; Nishimoto et al., 2011; Hanke et al., 2014). In this new approach, patients are presented with naturalistic audiovisual stimuli, such as scenes from movies, and the resultant patterns of activity across multiple brain regions are identified and analyzed.

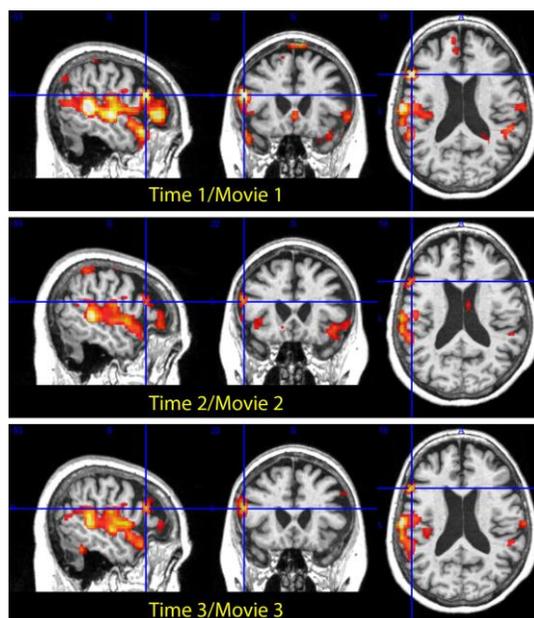
To date, the naturalistic fMRI approach has been investigated in healthy volunteers. However the approach holds great promise as a tool for investigating brain function in clinical populations, because it offers several distinct advantages over the other two approaches. First, since patients are not required to perform a task, naturalistic paradigms will be more appropriate for severely impaired patients. Second, because naturalistic stimuli modulate numerous functional networks in a predictable way (i.e. auditory, visual, social, emotional, etc.), multiple functional domains can be mapped based on a single functional scan. Third, naturalistic stimuli offer the same ability to map functionally connected networks as resting state fMRI, but with the added advantage that the specific functions of the networks identified can be determined because the input is controlled. In short, naturalistic protocols make less demands on patients than task-based fMRI, and potentially provide richer information about brain function than either task-based or resting state fMRI.

A prerequisite to using naturalistic fMRI to map functional regions in clinical populations is to determine whether maps derived from naturalistic fMRI resemble those generated by task-based fMRI, and to quantify the reproducibility of the generated maps.

Preliminary Data: In order to investigate the reproducibility of functional maps derived from naturalistic fMRI, we created three comparable movies, each 7 minutes long. The movies were constructed by editing three different episodes of the same TV program, so as to create three coherent storylines of exactly 7 minutes each, with equal proportions of time with and without language, and with content appropriate for clinical populations (i.e. the general public).

A 73-year-old healthy female volunteer was scanned with functional MRI while viewing each of the three movies on three separate occasions (one movie per session). In our initial analysis, we identified regions that showed signal change (reflecting neural activity) for those parts of the movies that contained language, after factoring out auditory-related activity. The figure shows three maps of this subject's language network, obtained during the three sessions, each with a different movie.

It can be seen that very similar language regions were identified on each of the three occasions, suggesting excellent reproducibility in this single subject. The language regions were left lateralized as expected, and were localized to frontal and temporal regions adjacent to the Sylvian fissure as expected.



Proposed One-Year and Long-Term Outcomes: At the end of the budget period (one year), we will have quantified the validity and reproducibility of functional mapping using the proposed method.

The P.I. is currently carrying out an NIH-funded longitudinal study of neuroimaging correlates of recovery from aphasia after acute stroke, using a traditional task-based fMRI protocol (R01 DC013270). If a naturalistic protocol can be shown to be superior to a traditional task-based protocol for mapping language regions, as we hypothesize, this would be a compelling innovation to contribute to competitive renewal of this project in 2019.

Year End Progress Report: Five neurologically normal older adults were scanned on each of the four paradigms on four separate occasions. Validity was assessed in terms of whether activation patterns reflected the known typical organization of language regions, that is, lateralization to the left hemisphere, and involvement of the left inferior frontal gyrus and the left middle and/or superior temporal gyri. Reliability (test-retest reproducibility) was quantified in terms of the Dice coefficient of similarity, which measures overlap of activations across time points. We explored the impact of different absolute and relative voxelwise thresholds, a range of cluster size cutoffs, and limitation of analyses to a priori potential language regions.

We found that the naturalistic paradigm resulted in highly reproducible activation patterns (Dice coefficient of similarity = 0.50, indicating 50% overlap between activation maps on separate occasions). However the laterality index was only 0.20 indicating that the paradigm tends to show somewhat bilateral activation patterns (whereas we know language to be left-lateralized in most individuals). Sensitivity was 75% for frontal regions and 100% for temporal regions.

The naturalistic paradigm did not perform quite as well as some other paradigms that were investigated, specifically narrative comprehension or sentence completion. However the naturalistic paradigm affords opportunities for further analyses that we will now undertake, e.g. looking at connectivity patterns, and looking at intersubject correlations.

The findings from this project are reported in a manuscript submitted for publication, which has been reviewed, revised, and resubmitted (Wilson et al., submitted).

2015– 2016
Publications, Manuscripts,
& Grants

2015 Publications and Manuscripts

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Current and Pending Grants

Current Grants

R01 Grant, R01 AG028084: from National Institute on Aging

PI: Heather Bimonte-Nelson, Variations in hormones during menopause: effects on cognitive and brain aging. Active 10/01/07 - 5/31/18.

National Science Foundation (NSF) Graduate Research Fellowship:

Co-mentors: Bimonte-Nelson and Rachael Sirianni (Barrow Neurological Institute),

Student: Alesia Prakapenka,

Development of targeted delivery of estrogen to examine its effect on cognitive function.

K01AG037562,

PI: Ann Cohen, Mentor: William Klunk,

Collaborator: Heather Bimonte-Nelson. (Training K recipient on maze testing).

National Institute on Aging.

Effects of environmental enrichment on cognitive survival: Role of A β & metabolism.

Active 07/11-6/16.

Alzheimer's Disease Core Center (Arizona),

State of Arizona (ADHS14-052688) and NIH (5P30AG019610-13):

PI: Heather Bimonte-Nelson.

Pulses of estrogen as a transient hormone therapy in young versus old age.

Active 7/15-6/16.

Mayo Clinic Arizona:

ASU PI: Rosa Krajmalnik-Brown, ASU Co-Inv: Heather Bimonte-Nelson.

Mayo PI: Julia Files, Mayo Co-Inv: Anita Mayer.

The influence of estrogen on the rat gut microbiome.

Active 8/1/2015 - 12/31/2015.

ASU-Mayo Seed Grant (Brafman)

01/2016-12/31/2017

Using human induced pluripotent stem cells (hiPSCs) to investigate the contribution of APOE genotype to Alzheimer's disease risk.

Role: PI

NIH 1R21EB020767 (Brafman)

07/01/2016- 06/30/2018

Synthetic substrates for the expansion and differentiation of hPSC-derived NPCs

Role: PI

028344-001 (Coon & McCarthy) 08/01/14 – 06/30/15 (no cost extension) 1.20 calendar

Phoenix Symphony \$100,568

Music Performance & Music Therapy: An Interprofessional Partnership in Dementia Care.

Role: Site PI

FP3247 (Kennedy) HHS-HRSA Empowering Caregiver Self-Care. Role: Co-Investigator	07/01/15 – 06/30/18 \$200,000	.55 calendar
14020255 (Besst) U.S. Administration on Aging Creating and Sustaining Dementia-Capable Service Systems for People with Dementia and their Family Caregivers. Role: Site PI	07/01/15 – 06/30/17 \$251,572	.80 calendar
13074706 (Mahoney & Burleson) National Institute for Nursing Research Technology In-home Intervention to Sustain Dementia Patients. Role: Co-Investigator	04/03/14 – 02/28/16 \$211,746	.60 calendar
14092421 (Reiman) NIA - Arizona Alzheimer's Disease Center Outreach, Recruitment and Education Core ORE Core Leader for the Arizona Alzheimer's Disease Consortium fostering education, outreach and recruitment, particularly of diverse participants into the clinical core. Role: ORE Core Leader	07/01/2015 - 6/30/2016 \$71,153	.48 calendar
FP0243 (Carvajal) Centers for Disease Control Arizona Healthy Brain Initiative Collaborating Center Role: Site PI	09/30/14 – 09/29/19 \$61,865	1.24 calendar
FP4307 (Doucet) U.S. Administration on Living/U.S. Admin on Aging Nevada's ACL: Dementia Capability for Persons with Alzheimer's disease and Related Dementias Role: Site PI	09/01/14 – 08/30/17 \$15,000	.60 calendar
FP4310 (Najafi & Mohler) Flinn Foundation Promoting Translational Research in Precision Medicine: Arizona Aging & Cognition Collaboration Project. Role: Co-Investigator		
Project #: 1R01AG037637-01 NIH – National Institute on Aging Molecular interplay between Abeta, tau and mTOR: Mechanisms of neurodegeneration Period: 08/2011 - 05/2016 Role: Principal Investigator Total Costs: \$1,527,250.00		

Alzheimer's Drug Discovery Foundation
Reducing mTOR activity as a treatment for Alzheimer's disease
Period: 08/2013 - 03/2016 –Under no cost extension
Role: Principal Investigator
Total Costs: \$242,000

Arizona Alzheimer's Consortium
Dissecting the role of tau in the adult mouse brain
Period: 07/2015 - 06/2016
Role: Principal investigator
Total Direct Costs: \$40,000

Alzheimer's Drug Discovery Foundation
Development of selective DYRK1A inhibitors as a treatment for Alzheimer's disease
Period: 11/2014 - 10/2016
Role: Collaborator (PI –Travis Dunckley)
Total Direct Costs for Oddo's laboratory: \$120,000

PO 294145 (Coleman,Paul David) 7/1/2015-3/31/2016 Cal: 2.4
UNIV OF AZ \$282,998.00 Acad: 0
Epigenetic Neuroimaging Behavioral Effects of Hypertension in the Aging Brain Sumr: 0

FP00004649 - OAF (Decourt,Boris) 1/1/2016-3/31/2016 Cal: 6
HHS-NIH \$0.00 Acad: 0
Pre-clinical Testing of Lenalidomide as Pleiotropic Therapeutics of Alzheimer's Disease
Sumr: 0

ADHS16-104646 (Mastroeni,Diego Fernando) 7/1/2015-10/22/2016 Cal: 0
ABRC \$107,739.00 Acad: 0
A Novel Compound to Protect Mitochondria against Oligomeric Abeta Toxicity Implications for
the Synapses Sumr: 0

(Mastroeni,Diego Fernando)
Alzheimer's Association
Alzheimers Association, Profiling the glia-ome in Alzheimers disease

CH 09/30/15 (Oddo,Salvatore) 7/1/2015-6/30/2016 Cal: 1.35
Arizona Alzheimer's Disease Consortium \$21,000.00 Acad: 0
FY16: Arizona Alzheimer's Consortium Sumr: 0

OAF 10/29/15 (Oddo,Salvatore)
9/1/2015-9/27/2016 Cal: 0
ASU FDN (Banner Sun Health Research Institute) \$28,059.00 Acad: 0
Reducing mTOR activity as a treatment for Alzheimers disease Sumr: 0.682

OAF 9/17/15 (Oddo,Salvatore)
9/1/2015-2/28/2016 Cal: 3.15
HHS-NIH \$53,749.00 Acad: 0
Molecular Interplay Between Abeta Tau and mTOR: Mechanisms of Neurodegeneration
Sumr: 0

FP00005256 (Talboom,Joshua S) 7/1/2016-6/30/2018 Cal: 0.948
ASU Foundation (BrightFocus Foundation) \$49,671.00 Acad: 0
Mechanisms of cognitive deficits in Alzheimer s disease Sumr: 0

FP00005583 (Walker,Douglas Gordon) 7/1/2015-6/30/2016 Cal: 0.6
Banner Sun \$19,240.00 Acad: 0
Alzheimer's Disease Core Center Consortium (ADCC Consortium) Sumr: 0

Sabbagh MN (PI) 10/23/14-10/22/17
ADHS14-00003606 \$223,816 Annual DC
Arizona Biomedical Research Commission
Longitudinal Assessment of Florbetapir FET, FDG PET, and MRI in Down Syndrome

Mufson, E.J. (PI) 12/01/2014 – 1/31/2019
PO1AG14449 \$341,627.79 (DC)
Neurobiology of Mild Cognitive Impairment in the Elderly

Mufson, E.J. (PI) \$538,953.78 (DC)
RO1AG43775 1/15/2015 – 5/31/2018
Cellular and Molecular Medial Temporal lobe pathology in elderly with PreMCI

Mufson, E.J. (PI) 07/01/2015 – 6/30/2018
Barrow and Beyond \$50,000 (DC)
Genetic signature of cortical neurons in sporadic AD

Mufson, EJ (site PI) 9/30/2014 – 8/31/2019
Cifu, D. (PI, Virginia Commonwealth University) \$594,745.46 (DC)
Department of Defense
PT108802-SC106187
Chronic Effects of Neurotrauma

Han, Peng Cheng (PI) 2013-2015
BNI-UA-Phoenix Joint Translation Neuroscience \$50,000 (DC)
PACAP deficit in AD.

Shi, Jiong (PI) 2009-2015
Eli Lilly \$510,036 (TC)
Effect of LY2062430, an Anti-Amyloid Beta Monoclonal Antibody, on the Progression of
Alzheimer’s Disease as Compared with Placebo (H8A-MC-LZAM).

Shi, Jiong (PI) Avanir Pharmaceuticals, Inc A Prospective, Open-label Study to Assess the Safety and Efficacy of Nuedexta (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect (PBA) in Patients with Alzheimer's Disease.	2013-2015 \$180,000 (TC)
Shi, Jiong (PI) Merck & Co. 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).	2014-2016 \$460,500 (TC)
Shi, Jiong (PI) GE Healthcare A Principal Open-label Study to Assess the Prognostic Usefulness of Flutemetamol (18F) Injection for Identifying Subjects with Amnesic Mild Cognitive Impairment Who Will Convert to Probable Alzheimer's Disease.	2010-2015 \$86,437 (TC)
Shi, Jiong (PI) Navidea Biopharmaceuticals A Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of [18F] AZD4694 PET in the Detection of Beta Amyloid in Subjects with Probable Alzheimer's Disease, Older Healthy Volunteers, and Young Healthy Volunteers.	2012-2015 \$307,625 (TC)
Department of Defense (Baxter PI) W81XWH-14-ARP-IDA "Cognitive and Neural Correlates of Aging in Autism Spectrum Disorder"	6/01/2015 – 5/30/2018 \$358,757 (DC)
Baxter, Leslie (PI) Institute for Mental Health Research "Depression and anxiety in the aging autism spectrum disorders cohort"	7/1/15-8/1/16 \$20,000 (DC)
Baxter, Leslie (co-PI; Theodore BNI PI; Sierkes PI) Oligomeric Neuronal Protein Aggregates as Biomarkers for Traumatic Brain Injury (TBI) and Alzheimer's disease (AD)	9/25/12-6/24/15 \$339,424 27,999 (BNI: DC)
Baxter, Leslie (co-PI; Reiman PI) NIA AG019610 Arizona Alzheimer's Disease Core Center	07/01/11 – 06/30/16 \$53,272 (TC)
Baxter, Leslie (Co-Pi PI: Pipe, Schmainda) RO1 CA092500 "MRI contrast agent methods in GBM"	2012-2017 \$28,373 (DC)
Baxter, Leslie (PI), Jiong Shi, Elliot Mufson State of Arizona/Barrow Subcontract Alzheimer's Disease and Aging Studies at BNI	07/01/14 - 06/30/15 \$150,000 (TC) \$150,000 (BNI Match)

ADHS12-010553 State of Arizona, DHS (Caselli) Arizona Alzheimer's Research Center (Consortium) Normal and Pathological Aging (Preclinical Alzheimer's Disease) Role: Principle Investigator	7/1/11 – 6/30/16 \$272,727
P30 AG019610 (Reiman) National Institute on Aging Arizona Disease Core Center Role: Associate Director and Clinical Core Director	8/15/11 - 6/30/16 1.8 calendar \$103,627
P30 AG019610 (Caselli) National Institute of Health Arizona Alzheimer's Disease Center Plasma/Serum Storage at MCA Bio-repository Role: Principle Investigator	7/1/13 – 6/30/16 0.12 calendar \$19,584
R21 AG043760 (Yalin Wang) National Institutes of Health MRI Biomarker Discovery for Preclinical Alzheimer's Disease with Geometry Methods Role: Co-Investigator	7/1/13 – 6/30/16 0.36 calendar \$19,134 (No Cost Extension)
MK-8931-017 (Caselli) 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 Role: Principal Investigator	11/1/13 – 10/31/20 0.12 calendar \$81,781
MK-8931-019 (Caselli) Merck & Co., Inc. IRB 13-006525/Protocol No. MK-8931-019 A Phase III, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Clinical Trial Role: Principal Investigator	11/1/13 – 10/31/20 0.24 calendar \$90,659
(Stonnington) CIM - Center for Individualized Medicine 12-006469 The Cognitive Effects of Lorazepam in Healthy Older Individuals with TOMM40 variable-length polymorphisms Role: Principal Investigator	01/2013 - present
(Stonnington) Development - Gifts from benefactors Mayo funds: Center for Individualized Medicine/ Normal and Pathological Aging, the "Arizona APOE Cohort": Mayo funding: Center for Individualized Medicine/ Normal and Pathological Aging, the "Arizona APOE Cohort". Role: Co-Investigator	07/2010 - present

5U01 AG006786-26-4 Petersen (PI) 09/01/14-06/30/19
Alzheimer's Disease Patient Registry – The Mayo Clinic Study of Aging
Role: Co-Investigator
EU #1-NEURO2 Geda (PI) 01/01/11-12/31/20

Neuroepidemiology – Aging, Pre-Clinical Alzheimer's Disease, and Dementia
Role: PI of Aging Project
Development Funding, Mayo Clinic (Geda) 9/1/2015 – 8/31/2016 0.12 calendar
Benefactor Gift \$40,687

Brain Imaging and Committed Actions for Successful Aging (CASA)
The major goal of this project is to conduct a novel, mentally-stimulating behavioral intervention
and to investigate the effects on default mode network using fMRI.
CCaTS Geda 02/15/2015 – 02/14/2016 Internal Award
Culture and language neutral computerized cognitive screening test among Latinos: A Feasibility
Study
Role: PI

(Huentelman MJ)
P30 AG019610 (Reiman) 07/01/11 - 06/30/16, 0.36 calendar mo.
NIH/NIA \$13,294/year direct costs
Arizona Alzheimer's Disease Core Center
Role: Co-Investigator

R01 AG041232 (Myers) 07/01/13 - 04/30/18, 1.2 calendar mos.
NIH/NIA \$125,000
APOEomic: Searching for APOE interacting risk factors using omics data
Role: Co-Investigator

UH2/UH3TR0000891 (Jensen/Huentelman) 08/01/13 - 07/31/18, 1.2 calendar mo.
NIH/Trans-NIH Research \$242,183
exRNA signatures predict outcomes after brain injury
Role: Multi-Principal Investigator

AAC - DHS (Huentelman) 07/01/15 – 06/30/16, 1.2 calendar mos.
State of Arizona, DHS \$65,000 direct costs
AARC FY 16: Alzheimer's Projects
Role: Principal Investigator

R0AG048907 (Huentelman/Barnes) 09/15/14 – 09/14/18, 1.2 calendar mos.
NIH/NIA \$245,145/year direct costs
CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox
Role: Principal Investigator (multi-PI)

RO1 AG049465 (Barnes) 08/01/14 – 03/31/19, 1.2 calendar mos.
NIH/NIA \$545,494/year direct costs
Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging
Role: Co-Investigator

1 RO1 AG049464 (Coleman/Barnes/Alexander) 08/01/14 – 07/31/19, 1.2 calendar mos.
NIH/NIA \$412,301/year direct costs
Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain
Role: Co-Investigator

R21 (Huentelman) 09/01/15 – 08/30/17, 0.96 calendar months
NIH \$200,000
Identification of pathogenic mechanisms important in multiple system atrophy
Role: Principal Investigator

Grant#1994(Trent) 12/23/2014 – 12/31/2016, 1.2 calendar mos.
Flinn Foundation Grant \$171,275
Role: Co Investigator

1UH2/UH3 TR000891 (Jensen/Huentelman) 08/01/2013 - 07/31/2015, 0.96 mos.
NIH/Trans-NIH Research \$242,183
exRNA signatures predict outcomes after brain injury
Role: Multi-Principal Investigator (Lead)

Grant (Jensen) 08/01/2015 – 07/31/2018, 1.2 calendar mos.
ALS Foundation \$80,000
Assessment of extracellular vesicle contents in patients with ALS
Role: Principal Investigator

Grant (Huentelman) 07/01/2015 - 06/30/2016, 0.84 calendar mos.
Arizona Department of Health Services \$37,500
TGen AARC FY15 Projects
Role: Co-Investigator

Grant (Skog/Jensen) 10/15/2013 – 4/31/2016, 1.44 calendar mo.
MJFF \$61,422
Identification of enriched RNAs in AGO2 and exosome pellets compared to the RNA found in the whole sample
Role: Co-Investigator

Grant (Jensen) 04/03/2014 – 04/03/2016, 1.8 calendar mos.
MJFF \$61,422
miRNA biomarkers of dementia
Role: Principal Investigator

R03NS09001301A1 (Lifshitz) 06/01/2015 – 05/31/2016, 0.48 calendar mo.
NIH/NINDS \$7,928
Gene Expression of Foci of TBI Neuropathology and Rod Microglia Interactions
Role: Co-Investigator

W81XWH-14-1-03 (Javaherian) 09/04/2015 – 08/31/2016, 0.6 calendar mo.
DoD \$10,991
Exosome-Mediated Transmission of Neurodegeneration in Amyotrophic Lateral Sclerosis Using Patient Induced Pluripotent Stem Cell-Derived Neurons and Astrocytes, Role: Co-Investigator

2R56NS061867-07 (Bowser) 09/01/2014 – 08/31/2016(NCE), 0.6 mo.
NIH \$156,000
Peptide and protein biomarkers for amyotrophic lateral sclerosis (ALS)
Role: Investigator

Grant (Trent) 10/01/2014 – 03/30/2016, 0.6 mo.
Flinn Foundation Grant \$100,000
Role: Co Investigator

Grant12401 (Jensen) 04/01/2014 – 03/30/2016, 1.2 & 0.6 mos.
MJFF \$91,223
Pre-analytical extracellular vesicle enrichment for increased reliability for alpha-synuclein
detection in plasma and CSF
Role: Principal Investigator

(Liang WS)
Contract (John Carpten) 09/01/2011 -08/31/2019, 1.2 calendar mos.
MMRF \$304,504
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)
Role: Investigator

Grant (Matt Huentelman) 07/01/2014 - 06/30/2015, 0.12 calendar mo.
AzDHS \$10,000
AARC FY 15 : Alzheimer's Projects
Role: Investigator

KG111063PP (Wicha/LoRusso/Trent) 04/01/2011 - 03/31/2016
Susan G. Komen for the Cure \$275,451
Targeting Stem Cells in Triple-Negative Breast Cancer (TNBC) in Different Racial Populations
Role: Investigator

Grant (Dunckley) 01/01/2016 - 12/31/2017
MJFox Foundation
Identification of epigenetic signatures in blood as biomarkers for Parkinson's disease.
Role: Co-Principal Investigator

Grant (Dunckley) 01/01/2016 – 12/31/2017
Alzheimer's Drug Discovery Foundation
Development of selective DYRK1A inhibitors as a treatment for Alzheimer's disease.
Role: Principal Investigator

Ahern, Geoff (co-investigator) 07/01/15 – 06/30/16
NIH/NIA P30 AG019610 \$43,084 Annual DC
Arizona Alzheimer's Disease Core Center (UA Clinical Core)

Ahern, Geoff (co-investigator) 07/01/15 – 06/30/16
State of Arizona, DHS Grant \$6,500 Annual DC

Arizona Alzheimer's Consortium - Patient Recruitment and Outreach for Alzheimer's Disease and Related-Disorders

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.	
Ahern, Geoff (PI) EnVivo Pharmaceuticals	2013 – present \$37,069/patient
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 26-Week, Phase 3 Study of Two Doses of EVP-6124 or Placebo in Subjects with Mild to Moderate Alzheimer's Disease Currently or Previously Receiving an Acetylcholinesterase Inhibitor Medication. Protocol # EVP-6124-025	
Ahern, Geoff (PI) EnVivo Pharmaceuticals	2013 – present \$27,944 / patient
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 26-Week, Phase 3 Study of Two Doses of EVP-6124 or Placebo in Subjects with Mild to Moderate Alzheimer's Disease Currently or Previously Receiving an Acetylcholinesterase Inhibitor Medication. Protocol # EVP-6124-025	
Alexander, Gene (PI, multi-PI) NIH/NIA 1 RO1 AG049464	08/01/14 – 03/31/19 \$485,845 Annual DC
Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain	
Alexander, Gene (PI, multi-PI) McKnight Brain Research Foundation	01/01/15 – 12/31/18 \$310,587 Annual DC
McKnight Inter-institutional Neuroimaging Core and Brain Aging Registry	
Alexander, Gene (PI, multi-PI) McKnight Brain Research Foundation	01/01/15 – 12/31/18 \$266,667 Annual DC
McKnight Inter-institutional Cognitive Aging Assessment Core	
Alexander, Gene (PI) State of Arizona, DHS Grant	07/01/15 – 06/30/16 \$62,000 Annual DC
Arizona Alzheimer's Consortium – Risk Factors for Brain Aging and Cognitive Health.	
Alexander, Gene (Co-Investigator) NIH/NIA 1 RO1 AG049465	08/01/14 – 3/31/19 \$558,872 Annual DC
Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging	

Alexander, Gene (PI, UA Subcontract) NIA/Banner Health Subcontract 3 RO1 AG031581 Brain Imaging, APOE and the Preclinical Course of Alzheimer's Disease	04/01/14 – 03/31/19 \$9,531 Annual DC
Alexander, Gene (PI, multi-PI) University of Arizona BIO5 Fellowship BIO5FLW2014-03 Cognitive Training to Enhance Brain Aging	11/01/14 – 05/31/16 \$30,000 Annual DC
Alexander, Gene (PI, multi-PI) TLA Wheelhouse Evaluation of the aerobic and cognitive training system for enhancing cognitive performance in older adults	02/05/15 – 04/31/16 \$106,769 TDC
Barnes, Carol (PI) NIH/NIA 1 RO1 AG049465 Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging	08/01/14 – 3/31/19 \$558,872 Annual DC
Barnes, Carol (PI, multi-PI) NIH/NIA 1 RO1 AG049464 Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain	08/01/14 – 03/31/19 \$485,845 Annual DC
Barnes, Carol (PI) NIH/NIA 1 R01 AG050548 Cell Assemblies, Brain Adaptation and Cognitive Brain	09/1/15 – 05/31/20 \$184,347 Annual DC
Barnes, Carol (PI) NIH/NIA 1 R37 AG012609 Cell Assemblies, Pattern Completion and the Aging Brain	7/1/09 – 6/30/15 \$184,347 Annual DC
Barnes, Carol (PI) NIH/NIA 1 RO1 AG003376 Neurobehavioral Relations in Senescent Hippocampus	01/01/16 – 11/30/20 \$597,557 Annual DC
Barnes, Carol (PI, multi-PI) NIH/NIA 1 RO1 AG048907 CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox	09/30/14 – 05/31/18 \$245,145 Annual DC
Barnes, Carol (co-investigator) NIH/NIA 5 P30 AG019610 Arizona Alzheimer's Disease Core Center Ad Hoc Review Program	07/01/11 – 06/30/16 \$12,831 Annual DC
Barnes, Carol A. (co-investigator) McKnight Brain Research Foundation Evelyn F. McKnight Inter-Institutional Bio-Informatics Core	12/10/13 – 12/01/16 \$150,000 Annual DC
Glisky, Elizabeth (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Memory, Executive Function, and Prospective Memory Training	07/01/15 – 06/30/16 \$32,000 Annual DC

Glisky, Elizabeth (mentor) Mind and Life Institute Developing an Objective Measure of Mindfulness in Daily Life (Polsinelli training award)	06/01/15 – 05/31/17 \$14,760 Annual DC
Glisky, Elizabeth (co-investigator) McKnight Brain Research Foundation McKnight Inter-institutional Cognitive Aging Assessment Core	01/01/15 – 12/31/18 \$266,667 Annual DC
Hay, Meredith (PI) Gooter Foundation Angiotensin (1-7) Treatment to Improve Cognitive Functioning in Heart Failure Patients	2015 – 2016 \$25,000 DC
Raichlen, David (PI, multi-PI) The National Science Foundation BCS-1440867 The evolutionary basis of human inactivity physiology.	09/15/14 – 08/31/17 \$ 268,953 TC
Raichlen, David (PI, multi-PI) University of Arizona BIO5 Fellowship BIO5FLW2014-03 Cognitive Training to Enhance Brain Aging	11/01/14 – 05/31/16 \$30,000 Annual DC
Raichlen, David (PI, multi-PI) TLA Wheelhouse Evaluation of the aerobic and cognitive training system for enhancing cognitive performance in older adults	02/05/15 – 04/31/16 \$106,769 TDC
Rapcsak, Steve (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium - Patient Recruitment and Outreach for Alzheimer's Disease and Related-Disorders	07/01/15 – 06/30/16 \$6,500 Annual DC
Rapcsak, Stephen (co-investigator) NIH/NIDCD 5 RO1 DC07646 Developing Evidence-Based Treatment Continuum for Spoken and Written Language	02/04/11 – 01/31/16 \$282,858 Annual DC
Rapcsak, Stephen (co-investigator) U.S. Department of Veteran Affairs Medial Temporal Lobe Contribution to Future Thinking: Evidence from Amnesia	01/20/14 – 01/19/17 \$44,614 TC
Rapcsak, Stephen (co-investigator) NIH/NIDC R01 DC013270 Neural Correlates of Recovery from Aphasia after Acute Stroke	06/01/14 – 05/31/19 \$297,230 Annual DC
Ryan, Lee (PI; co-I's Hay, Sweitzer, Konhilas, Glisky) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Angiotensin (1-7) Treatment to Improve Cognitive Functioning in Heart Failure Patients	07/01/15-06/30/16 \$98,505 Annual DC

Ryan, Lee (co-investigator) McKnight Brain Research Foundation McKnight Inter-institutional Cognitive Aging Assessment Core	01/01/15 – 12/31/18 \$266,667 Annual DC
Trouard, Ted (co-investigator) 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-investigator) Department of Defense W81XWH-12-1-0386 Model for Predicting Cognitive and Emotional Health from Functional Neurocircuitry	07/01/14 – 07/31/17 \$553,327
Trouard, Ted (co-investigator) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Enhanced Delivery of Therapy to the Brain in Mice	07/01/15 – 06/30/16 \$60,000 Annual DC
Trouard, Ted (co-investigator) NIH/NIA 1 RO1 AG049464 Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain	08/01/14 – 03/31/19 \$485,845 Annual DC
Trouard, Ted (co-Investigator) NIH/NIA 1 RO1 AG049465 Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging	08/01/14 – 3/31/19 \$558,872 Annual DC
Trouard, Ted (member) NIH/NIBIB T32 EB000809 Graduate Training in Biomedical Imaging and Spectroscopy	07/01/06 – 06/30/18
Wilson, S. (PI) State of Arizona, DHS Grant Arizona Alzheimer's Consortium – Validity and reproducibility of functional maps derived from naturalistic audiovisual stimuli	07/01/15 – 06/30/16 \$9,370 Annual DC
Wilson, S. (PI) NIH/NIDCD R01 DC013270 Neural correlates of recovery from aphasia after acute stroke	06/01/14 – 05/31/19 \$297,230 Annual DC
Wilson, S. (PI, multi-PI) BIO5 Fellowship to Develop Collaborative Life Sciences Project Neuroimaging correlates of recovery of language function after stroke	2015 - 2016 \$30,000 Annual DC
Zarnescu, Daniela (PI) NIH/NIA 5 P30 AG019610 A Drosophila Model of Dementia Based on TDP-43 (ADC pilot grant)	07/01/15 – 06/30/16 \$30,000 Annual DC
Zarnescu, Daniela (PI) NIH/NINDS R01 NS091299 Translation Dysregulation in Neurodegeneration	09/01/15 – 05/31/20 \$228,296 Annual DC

Zarnescu, Daniela (mentor) 01/01/15 – 08/31/17
NIH/NINDS F31 NS090829 \$40,525 Annual DC
Determining the Role of FoxO in TDP-43 Toxicity

Burke, Anna MD
2P30AG019610 (Reiman) 7/1/11-6/30/16 0.36 Calendar
NIH/NIA \$67,240 Annual Direct Costs
Arizona Alzheimer's Disease Core Center – Clinical Core
Role: Site PI

Burke, Anna MD
AARC (Reiman) 7/1/15-6/30/16 0.12 Calendar
State of Arizona \$55,000 Annual Direct Costs
Native American Outreach and Native American Clinical Core
Role: Core PI

Chen, K.
P30 AG019610 (Reiman) 7/1/11-6/30/16 0.31 Calendar
NIH/NIA \$1,145,275 Annual Direct Costs
Arizona Alzheimer's Disease Core Center
Role: Site PI

Chen, K.
2 R01 AG031581 (Reiman) 5/01/08-3/31/19 3.6 calendar
NIH/NIA \$1,110,690 Annual Direct Costs
Bain Imaging, APOE, & the Preclinical Course of Alzheimer's disease
Role: Co-Investigator

Chen, K.
5U01AG024904-08 (Weiner) 9/01/12-8/31/16 0.60 Calendar
NIH/Northern California Institute Res & Educ. \$216,462 Annual Direct Costs
Amyloid Imaging, VMCI and Analysis, for ADNI
Role: Site Co-PI

Chen, K.
W81XWH-12-2-0012 (Weiner) 2/21/13-2/20/16 0.60 Calendar
NIH/Northern California Institute Res & Educ. \$24,209 Annual Direct Costs
Effects of traumatic brain injury and post-traumatic stress disorder on Alzheimer's disease (AD)
in Veterans using ADNI.
Role: Co-Investigator

Chen, K.
Arizona Alzheimer's Research Consortium (Reiman) 7/1/11-6/30/16 0.60
Calendar
State of Arizona \$67,500 Annual Direct Costs
Advanced Image Analysis Techniques for the Detection and Tracking of Alzheimer's disease
and its prevention
Role: Project PI

Chen, K. 1R01NS075075-01A1 (Rogalski) Calendar NIH/NINDS Determinants of Neurodegenerative Decline in Primary Progressive Aphasia Role: Site PI	4/1/12-3/31/17	0.30	\$5,453 Annual Direct Costs
Chen, K. 1RF1AG041705-01A1 (Reiman/Tariot/Lopera) Calendar NIH/NIA Alzheimer's Prevention Initiative Role: Co-Investigator	5/18/12-4/30/17	1.20	\$12,302,690 Total NIH Direct Costs
Chen, K. 1UF1AG046150-01 (Reiman/Tariot) NIH/NIA Alzheimer's Prevention Initiative APOE4 Trial Role: Co-Investigator	9/1/13-8/31/18	180.6 Calendar	\$22,280,073 Total NIH Direct Costs
Chen, K. 4UH3TR000967-02 (Strittmatter/Van Dyck) NIH/Yale University Fyn Inhibition by AZD0530 for Alzheimer's disease Role: Co-Investigator	6/18/13-5/31/16	0.36 Calendar	\$92,943 Annual Direct Costs
Chen, K. R44 AG049510 (Didsbury/de la Monte) NIH/T3D Therapeutics, Inc. Clinical Evaluation of T3D-959 as a Potential Disease Remedial Therapeutic for the Treatment of Alzheimer's disease Role: Co-Investigator	3/5/15-2/28/17	170.72 calendar	\$45,154 Annual Direct Costs
Jessica Langbaum, PhD 2 R01 AG031581 (Reiman) NIH/NIA Brain Imaging, APOE, & the Preclinical Course of Alzheimer's Disease Role: Principal Scientist	5/01/08-3/31/19	0.12 calendar	\$1,110,690 Annual Direct Costs
Jessica Langbaum, PhD Arizona Alzheimer's Research Consortium (Langbaum) State of Arizona Arizona Alzheimer's Registry	7/1/11-6/30/16	0.0 Calendar	\$12,149 Annual Direct Costs Role: Principal Investigator
Jessica Langbaum, PhD 1RF1AG041705-01A1 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative	5/18/12-4/30/17	3.0 Calendar	\$12,302,690 Total NIH Direct Costs Role: Co-Investigator

<p>Jessica Langbaum, PhD 1UF1AG046150-01 (Reiman/Tariot) 9/20/13-8/31/18 NIH/NIA Alzheimer's Prevention Initiative APOE4 Trial Role: Co-Investigator</p>	<p>6.0 Calendar \$22,280,073 Total Project DC</p>
<p>Jessica Langbaum, PhD Alzheimer's Association/GHR/FBRI (Reiman/Tariot/Langbaum)1/1/16-12/31/20 Alzheimer's Prevention Initiative APOE4 Trial Role: Co-Principle Investigator</p>	<p>0.6 Calendar \$10,000,000 Total Project Costs</p>
<p>Jessica Langbaum, PhD Flinn Foundation (Reiman/Tariot/Langbaum) Alzheimer's Prevention Initiative Role: Co-Principal Investigator</p>	<p>1/1/14-12/31/18 0.6 Calendar</p>
<p>Reiman, Eric M. 5 P30 AG19610 (Reiman) NIH/NIA Arizona Alzheimer's Disease Core Center</p>	<p>9/30/01-6/30/16 1.2 calendar \$1,145,275 Annual Direct Costs</p>
<p>Reiman, Eric M. 2 R01 AG031581 (Reiman) NIH/NIA Brain Imaging, APOE, & the Preclinical Course of Alzheimer's Disease</p>	<p>5/01/08-3/31/19 1.2 calendar \$1,110,690 Annual Direct Costs</p>
<p>Reiman, Eric M. 1RF1AG041705-01A1 (Reiman/Tariot/Lopera) NIH/NIA Alzheimer's Prevention Initiative</p>	<p>5/18/12-4/30/17 2.4 calendar \$12,302,690 Total Direct Costs</p>
<p>Reiman, Eric M. 1UF1AG046150-01 (Reiman/Tariot) NIH/NIA Alzheimer's Prevention Initiative APOE4 Trial</p>	<p>9/20/13-8/31/18 2.4 calendar \$22,280,073 Total Direct Costs</p>
<p>Reiman, Eric M. TGen Professional Services Agreement (Reiman) Translational Genomics Research Institute</p>	<p>7/1/08 - 6/30/16 0.6 calendar \$41,872 Annual Direct Costs</p>
<p>Reiman, Eric M. 5U01AG024904-08 (Weiner) NIH/Northern California Institute Res & Educ. Alzheimer's Disease Neuroimaging Initiative-2 (ADNI2)</p>	<p>9/01/10-7/31/16 0.24 calendar \$216,462 Annual Direct Costs</p>
<p>Reiman, Eric M. W81XWH-12-2-0012 (Weiner) NIH/Northern California Institute Res & Educ.</p>	<p>2/21/13-2/20/17 0.12 calendar \$3,756 Annual Direct Costs</p>

Effects of traumatic brain injury and post-traumatic stress disorder on Alzheimer's disease (AD) in Veterans using ADNI.

Reiman, Eric M.

W81XWH-13-1-0259 (Weiner) 9/30/13-9/29/16 0.01 calendar
NIH/Northern California Institute Res & Educ. \$4,214 Annual Direct Costs

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).

Reiman, Eric M.

4UH3TR000967-02 (Strittmatter/Van Dyck) 6/18/13-5/31/16 0.24 calendar
NIH/Yale University \$92,943 Annual Direct Costs

Fyn Inhibition by AZD0530 for Alzheimer's Disease

Reiman, Eric M.

R44 AG049510 (Didsbury/de la Monte) 3/5/15-2/28/17 0.12 calendar
NIH/T3D Therapeutics, Inc. \$45,154 Annual Direct Costs

Clinical Evaluation of T3D-959 as a Potential Disease Remedial Therapeutic for the Treatment of Alzheimer's Disease

Reiman, Eric M.

U01NS093334-01 (Cummings/Reiman/Shenton/Stern) 12/15/15-11/30/22 0.6 calendar
Boston University via Mayo Clinic Arizona \$436,318 Total Project Direct Costs

Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course and Risk Factors

Beach, Thomas

U24 NS072026 (Beach) 9/1/11-6/30/16
NIH \$1,153,716 Annual DC

National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Beach, Thomas (Core Leader)

P30 AG019610 (Reiman) 7/1/11 to 6/30/16
NIH/NIA \$1,145,275 Annual DC

Arizona Alzheimer's Disease Core Center

Beach, Thomas

U01 (Scherzer) 9/30/12-8/31/15
Brigham and Women's Hospital \$22,598 Annual DC

Biomarkers for early detection and intervention in Parkinson's disease

Beach, Thomas

MJFF 2015 6270.04 (Beach/Adler) 10/1/15-4/30/16
Michael J. Fox Foundation for Parkinson's Research \$10,866 Total Costs

Submandibular Gland Needle Biopsy for the Diagnosis of Early Parkinson's Disease Supplement

Beach, Thomas

MJFF 2015 9035.01 (Beach/Derkinderen, Kordower/Munoz) 10/1/15-4/30/16
Michael J. Fox Foundation for Parkinson's Research \$31,542 Total Costs

Follow-up Autopsy Study: Evaluation of alpha-synuclein immunohistochemical methods for the detection of Lewy-type synucleinopathy in gastrointestinal biopsies

Beach, Thomas
MJFF 2013 9035 (Beach/Derkinderen) 11/25/13-11/30/15
Michael J. Fox Foundation for Parkinson's Research \$132,686 Annual DC
Evaluation of alpha-synuclein immunohistochemical methods for the detection of Lewy-type synucleinopathy in gastrointestinal biopsies.

Beach, Thomas
MJFF (Beach) 1/01/14 – 12/31/16
Michael J. Fox Foundation for Parkinson's Research \$36,250 Total Costs
Resources Utilization Grants Program

Beach, Thomas
MJFF (Multi PI Cuenca, Beach, Walker, Adler) 9/1/14-4/30/16
MJFF \$90,120 Annual DC
Retinal Pathology in Parkinson's Disease: Implications for Vision and Biomarkers

Beach, Thomas
GE Healthcare (Beach) 8/1/10 to present
Postmortem Correlation for Amyloid Imaging Ligand GE-067-007

Beach, Thomas
Schering-Bayer Pharmaceuticals, Inc. (Beach) 11/1/09 to present
Schering-Bayer Pharmaceuticals, Inc.
Postmortem Correlation for Amyloid Imaging Ligand Bay 94-9172

Beach, Thomas
Avid Radiopharmaceuticals, Inc. Beach (PI) 1/10/09 to present
Postmortem Correlation for the Amyloid Imaging Ligand AV45-A07 and AV45-A16.

Beach, Thomas
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
Janssen Research & Development 9/01/2014 to present
A Brain Donation Study for Subjects Who Participated in Clinical Trials for the Alzheimer Immunotherapy Program

Beach, Thomas
R01 AG044372-02 (PI: Kanaan) 9/30/14-4/30/19
NIH via Michigan State University \$12,300 Annual DC
Tau-induced axonal degeneration in Alzheimer's disease and tauopathies

Beach, Thomas
R01 AG044723-02 (PI: Migrino) 9/15/14-8/31/16

NIH via Phoenix VA Human Vascular model to study Alzheimer's Disease	\$2,532 Annual DC
Beach, Thomas 1R21NS093222 (Huentelman) NIH via TGEN Identification of pathogenic mechanisms important in multiple system atrophy	7/1/14 - 6/30/17 \$16,000 Annual DC
Beach, Thomas ABRC ESI (Mastroeni) Arizona Biomedical Research Commission A Novel Compound to Protect Mitochondria against Oligomeric Abeta Toxicity, Implications for the Synapse	10/23/14-10/22/17 \$68,167 Annual DC
Beach, Thomas AARC (Reiman, Project PI: Beach) AZ DHS via AARC Establishing an in-vivo blood biomarker repository with post-mortem diagnosis confirmation	7/1/15 – 6/30/16 \$78,300 Annual DC
Beach, Thomas AARC (Reiman, Project PI: Dugger) AZ DHS via AARC Validation of submandibular gland tau species to determine Braak NFT staging	7/1/15 – 6/30/16 \$27,000 Annual DC
Belden, Christine P30 AG019610 (Reiman) NIH/NIH Arizona Alzheimer's Disease Core Center – Clinical Core	7/1/11-6/30/16 \$1,145,275 Annual DC
Belden, Christine U24NS072026 (Beach) NIH National Brain and Tissue Resource for Parkinson's Disease and Related Disorders	9/1/11-6/30/16 \$1,153,716 Annual DC
Serrano, Geidy New Investigator Grant (Serrano) ABRC The effects of APOE genotype on APP/A β levels in human liver and brain	11/1/14-10/31/17 \$68,030 Annual DC
Serrano, Geidy U01 (Scherzer) Brigham and Women's Hospital Biomarkers for early detection and intervention in Parkinson's disease	9/30/12-8/31/15 \$22,598 Annual DC
Serrano, Geidy MJFF 2015 6270.04 (Beach/Adler) Michael J. Fox Foundation for Parkinson's Research Submandibular Gland Needle Biopsy for the Diagnosis of Early Parkinson's Disease Supplement	10/1/15-4/30/16 \$10,866 Total Costs

Serrano, Geidy
MJFF 2015 9035.01 (Beach/Derkinderen, Kordower/Munoz) 10/1/15-4/30/16
Michael J. Fox Foundation for Parkinson's Research \$31,542 Total Costs
Follow-up Autopsy Study: Evaluation of alpha-synuclein immunohistochemical methods for the detection of Lewy-type synucleinopathy in gastrointestinal biopsies

Serrano, Geidy
MJFF 2013 9035 (Beach/Derkinderen) 11/25/13-11/30/15
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Evaluation of alpha-synuclein immunohistochemical methods for the detection of Lewy-type synucleinopathy in gastrointestinal biopsies.

Serrano, Geidy
MJFF (Multi PI Cuenca, Beach, Walker, Adler) 9/1/14-4/30/16
MJFF \$90,120 Annual DC
Retinal Pathology in Parkinson's Disease: Implications for Vision and Biomarkers

Serrano, Geidy
Avid Radiopharmaceuticals, Inc. Beach (PI) 1/10/09 to present
Postmortem Correlation for the Amyloid Imaging Ligand AV45-A07 and AV45-A16.

Serrano, Geidy
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.

Serrano, Geidy
Janssen Research & Development 9/01/2014 to present
A Brain Donation Study for Subjects Who Participated in Clinical Trials for the Alzheimer Immunotherapy Program

Serrano, Geidy
R01 AG044372-02 (PI: Kanaan) 9/30/14-4/30/19
NIH via Michigan State University \$12,300 Annual DC
Tau-induced axonal degeneration in Alzheimer's disease and tauopathies

Shprecher, David
Grant (Shprecher) 7/2013-present
Sun Health Foundation \$97,300 Annual Direct Costs
Feasibility study of an early wellness program in Parkinson's disease and impact on quality of life

Taylor, Peter
U24 NS072026 (Beach) 9/1/11-6/30/16
NIH \$ 1,153,716 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Taylor, Peter
P30 AG019610 (Reiman) 7/1/11-6/30/16

NIH/NIH \$1,145,275 Annual DC
Arizona Alzheimer's Disease Core Center – Clinical Core

Zamrini, Edward
U24 NS072026 (Beach) 9/1/11-6/30/16
NIH \$ 1,153,716 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Zamrini, Edward
P30 AG019610 (Reiman) 7/1/11-6/30/16
NIH/NIH \$1,145.275 Annual DC
Arizona Alzheimer's Disease Core Center – Clinical Core

Zamrini, Edward
AARC (Reiman, Project PI: Zamrini) 7/1/15 – 6/30/16
AZ DHS via AARC \$119,700 Annual DC
Development of an enhanced "Longevity Study" in older and oldest old adults

Pending Grants

NIH 1R01EB023331 (Brafman)
09/01/2016-08/31/2021
Taking lessons from development to engineer a hematopoietic stem cell
Role: PI

NIH 1R01GM121698 (Brafman)
09/01/2016-08/31/2021
Investigating the mechanisms of a multi-state model of Wnt signaling
Role: PI

NSF 1604231 (Brafman)
06/1/2016- 05/31/2019
Bioreactor for the large-scale expansion and directed neuronal differentiation of hNPCs

FP5296 (Reiman/Johnson) 07/01/16 – 06/30/21 .90 calendar
NIH – Arizona Alzheimer's Disease Center \$459,230
Outreach, Recruitment and Education Core. ORE Core Leader for the Arizona Alzheimer's Disease Consortium fostering education, outreach and recruitment, particularly of diverse participants into the clinical core.
Role: ORE Core Leader

R01AG049895 (Coon) 01/01/16 – 12/31/20 3.60 calendar
NIH-NIA \$3,806,280
EPIC: A group-based intervention for Early-stage AD Dyads in Diverse Communities
Role: PI

R01NR015450 (Evans & Coon) 04/01/16 – 03/31/21 3.00 calendar
NIH-NINR \$3,865,631
An Early Palliative & End of Life Care Intervention with Hispanic/Latino Families, Role: Co-PI

FP1194 (Okun) 10/01/15 – 09/30/17 1.6 calendar
National Institute on Aging \$500,076
Advancing Person Centered Care through On-Line Social Intelligence Training. This SBIR submission evaluates a Social Intelligence based training program for providers in long term care settings. (Scored, resubmitted 4/1/15 for review, but unfunded)
Role: Co-I

Funding Agency: NIH – National Institute on Aging
Title: Molecular interplay between Abeta, tau and mTOR: Mechanisms of neurodegeneration (competitive renewal)
Period: 07/2016 - 06/2021
Role: Principal Investigator
Total Costs: \$1,900,000

Funding Agency: NIH – National Institute on Aging
Title: Dissecting the mechanisms of cognitive deficits in Alzheimer's disease
Period: 07/2016 - 06/2021
Role: Principal Investigator
Total Direct Costs: \$1,722,000

Funding Agency: NIH – National Institute of Neurological Disorders and Stroke
Title: Nrf2, Chronic Oxidative Stress, and TDP-43: Mechanisms of Neuropathogenesis
Period: 07/2016 - 06/2021
Role: Principal Investigator
Total Direct Costs: \$1,250,000

Funding Agency: NIH – National Institute of Neurological Disorders and Stroke
Title: Tau conditional knockout mice to elucidate the function of tau in the adult brain
Period: 07/2016 - 06/2019
Role: Principal Investigator
Total Direct Costs: \$ 450,000

Funding agency: NIH –National Institute on Aging
Title: Targeting toxic tau and A β variants as a therapeutic strategy for treating AD
Period: 07/2016 - 06/2019
Role: Collaborator (PI, Michael Sierks)
Total Direct Costs for the Oddo's lab: \$33,000

FP00005135 (Mastroeni, Diego) 10/1/2016-9/30/2021 Cal: 1.2
HHS-NIH \$435,851.00 Acad: 0
5-hydroxymethylation Levels Dictate Precursor Cell Fate in Alzheimer's Disease Sumr: 0

FP00006017 (Coleman,Paul David) 7/1/2016-6/30/2021 Cal: 1.2
Massachusetts General Hospital (HHS-NIH) \$57,530.00 Acad: 0
Comparative Gene Expression in Human vs Rodent Stroke Models Sumr: 0

FP00006283 (Oddo, Salvatore) 7/1/2016-6/30/2021 Cal: 0.6
HHS-NIH-NIA \$348,974.00 Acad: 0

Identifying novel therapeutic targets for Alzheimer's disease using post mortem human brains and animal models Sumr: 0

FP00005208 (Velazquez, Ramon) 7/1/2016-6/30/2018 Cal: 0.01
ASU Foundation (BrightFocus Foundation) \$49,797.00 Acad: 0
Maternal choline supplementation: epigenetic effects on AD pathogenesis Sumr: 0

FP00006869 (Coleman,Paul David) 5/1/2016-4/30/2019 Cal: 0
Alzheimer's Association \$86,528.00 Acad: 1.0
Regional and Gender Effects On the Aging Brain, A Hormonal-Synaptic Theory Sumr: 0

(Mastroeni,Diego Fernando) 10/1/2016-9/30/2021 Cal: 0
HHS-NIH \$3,164,498.00 Acad: 0
5-hydroxymethylation Levels Dictate Precursor Cell Fate in Alzheimers Disease Sumr: 0

Alzheimer's Association 5/1/2016-4/30/2019 Cal: 0
\$249,923.00 Acad: 0
Regional and Gender Effects On the Aging Brain, A Hormonal-Synaptic Theory Sumr: 0

FP00005732 (Sierks, Michael) 7/1/2016 - 6/30/2019 Cal: 0.01
ASU Foundation (Bright Focus Foundation) \$100,000.00 Acad: 0
Targeting toxic tau and abeta variants as a therapeutic strategy for treating AD Sumr: 0

FP00007068 (Sierks, Michael) 9/1/2016-8/31/2018 Cal: 0
HHS-NIH \$150,000.00 Acad: 0
Targeting toxic tau and abeta variants as a therapeutic strategy for treating AD Sumr: 0.31

FP00005778 (Hiroi DuBay, Sheri) 4/1/2016-3/31/2018 Cal: 0
ASU Foundation (Alzheimer's Association) \$48,759.00 Acad: 0.03
Sex-specific effects of an antidepressant in an Alzheimer's mouse model Sumr: 0

FP00005815 (Oddo,Salvatore) 7/1/2016-6/30/2021 Cal: 2.40
HHS-NIH-NCI \$265,092.00 Acad: 0
Molecular interplay between A β , tau and mTOR: Mechanisms of neurodegeneration

FP00004837 (Oddo,Salvatore) 10/1/2015-3/31/2017 Cal: 0.60
TGen (ADDF) \$48,148.00 Acad: 0
Testing of selective DYRK1A inhibitors as a novel treatment for AD Sumr: 0

FP00005135 (Mastroeni, Diego) 10/1/2016-9/30/2021 Cal: 0
HHS-NIH \$435,851.00 Acad: 0
5-hydroxymethylation Levels Dictate Precursor Cell Fate in Alzheimer's Disease Sumr: 1.00

FP00005208 (Velazquez, Ramon) 7/1/2016-6/30/2018 Cal: 0.01
ASU Foundation (BrightFocus Foundation) \$49,797.00 Acad: 0
Maternal choline supplementation: epigenetic effects on AD pathogenesis Sumr: 0

FP00006283 (Oddo,Salvatore) 7/1/2016-6/30/2021 Cal: 2.40
HHS-NIH-NIA \$348,974.00 Acad: 0

Identifying novel therapeutic targets for Alzheimer's disease using post mortem human brains and animal models Sumr: 0

FP00006335 (Oddo,Salvatore) 9/1/2016-8/31/2018 Cal: 0.60
HHS-NIH-NINDS \$125,000.00 Acad: 0
Tau conditional knockout mice to elucidate the function of tau in the adult brain Sumr: 0

FP00005256 (Talboom, Joshua) 7/1/2016-6/30/2018 Cal: 0.01
ASU Foundation (BrightFocus Foundation) \$49,671.00 Acad: 0
Mechanisms of cognitive deficits in Alzheimer's disease Sumr: 0

FP00005263 (Velazquez, Ramon) 5/1/2016-4/30/2018 Cal: 0.01
NSF \$71,618.00 Acad: 0
Elucidating the molecular mechanisms linking maternal choline supplementation to healthy cognitive aging Sumr: 0

FP00005409 (Bimonte-Nelson, Heather) 7/1/2016-6/30/2021 Cal: 0.60
HHS-NIH-NIA \$250,000.00 Acad: 0
Menopause as a mediator of memory and pathology in Alzheimer's Disease Sumr: 0

(Velazquez,Ramon) 7/1/2016-6/30/2018 Cal: 10.56
ASU FDN \$49,797.00 Acad: 0
Maternal choline supplementation: epigenetic effects on AD pathogenesis Sumr: 0

(Velazquez,Ramon) 5/1/2016-4/30/2018 Cal: 12
NSF \$71,618.00 Acad: 0
Elucidating the molecular mechanisms linking maternal choline supplementation to healthy cognitive aging Sumr: 0

FP00005550 (Walker,Douglas Gordon) 7/1/2016-6/30/2021 Cal: 3.0
HHS-NIH \$273,643.00 Acad: 0
Neuronal-Microglial cross-regulation of inflammation: Role of CD200R and TREM2

FP00005593 (Walker,Douglas Gordon) 10/1/2015-9/30/2016 Cal: 2.0
Banner Sun \$58,508.00 Acad: 0
National Brain and Tissue Resource for Parkinson's Disease and Related Resources Sumr: 0

FP00005193 (Lue, Lih-Fen) 4/1/2016-3/31/2019 Cal: 1.2
HHS-NIH \$335,161.00 Acad: 0
Ultra sensitive immunomagnetic reduction assay for a-synuclein species Sumr: 0

FP00006263 (Walker,Douglas Gordon) 1/1/2016-12/31/2016 Cal: 1.0
HHS-NIH \$42,085.00 Acad: 0
Is Toll-like receptor - 3 signaling involved in Alzheimer's disease? Sumr: 0

FP00004652 (Lue, Lih-Fen) 10/1/2015-3/31/2016 Cal: 1.0
MAYO CLINIC ARIZONA \$33,717.00 Acad: 0
Validation of Novel and Traditional Quantitative EEG Biomarkers Sumr: 0

FP00005680 (Reiman, Eric)	7/1/2016-6/30/2021	Cal: 0.6
HHS-NIH	\$1,721,205.00	Acad: 0
Arizona Alzheimer's Disease Core Center Sumr: 0		
FP00004974 (Walker,Douglas Gordon)	4/1/2016-3/31/2018	Cal: 3
HHS-NIH	\$128,162.00	Acad: 0
Is O-GlcNAcylation involved in Alzheimer's disease neuroinflammation? Sumr: 0		
FP00006882 (Lue, Lih-Fen)	10/1/2016-9/30/2021	Cal: 2.4
HHS-NIH	\$250,000.00	Acad: 0
Interactive mechanisms for modulating microglia activation in neurodegeneration Sumr: 0		
B. Blair Braden (PI; Baxter, Co-PI)		
Autism Science Foundation		
Cognitive and Neural Correlates of Aging in Autism Spectrum Disorder: Interactions with Gender		
MJ Huentelman	04/01/2016 – 03/30/2021	
R01 (Oddo)	0.6 calendar mos.	
NIH	54,907	
Dissecting the mechanisms of cognitive deficits in Alzheimer's disease		
Role: Investigator		
R01 (Madhavan)	04/01/2018 – 06/30/2021, 1.2 calendar mo.	
NIH	\$37,502	
Nrf2 as a regulator of neural stem cell function during aging		
Role: Co-Investigator		
R21 (Neisewander)	04/01/2016 – 03/30/2018, 1.2 calendar mo.	
NIH	\$84,967	
Identification of Extracellular RNA Biomarkers of Cocaine Use		
Role: Co-Investigator		
R01 (Kaczorowski)	04/01/2016 – 03/31/2021, 0.6 calendar mo.	
NIH	\$9,734	
Systems Genetics of Cognitive Aging and Alzheimer's Disease		
Role: Co-Investigator		
P30 AG019610 (Reiman) Competitive renewal	07/01/2016 - 06/30/2021, 0.48 calendar mo.	
NIH/NIA	\$12,190	
Arizona Alzheimer's Disease Core Center		
Role: Co-Investigator		
R01 (Oddo)	07/01/2016 – 06/30/2021, 0.6 calendar mo.	
NIH	\$54,907	
Identifying novel therapeutic targets for Alzheimer's disease using post mortem human brains and animal models		
Role: Co-Investigator		

R21 (Huentelman)		07/01/2016 – 06/30/2018, 0.6 calendar mo.
NIH		\$64,981
A longitudinal molecular profiling approach to study relapse-remitting multiple sclerosis using dried blood spots.		
Role: Principal Investigator		
R01 (Peter)		09/01/2016 – 08/31/2019, 0.24 calendar mo.
NIH		\$51,155
Genetics of speech sound disorders		
Role: Co-Investigator		
(R01) (Dickinson)		09/01/16 – 08/31/2021, 0.24 calendar mo.
NIH		\$47,285
Novel exercise preconditioning strategy for the prevention of anthracycline medicated cardiac and skeletal muscle		
Role: Co-Investigator		
R01 (Huentelman)		09/01/2016 – 08/31/2021, 1.2 calendar mo.
NIH		\$215,000
Genetic mechanisms of multi-sensory processing		
Role: Co-Investigator		
R01 (Vargas)		09/01/2016 – 08/31/2018, 0.24 calendar mo.
NIH		\$39,115
Predicting Cancer Treatment Related Cardiac Damage Employing Quantitative and Qualitative MRI Image Analysis and RNA Biomarker Profiling		
Role: Co-Investigator		
K Jensen		
R01	(Bowser)	07/01/2016 – 06/30/2021, 0.6 calendar mo.
NIH		\$
Peptide and protein biomarkers for amyotrophic lateral sclerosis (ALS)		
Role: Co-Investigator		
R01	(Bowser)	07/01/2016 – 06/30/2021, 0.6 calendar mo.
NIH		\$26,100
Nuclear stress bodies and RBM45 mediated protein/RNA interactions: Implications for stress response in ALS		
Role: Co-Investigator		
R01	(Newbern)	07/01/2016 – 06/30/2021, 0.48 calendar mo.
NIH		\$45,494
Functions of ERK/MAPK Signaling in GABAergic Circuit Development		
Role: Co-Investigator		
Grant	(Lancaster)	09/01/2016 – 08/31/2017
		0.6 calendar mo.
PAC-12		\$519,864
Head Trauma: Evaluation of extracellular RNA changes associated with concussive and		

repetitive head impact exposure

Role: Co-Investigator

R01 (Kusumi) 09/01/2016 – 08/31/2021

0.6 calendar mo.

NIH \$90,606

RegenerationCODE: Identifying the genetic toolkit for vertebrate regeneration

Role: Co-Investigator

Liang WS 07/01/2016 – 06/30/2019

R01 (Rangasamy) 1.2 calendar mos.

NIH \$14,705

Dysregulation of mTOR signaling in the pathogenesis of MeCP2-related disorders

Role: Co-Investigator

WS Liang 07/01/2016 -6/30/21

R01 (Trent) 1.2 calendar mos.

NIH \$11,055

SMARCB1 loss promotes SWI/SNF complex instability and component degradation

Role: Co-Investigator

WS Liang 09/01/16 – 08/31/21

P01 (Esserman) 0.24 calendar mos.

NIH \$4,721

I-SPY 2+: Evolving the I-SPY 2 TRIAL to include MRI-directed, adaptive sequential treatment in the setting of non-response

Role: Co-Investigator

Grant (Dunckley) 06/01/2016 – 05/31/2018

Ruth K Broad Foundation

Testing a novel DYRK1A inhibitor as an AD therapeutic

Ahern, Geoffey. (co-investigator) 07/01/16 – 06/30/21

NIH/NIA 2 P30 AG019610 \$43,084 Annual DC

Arizona Alzheimer's Disease Core Center – Clinical Core

Alexander, Gene (PI, multi-PI) 07/01/16 – 06/30/21

NIH/NIA RO1 \$184,020 Annual DC

Augmenting Cognitive Training in Older Adults

Alexander, Gene (PI) 07/01/16 – 06/30/19

Arizona Biomedical Research Commission \$227,212 Annual DC

A Novel Aerobic & Cognitive Training (ACT) Intervention to Improve Brain Aging & Cognitive Health

Alexander, Gene (co-investigator) 06/01/16 – 11/30/18

NIH/NINDS 1 R42 NS095413 \$139,801 Annual DC

Cloud-based Evaluation of Clinical Human Brain Scans

Alexander, Gene (co-investigator) NIH/NIA 2 P30 AG019610 Arizona Alzheimer's Disease Core Center – Data Management and Statistics Core	07/01/16 – 06/30/21 \$12,345 Annual DC
Alexander, Gene (co-investigator) NIH/NIA R03 Ultra-sensitive and label-free detection of Alzheimer's disease biomarkers	09/01/16 – 08/31/18 \$55,800 Annual DC
Barnes, Carol A. (co-investigator) NIH/NIA 2 P30 AG019610 Arizona Alzheimer's Disease Core Center Ad Hoc Review Program	07/01/16 – 06/30/21 \$15,945 Annual DC
Barnes, Carol A. (co-investigator) NIH R21 Chemogenetic Tools to Remotely Stimulate Neuronal Networks in Alzheimer's Disease	04/01/16 – 03/31/18 \$12,345 Annual DC
Barnes, Carol A. (co-investigator) NIH R01 Nrf2 as a Regulator for Neural Stem Cell Function During Aging	04/01/16 – 03/31/18 \$12,345 Annual DC
Barnes, Carol A. (co-investigator) National Science Foundation 2016 Bisgrove Scholar Program	07/01/16 – 06/30/18 \$12,345 Annual DC
Glisky, Elizabeth (PI) NIH R21 Improving medication adherence in heart failure patients: A prospective memory intervention.	09/01/16 – 08/31/18 \$275,000 Total DC
Rapcsak, Stephen (co-investigator) NIH/NIA 2 P30 AG019610 Arizona Alzheimer's Disease Core Center – Clinical Core	07/01/16 – 06/30/21 \$43,084 Annual DC
Ryan, Lee (PI) Alzheimer's Association Angiotensin (1-7) Treatment to Improve Cognitive Functioning in MCI	5/1/16 – 4/30/18 \$1,000,000
Trouard, Ted (PI) NIH RO1 Ultrasound-mediated Delivery of Neurotherapy in Alzheimer's and NPC Disease	07/01/16 – 06/30/21 \$1,108,200 Total DC
Zarnescu, Daniela (PI) NIH/NINDS R21 NS098267 Metabolic Dysregulation in ALS	07/01/16 – 06/30/18 \$150,000 Annual DC
Zarnescu, Daniela (PI) MDA #418515 Metabolic Dysregulation in ALS	07/01/16 – 06/30/19 \$90,000 Annual DC

Zarnescu, Daniela (co-investigator) 10/01/16 – 09/30/18
NIH/NINDS \$50,000 Annual DC
Functional Genomics Analysis of Zinc Homeostasis with Rapid Follow-up in Drosophila Models of ALS

Dunckley, Travis L
2/1/2016-4/30/2016

Cal: 0.60

ASU Foundation (Alzheimer's Drug Discovery Foundation [ADDF]) \$163,346.00, Acad: 0
Testing of selective DYRK1A inhibitors as a novel treatment of AD Sumr: 0

Reiman, Eric M.

R01 (Handen) 9/30/15-9/30/20 0.4 calendar

NIH via University of Pittsburgh \$263,470 Annual Direct Costs

Neurodegeneration in Aging Down Syndrome (NiAD): A Longitudinal Study of Cognition and Biomarkers of Alzheimer's Disease

Reiman, Eric M.

P30 7/1/2016-6/30/2021 1.2 calendar

NIH \$1,682,234 Annual Direct Costs

Arizona Alzheimer's Disease Core Center Renewal

Reiman, Eric M.

ADHS14-00003606 (Sabbagh) 10/23/2015-10/22/2017 0.36 calendar

Arizona Biomedical Research Commission (ABRC)/HHS \$161,707 Annual Direct Costs

Prime award received by St. Joseph's Hospital & Medical Center.. Subaward agreement pending execution.

Longitudinal Assessment of Florbetapir PET, FDG PET, and MRI in Down Syndrome Individuals with and without Alzheimer's Dementia

Reiman, Eric M.

1UG3OD023171-01 (Ojo, Calhoun, Groves) 7/1/2016-6/30/2021 0.6 calendar

NIH/ University of Arizona \$2,161,976 Annual Direct Costs

University of Arizona-Banner Health Precision Medicine Initiative Cohort Enrollment Center

Beach, Thomas

9/1/16-8/31/18

NIH R21 via ASU (Walker)

\$5,453 Annual DC

Is O-GlcNAcylation involved in Alzheimer's disease neuroinflammation?

Beach, Thomas

8/1/16-7/31/21

NIH R01 via Harvard Medical School BIDMC (Gibbons)

\$16,065 Annual DC

Skin Biopsy in the Central Alpha-Synucleinopathies

Beach, Thomas

10/1/16-9/30/21

NIH R01 via ASU (Mastroeni)

\$4,181 Annual DC

Profiling and predicting precursor cell fate through the actions of 5-hydroxymethylation

Beach, Thomas

7/1/16-6/30/21

NIH R01 via Arizona State University (Oddo)

\$10,382 Annual DC

Molecular interplay between A β , tau and mTOR: Mechanisms of neurodegeneration

Beach, Thomas 7/1/16-6/30/21
NIH R01 via Arizona State University (Oddo) \$10,382 Annual DC
Identifying novel therapeutic targets for Alzheimer's disease using post mortem human brains and animal models

Beach, Thomas 8/1/16-7/31/121
NIH R01 via ASU (Walker) \$8,404 Annual DC
Neuronal-Microglial cross-regulation of inflammation: Role of CD200R and TREM2?

Beach, Thomas 12/1/16-11/30/17
NIH R03 via University of Arizona (Su) \$10,000 Annual DC
Ultra-sensitive and label-free detection of Alzheimer's disease biomarkers

Beach, Thomas 10/1/16-9/30/18
NIH R21 via Linda Loma University (Dashtipour) \$18,901 Annual DC
DNA Methylation patterns provide information regarding susceptibility to and protection against Parkinson's Disease

Beach, Thomas & Serrano, Geidy 12/1/16-11/30/17
NIH R21 via UCSF (Dugger) \$8,100 Annual DC
Tau in human peripheral tissues

Serrano, Geidy 9/1/16-8/31/18
NIH R21 via ASU (Walker) \$5,453 Annual DC
Is O-GlcNAcylation involved in Alzheimer's disease neuroinflammation?

Serrano, Geidy 8/1/16-7/31/21
NIH R01 via Harvard Medical School BIDMC (Gibbons) \$16,065 Annual DC
Skin Biopsy in the Central Alpha-Synucleinopathies

Serrano, Geidy 10/1/16-9/30/21
NIH R01 via ASU (Mastroeni) \$4,181 Annual DC
Profiling and predicting precursor cell fate through the actions of 5-hydroxymethylation

Serrano, Geidy 7/1/16-6/30/21
NIH R01 via Arizona State University (Oddo) \$10,382 Annual DC
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Serrano, Geidy 7/1/16-6/30/21
NIH R01 via Arizona State University (Oddo) \$10,382 Annual DC
Identifying novel therapeutic targets for Alzheimer's disease using post mortem human brains and animal models

Serrano, Geidy 8/1/16-7/31/121
NIH R01 via ASU (Walker) \$8,404 Annual DC
Neuronal-Microglial cross-regulation of inflammation: Role of CD200R and TREM2?

Serrano, Geidy 12/1/16-11/30/17
NIH R03 via University of Arizona (Su) \$10,000 Annual DC
Ultra-sensitive and label-free detection of Alzheimer's disease biomarkers

Serrano, Geidy 10/1/16-9/30/18
NIH R21 via Linda Loma University (Dashtipour) \$18,901 Annual DC
DNA Methylation patterns provide information regarding susceptibility to and protection against
Parkinson's Disease



**Arizona Alzheimer's Consortium
18th Annual Scientific Conference
Thursday, May 19, 2016**

**Translational Genomics Research Institute (Host Institution)
University of Arizona College of Medicine
Phoenix, Arizona**

Poster Abstracts

Poster 1

PHENOTHIAZINE ANALOGUES: THERAPEUTIC AGENTS FOR MITOCHONDRIAL AND NEURODEGENERATIVE DISEASES. Bandyopadhyay I, Chowdhury SR, Khmour OM, Hecht SM. Arizona State University; Arizona Alzheimer's Consortium.

Background: Mitochondrial dysfunction is a major hallmark of various neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, and Friedreich's ataxia (FRDA). Severe metabolic deficit has been shown to be a prominent feature of Alzheimer's disease in human brain, animal models, and in vitro models. Given the evidence suggesting that mitochondrial dysfunction and oxidative damage play a role in neurodegeneration, therapies based on agents that enhance mitochondrial health and restore the bioenergetic deficit may eventually play a role in the treatment of Alzheimer's disease and other mitochondrial and neurodegenerative conditions. Methylene blue (MB), a clinically used redox-active drug that can bypass compromised complexes I-III, and can effectively attenuate electron transport chain (ETC) dysfunction. We and others have observed that high doses of MB are detrimental and rather increase pathology and cytotoxicity. MB has a hormetic dose-response in which its beneficial effects are optimal in the lower doses. It stimulates energy metabolism and has antioxidant effects at lower doses, whereas it decreases energy metabolism and acts as a pro-oxidant at higher doses.

The goal of the study is to design and optimize MB in order to get the maximum beneficial effect by increasing the antioxidant activity and decrease its pro-oxidant effect and eliminate any cytotoxicity and side effect. Here we have prepared and evaluated several MB and hydroxyl analogues which are capable of quenching ROS and diminishing the degradation of cellular macromolecules, in addition to supporting ATP synthesis in a broader range of mitochondrial and neurological diseases. Compounds with such properties may find utility in treating mitochondrial and neurodegenerative diseases such as FRDA and Alzheimer's disease.

Methods: A number of methylene blue analogues were prepared and tested for their ability to suppress ROS formation, restore ATP production and confer protection in cell lines from mitochondrial and neurological disease patients.

Results: The methylene blue analogues were found to protect the cells from oxidative stress induced by glutathione depletion and restore ATP levels in a differentiated SH-SY5Y model treated with amyloid beta (A β 1-42). Our results show that methylene blue was cytotoxic at higher concentration and longer incubation time. The modified methylene blue showed no sign of cytotoxicity even at higher concentrations and longer incubation times.

Conclusions: We have succeeded in preparing methylene blue analogues that lack cytotoxicity and are more protective against oxidative stress and enhance mitochondrial function more effectively than methylene blue itself. Agents with such properties may find utility in treating mitochondrial and neurodegenerative diseases such as FRDA and Alzheimer's disease.

Poster 2

AGE-ASSOCIATED REGIONAL NETWORK PATTERN OF MRI GRAY MATTER IN THE BONNET MACAQUE. Bharadwaj PK, Burke SN, Trouard TP, Chen K, Moeller JR, Barnes CA, Alexander GE. University of Arizona; University of Florida; Banner Alzheimer's Institute; Columbia University; Arizona Alzheimer's Consortium.

Background: Studies of healthy aging in humans have consistently observed brain atrophy, often preferentially involving frontal and selective temporal brain regions, which is associated with cognitive aging. We have previously reported regionally distributed patterns of magnetic resonance imaging (MRI) gray matter in healthy aging in humans and a nonhuman primate (rhesus macaque) model of aging (Alexander et al., 2006; 2008) using multivariate network analysis with the scaled subprofile model (SSM; Alexander & Moeller, 1994) and voxel-based morphometry (VBM). In this study we investigated the effects of aging on the regional pattern of MRI gray matter in a group of 13 healthy adult female bonnet macaques (BM) with ages ranging from 10.2 to 30.8 years (human equivalent age range of 31-92 years).

Methods: Volumetric T1 MRI scans were acquired on a GE 3T Signa scanner with 600 micron isotropic voxel resolution. Image processing for VBM included brain extraction, inhomogeneity correction, tissue segmentation with high dimensional warping and smoothing. Regional network analysis was performed on these smoothed gray matter maps with the SSM using Akaike information criterion with small sample correction (Burnham & Anderson, 2002). Behavioral testing was performed using a modified Wisconsin General Test Apparatus (WGTA) (Harlow & Bromer, 1938), to administer the training and testing phases of the delayed response (DR) task which assesses working memory performance over progressively increasing delay intervals (O'Donnell et al., 1999).

Results: Network analysis with SSM identified a linear combination of the first three component patterns of gray matter that were significantly associated with age, in this sample of 13 adult female bonnet macaques ($R^2=0.66$, $p=0.17$). This pattern was characterized by reductions mainly in bilateral prefrontal regions and a small area in the right posterior temporal/visual association region with increasing age, as well as including areas of relative increase in the bilateral primary motor/somatosensory region. Among the aged bonnet macaques (age range: 23.2–30.8 years), higher expression of this network pattern was associated with greater age (Kendall Tau-b = 0.73, $p = 0.039$). The total number of trials to reach criterion performance during the zero second delay training for the DR task was associated with higher expression of the age-related SSM pattern (Kendall's Tau-b=0.56, $p=0.037$). Performance on the DR task at the different delay intervals was not associated with the age-related pattern expression.

Conclusions: These findings indicate that aging in BM is associated with a regionally distributed pattern of MRI gray matter reduction involving selective frontal and temporal brain regions that are generally consistent with previous findings of structural covariance in human and other non-human primate models of aging. Higher expression of the age-related network pattern of gray matter atrophy was associated with greater number of trials needed to reach criterion performance on the Delayed Response task, suggesting reduced learning efficiency with higher expression of the age associated MRI pattern in this sample. Together these findings provide further support for multivariate SSM VBM network analysis in identifying the effects of cognitive and brain aging in non-human primate models.

Poster 3

DEPRESSION AND ANXIETY IN THE AGING ASD COHORT: RELATIONSHIPS WITH COGNITION AND SOCIAL NETWORKS. Braden BB, Smith CJ, Glaspy T, Thompson A, Deatherage BR, Wood E, Vatsa D, Baxter L. Barrow Neurological Institute; Southwest Autism Research & Resource Center; Arizona Alzheimer's Consortium.

Background: The population of adults with autism spectrum disorder (ASD) is rapidly growing, yet there are few studies investigating the effects of aging. ASD individuals have high comorbidity with other psychiatric disorders, especially depression and anxiety. In typically developing (TD) individuals, psychiatric symptoms increase with age which is hypothesized to be related to decreased social support. Many ASD individuals struggle with decreased social support at even younger ages. It is critical to understand mood symptom changes with age, since these factors negatively affect cognition, which can further impair functioning of ASD individuals. To evaluate the relationship between age and mood measures in ASD, we utilized self-report measures of depression, anxiety, and social networks and related findings to cognitive scores. We hypothesized that psychiatric symptoms are exacerbated in older cohorts of ASD, and that symptoms are related to level of social support and predict cognition.

Methods: Data were obtained for 16 high-functioning middle-age (40-65 years) ASD, 11 young-adult ASD (18-25 years), and age-matched TD (16 middle-age; 9 young-adult) male participants. Self-report measures were Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI), and Social Network Index. Mood measures were correlated with cognitive measures of executive functioning, memory, and visual detail processing.

Results: Participants did not significantly differ in IQ ($p=0.18$). For all mood and social network measures, there were main effects for diagnosis, such that ASD participants reported higher levels of depression and anxiety and lower levels of social networks, as compared to TD (all $p<0.01$). Based on clinical cutoffs, 75% of the middle-age ASD group reported significant levels of anxiety and 44% reported significant depression, as compared to 45% in the young-adult ASD group for both anxiety and depression. Social network measures did not significantly correlate with mood measures in either middle-age or young-adult ASD participants. In young-adult ASD participants, mood measures significantly predicted performance on several cognitive measures, most pronounced for memory. However, mood measures did not correlate with cognitive performance in the middle-age ASD group. IQ levels did not account for a significant amount of the variance in any dependent measure and effects did not change when values were added as covariates.

Conclusions: Findings suggest older adults with ASD experience greater levels of depression and anxiety and less social support than their TD counterparts. Further, rates of clinically significant anxiety in this sample of older adults with ASD are higher than ever reported in younger samples, including the young-adults in the present study. Interestingly, mood symptoms did not correlate with measures of social support or cognition in middle-age ASD participants. This dissociation between mood and cognition suggests cognitive deficits in older adults with ASD may be mediated by other effects of aging. Further, increased rates of psychiatric symptoms may not be a result of lack of social support in older adults with ASD. Understanding age-related changes and accurately detecting symptoms through measures uniquely designed for the ASD population is essential to providing appropriate care plans and effective treatment interventions for mental health in ASD.

Poster 4

DISSECTING THE ROLE OF NRF2 IN ALZHEIMER'S DISEASE. Branca C, Caccamo A, Dave N, Negrich C, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common type of dementia in the elderly. Growing evidence links oxidative stress and free radical damage to the initiation and progression of AD; however the molecular mechanisms underlying the link between oxidative stress and AD pathogenesis remain elusive. Nrf2 is a master transcriptional regulator that controls the expression of several genes involved in antioxidant response.

Methods: To investigate the involvement of Nrf2 in AD pathogenesis, we used a crossbreeding strategy to remove the Nrf2 gene from the brain of APP/PS1 mice, a widely used model of AD.

Results: We found that removing both copies of the Nrf2 gene from the APP/PS1 mice increased behavioral deficits in several tasks, such as Morris water maze, radial arm water maze, and contextual fear conditioning. These deficits correlated with an increase in amyloid beta (A β) pathology, without affecting the APP processing. Mechanistically, we found that the increase in A β levels was not due to changes in turnover, as we found that autophagy induction and proteasome activity were similar between APP/PS1 with and without Nrf2. In contrast, we found that APP/PS1 mice lacking Nrf2 had higher levels of activated microglia and astrocytes, suggesting that the increase of A β might be mediated by an increase in brain inflammation.

Conclusions: These results provide a better understanding of the role of Nrf2, and oxidative stress in general, in the progression of AD.

Poster 5

CHOLINERGIC DYSFUNCTION AND MUSCARINIC RECEPTOR UNCOUPLING IN ALZHEIMER'S DISEASE. Burkart A, Hamada M, Arthur K, Jones D. Midwestern University; Arizona Alzheimer's Consortium.

Background: The major goal of this study was to characterize the mechanism(s) underlying muscarinic receptor uncoupling in Alzheimer's disease (AD) in a neuroblastoma cell model (SH-5YSY cells) and an AD mouse model (3xTG-AD mouse). Muscarinic receptor signaling is terminated by GRK phosphorylation, followed by β -arrestin binding, which begins the process of receptor uncoupling and internalization. We have demonstrated that muscarinic receptors were uncoupled from G-proteins in brains of patients with Alzheimer's disease (AD), as well as in non-demented controls with substantial β -amyloid deposition and neuritic plaque formation. Levels of β -arrestin were examined in four groups: patients diagnosed with Alzheimer's (AD), age matched controls with many amyloid plaques (MP), age matched controls with sparse plaques (SP), and age-matched controls with no plaques (NP). The extent of plaque formation was measured using an ELISA kit specific for β -amyloid and was positively correlated with loss of cholinergic neurons as assessed by choline acetyltransferase (ChAT) activity.

Methods: Western Immunoblotting, ELISA, IHC

Results: In the current study, using a neuroblastoma cell line that overexpresses APP695 shows that exposure to β -amyloid for 24 hrs caused a both a decrease in GRK-2 and an increase in β -arrestin levels indicating alterations in the coupling of the muscarinic receptor to its g-protein. The extent of uncoupling is positively correlated with an increase in β -amyloid levels as assed by ELISA. Cells overexpressing APP695 had greater levels of muscarinic uncoupling and amyloid levels indicating that increased levels of processing of β -amyloid may contribute to the uncoupling of the muscarinic receptor. Finally, we examined muscarinic receptor uncoupling in the 3xTg-AD mouse model of AD. Preliminary results indicate differences in brain β -arrestin levels at 6 and 9 months of age compared to non-TG control mice.

Conclusions: It is likely that alterations in GRK, coupled with a decrease in β -arrestin, could impair muscarinic receptor and g-protein recycling and contribute to the cholinergic dysfunction associated with AD. Thus, it may be beneficial to circumvent impairment of signal transduction by addressing cholinergic dysfunction in the treatment of Alzheimer's disease.

Poster 6

UNDERSTANDING TOXOPLASMA GONDII'S NEUROPROTECTION AGAINST A β DEPOSITION. Cabral C, Franco J, MacDonald WR, Koshy AA. University of Arizona; Arizona Alzheimer's Consortium.

Background: The generation of toxic beta-amyloid (A β) peptides that aggregate and form deposits or plaques is thought to be a major initiator and potentiator of Alzheimer's disease. Yet, we still lack effective therapies against this target. To broaden our therapeutic options, we have taken the novel approach of harnessing the interaction between the mammalian CNS and the neurotropic parasite *Toxoplasma gondii*. *T.gondii* is a ubiquitous intracellular parasite that naturally causes an asymptomatic chronic CNS infection in humans and rodents, suggesting that the mammalian CNS and *T.gondii* have co-evolved to tolerate each other. While such tolerance clearly benefits the parasite, it may also benefit the host, as suggested by a recent study in a human amyloid precursor protein (hAPP) mouse model that showed that chronic toxoplasmosis was protective against A β deposition and improved cognition (Jung et al Plos Path 2012.)

Methods: To extend this study and establish a model by which we could identify the mechanisms behind *T.gondii*-neuroprotection, we infected a different hAPP mouse model (J20) with one of three canonical *T.gondii* strains (type I, II, or III) and evaluated the CNS at 6 month post-infection (9 months of age) for A β deposition, immune cell infiltration, and global cytokine environment.

Results: We found that only infection with the type II *Toxoplasma* strain was protective against A β deposition (<20% of saline-injected (control) hAPP mice), despite both type II and type III strains establishing a chronic CNS infection. In addition, compared to control mice, both type II and type III- infected mice showed increased T-cell infiltration and elevated CNS pro-inflammatory cytokines, while neither group showed a > 2-fold elevation of TGF β or IL-10. Type II-infected mice had a 100-fold higher parasite burden and less microglial/macrophage activation than type III-infected mice. Type I-infected mice, which only experience an acute infection, showed no differences in any measured parameter compared to control mice.

Conclusions: In summary, we have shown that only type II-infection is associated with protection against A β deposition, and that acute infection has no lasting CNS effect. As type II-infection (protective) was associated with a higher CNS parasite burden and less macrophage activation, we hypothesize that parasite burden and immune cell polarization may be factors in driving the type II-protective effect. We are currently leveraging these *T.gondii* strain-specific differences to identify host pathways and immune cell changes specifically associated with protection against A β deposition. Understanding the mechanistic basis for the type II protection against A β deposition may offer novel therapeutic targets for effectively treating AD.

Poster 7

COMPARISON OF THREE FDG PET ANALYSIS TECHNIQUES IN THE TRACKING OF ALZHEIMER'S DISEASE AND EVALUATION OF DISEASE-MODIFYING TREATMENTS. Chen K, Kuang X, Luo J, Roontiva A, Lee W, Thiyyagura P, Bauer III R, Devadas V, Reiman EM. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: We sought to compare the ability of three different FDG PET image-analysis techniques to track Alzheimer's disease (AD) and evaluate disease-modifying treatments, including: 1) our statistical region of interest (sROI) method, which tracks cerebral glucose metabolism changes in an empirically pre-specified ROI that was found to be preferentially affected by AD, 2) our cross-sectional HCI (C-HCI), which characterizes the extent to which the magnitude and spatial extent of cerebral hypometabolism in each FDG-PET image correspond to that in AD dementia patients, and 3) our new longitudinal HCI (L-HCI) method, which characterizes the extent to which the magnitude and spatial extent of longitudinal cerebral metabolism declines correspond to that in AD dementia patients.

Methods: Baseline and 24-mo PET scans from 399 ADNI subjects were included. The three methods were used to track the AD-related CMRgl decline in amyloid-positive ($A\beta^+$) patients with the clinical diagnoses of probable AD dementia and mild cognitive impairment (MCI) due to AD and in $A\beta^+$ and $A\beta^-$ unimpaired older adults all whose baseline $A\beta^+$ was defined by florbetapir PET.

Results: The magnitude of AD-related CMRgl decline by each method was ranked as dementia due to AD > MCI due to AD > amyloid positive NC > amyloid negative NC ($p < 0.05$). We estimate the respective need for the 70, 94, and 109 AD $A\beta^+$ dementia patients per group and 154, 214, and 441 MCI $A\beta^+$ patients per group using the L-HCI, sROI and C-HCI methods to detect a 25% AD-slowing treatment effect in a twelve-month, multi-center RCT with 80% power and two-tailed $\alpha = 0.05$.

Conclusions: The sROI and L-HCI are capable of characterizing the cerebral glucose metabolism decline over time for patients characterized as $A\beta^+$ at baseline. Our findings provide additional support for the increased power associated with the uses of FDG and amyloid PET in anti- $A\beta$ trials.

Poster 8

ALLOPREGNANOLONE PROMOTES NEURAL STEM CELLS DIFFERENTIATION TO NEURONS AND OLIGODENDROCYTE PRECURSOR CELLS. Chen S, Brinton RD.
University of Arizona; Arizona Alzheimer's Consortium.

Background: Previous studies by our group demonstrate that the endogenous neurogenic steroid Allopregnanolone (Allo) promotes proliferation of both human and rodent neural stem cells (NSCs) *in vitro*, as well as *in vivo* in the triple transgenic mouse model of Alzheimer's disease (3xTgAD). In this study, we investigated the impacts of Allo on neural differentiation.

Methods: NSCs from embryonic rats, adult 3xTgAD mice were cultured for *in vitro* study. NSCs were cultured in differentiation medium containing Allo or vehicle for 7-days, fixed and then labeled neuronal and glial markers. To investigate the impact of Allo on neurogenesis and differentiation *in vivo*, 3xTgAD mice were treated with Allo once per week for 2 weeks and 4 doses of BrdU were injected. Brain tissue were collected and frozen for flow cytometry and immunoblotting analyses. Fixed brain tissue was prepared for immunohistochemistry studies.

Results: Allo significantly increased the ratio of MAP2-positive-neurons to GFAP-positive-astrocytes from embryonic rat and adult mouse NSCs. To further determine the *in vivo* effects of Allo, we investigated the impacts of Allo on neuronal differentiation in 5-month-old male 3xTgAD mice. Flow cytometry analysis of new generated cells indicated that Allo increased the number of newly generated neurons as indicated by the increase in the number of BrdU positive cells and BrdU/NeuN double positive cells. Allo enhanced expression of the neural proliferation marker, proliferation cell nuclear antigen, and the immature neuronal marker doublecortin, which was further confirmed by immunohistochemistry studies. Allo also increased the expression of Olig2, an oligodendrocyte precursor cell marker. The increases in neuronal and oligodendrocyte differentiation by Allo was paralleled by an increase in Brain-Derived Neurotrophic Factor.

Conclusions: Allo promotes neuronal differentiation from both embryonic rat and adult mouse neural stem cells *in vitro*. Allo increased neural stem cell differentiation in 3xTgAD mouse *in vivo*, as shown in flow cytometry analyses BrdU and BrdU/NeuN double positive cells increased, higher level PCNA and DCX expression in Western blot and more proliferation marker Ki67, immature neural marker DCX and mature neural marker NeuN were observed in Allo treatment brain. Allo treatment increased oligodendrocyte precursor cells. Collectively these findings suggest that Allo is a regenerative therapeutic candidate to prevent or delay neurogenic deficits associated with mild cognitive impairment and Alzheimer's disease.

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Poster 9

DIFFERENTIAL PATTERN OF ALTERED GENE EXPRESSION AMONG BRAIN REGIONS IN AGING AND ALZHEIMER'S DISEASE. Coleman PD, Mastroeni D, Delvaux E, Nolz J, Berchtold N, Cotman C. Arizona State University; Banner Sun Health Research Institute; University of California, Irvine; Arizona Alzheimer's Consortium.

Background: The relationship between "normal" aging and Alzheimer's disease has long been a subject for speculation. The fact that age is the major risk factor for sporadic Alzheimer's disease has led some to speculate that if we lived long enough we would all get Alzheimer's disease. On the other hand, examples of centenarians who remain cognitively intact suggest otherwise. At a molecular level, multiple studies have indicated correlated changes of gene expression in aging and AD. However these studies have, for the most part, been conducted in brain regions, such as association cortex, that are affected by both age and AD. We examined expression of synapse-related genes as a function of age and Alzheimer's in multiple brain regions, including one (primary somato-sensory neocortex of the post central gyrus) that is essentially unaffected in Alzheimer's disease.

Methods: 400 brain samples were obtained from 7 Alzheimer Disease Research Centers (ADRC or ADCC). Cases ranged in age from 20 to 100 years old. A subset of the older cases had been diagnosed with neuropathologically confirmed Alzheimer's disease. Four brain regions were sampled: hippocampus, entorhinal cortex, frontal association cortex and post central gyrus. The resulting samples were homogenized, RNA extracted and checked for quality. RNA samples were processed and hybridized to ~400 Affymetrix Hg-U133 plus 2.0 arrays at the University of California, Irvine. Expression values were determined from CEL files using GC-RMA and statistical analysis was conducted using GeneSpring 7.3.1. This resulted in a list of 662 probe sets which was reduced to 562 probe sets by the elimination of probe sets that were absent on more than 50% of the chips. These probe sets represented 340 synaptic genes. Significant probe sets were determined as previously described (Berchtold et al., 2008). Regression analyses were used to examine relationships between the effects of age and of AD on the expression of synapse-related genes among the 4 brain regions studied.

Results: Expression of synaptic genes in the postcentral gyrus was unchanged in Alzheimer's disease. However, this brain region exhibited major decreases of gene expression as a function of age. The correlation between expression changes in the aged postcentral gyrus with Alzheimer-related expression changes in the Alzheimer hippocampus was +0.89. Since the hippocampus is a source of both age and disease related changes we removed the age effect from the hippocampus data by means of partial regression analysis, which reduced the correlation to +0.82.

Conclusions: These data are consistent with the concept that cells have a limited repertoire of responses to stress, in this case stresses related to age or to Alzheimer's disease. However, the present findings that similar changes in gene expression are found in two different brain regions as a function of either aging or AD convincingly indicates that although age and AD may lead to similar expression profiles they do so in different brain regions. A conclusion that brain regions are differentially affected by age and by Alzheimer's disease provides persuasive evidence that these two are not the same. This conclusion is consistent with the conclusion reached in an unbiased stereological study of cell numbers in the sub regions of the hippocampus in the aging and Alzheimer's human brain showing that CA1 loses neurons in AD but not in aging (West et al., 1994)

Acknowledgments: Supported by R01 to C Cotman and 1R01AG036400 to PDC.

Poster 10

AN INTERDISCIPLINARY MUSIC-BASED INTERVENTION FOR PEOPLE WITH ADVANCED ADRD. Coon DW, Rosas V, Frye M, McCarthy M, O'Toole L, Rio R, Bontrager V, Todd M, Burluson M. Arizona State University; Dignity Health/St. Joseph's Medical Center; The Phoenix Symphony; Arizona Alzheimer's Consortium.

Background: This presentation focuses on the delivery of a unique music-based community-level intervention protocol provided to groups of residents with moderate to severe dementia residing in assisted-living directed care. It discusses findings related to the impact of this interdisciplinary (music, music therapy, nursing and behavioral science) protocol on quality of life indicators for project participants. The protocol was derived from the research team's experience as well as data from 5 focus groups (N=50) conducted separately with family caregivers, facility staff, and symphony musicians. Focus groups gathered participant perceptions of music's impact on people, including those with dementia, as well as ways to use music to enrich interactions between residents and others. Additionally, a model that integrated three parameters (receptive to active; observation to relationship; planned to improvisation) also emerged, and helped distinguish the weekly programs as music therapy was blended with music performance across time.

Methods: The intervention provided 7 music-based events across 6 weeks delivered primarily in groups of 4-5 symphony musicians and 10-12 residents. While the intervention was offered to the entire community, data was only collected on those with signed consent forms. Trained nurse raters evaluated resident affect before and after each music event while symphony musicians, facility staff, and family caregivers completed similar self-ratings. All participants and nurse raters (for residents) also provided ratings of structure and process of the intervention and the perceived benefit of the intervention for residents and themselves. Saliva samples were collected on all participants immediately before and after several of the events to investigate the impact on biomarkers of stress (salivary alpha-amylase and cortisol). A small sub-study also investigated the impact of music-events on a resident stressor (i.e. afternoon bathing).

Results: Results for this presentation focus primarily on residents (N=30) and musicians (N=19), since the schedules of facility staff and family caregivers precluded regular attendance at the events. Ratings of residents and self-ratings by musicians support the intervention's impact in terms of increases in positive mood and decreases in negative mood. Analyses of the salivary alpha-amylase coupled with mood ratings indicate that both residents and musicians experienced positive behavioral activation as a result of the music-based events. Results from the sub-study suggest that experiencing music events in the morning appears to have enabled the residents to better regulate their stress responses as measured by salivary cortisol around bathing later the same day. Ratings of perceived benefit across all types of participants were very high.

Conclusions: This community-level music-based project was feasible and acceptable and had a positive impact on quality of life indicators for both residents and the symphony musicians. Ratings of mood and behavior also supported the model that helped guide the protocol. These positive findings, including the impact of morning music events on a stressor later that same day, support the need for continued work around this protocol through a larger randomized trial.

Poster 11

LENALIDOMIDE TO MODULATE BRAIN BACE1 EXPRESSION. Decourt B, Grover AC, Macias MP, Walker A, Gonzales A, Malek-Ahmadi M, Sabbagh MN. Arizona State University; Banner Sun Health Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Currently, there is no cure for Alzheimer's disease (AD). Mounting genetic and pharmacological evidence implicates TNF α signaling in the disease progression. Previous reports showed that deletion of TNF receptor I decreased amyloid loads in the brain of AD transgenic mouse models. Recently, TNF α inhibitors of the thalidomide family have been used to reduce brain inflammation in AD models, which also resulted in lower amyloid pathology, though the molecular mechanisms remain unclear. In the present study we hypothesized that lenalidomide, a thalidomide analog approved by the FDA for human myeloplastic malignancies, could reduce brain BACE1 levels at early stages of AD-like pathology in APP23 mice.

Methods: The effects of lenalidomide 100 mg/kg administered intraperitoneally for 4 and 12 weeks to APP23 mice were evaluated. Non-transgenic (WT) littermates were used as controls. After sacrifice, brains were hemisected and used in histological and biochemical experiments. Brain sections were immunostained with an anti-amyloid beta antibody (6E10) and counterstained with thioflavin S. Quantitative PCR and Western blotting for TNF-alpha precursor and BACE1 were conducted on the cortex from the same animals. In addition, Western blots were conducted on whole half-brain (4 weeks of drug administration) and isolated brain regions (12 weeks of drug administration) lysates.

Results: Quantitative PCR showed lenalidomide decreased TNF α levels in both cortex and hippocampus. Western blots revealed a significant reduction in brain transmembrane BACE1 levels by 20% compared to vehicle. This was accompanied by a decrease in the number of total and dense cortical amyloid plaques, as well as a trend towards lower brain insoluble A β 40 and A β 42 levels. Interestingly, lenalidomide reduced immature BACE1 levels back to non-transgenic littermates physiological levels in APP23 mice. Finally, qPCR analysis suggested that lenalidomide decreases BACE1 mRNA levels in the cortex and hippocampus of APP23 mice. Our results echoed those reported in a heterozygous BACE1 mouse model of AD.

Conclusions: Our data suggest that the pluripotency of lenalidomide, i.e. anti-inflammatory and BACE1 modulation properties, could help preventing or slowing several AD neuropathological hallmarks. Additional experiments using animal models of tau pathology are in progress. If confirmed, our data will provide grounds for the rapid translation of lenalidomide for clinical application and therapeutic trials since the drug is already FDA-approved.

Poster 12

MULTIVARIATE ANALYSIS OF GENE EXPRESSION OF PERIPHERAL BLOOD LEUKOCYTES DIFFERENTIATES PERSONS AT RISK FOR ALZHEIMER'S DISEASE FROM PERSONS NOT AT RISK. Delvaux E, Mastroeni D, Nolz J, Marshall F, Coleman PD. Arizona State University; Banner Sun Health Research Institute; University of Rochester Medical Center; Arizona Alzheimer's Consortium.

Background: Multiple imaging, neuropathological, cognitive and molecular studies have established that Alzheimer's disease has a very long "preclinical" phase during which the disease is damaging nerve cells. The lack of success of current therapeutic interventions in clinically diagnosed persons has led to a shift in conceptual framework toward treating the disease prior to the point at which disease has become serious enough for clinical diagnosis. Although imaging and other methods are able to detect early stages of disease their expense, time consuming or intrusive nature preclude their utility for detecting disease in the general population. An inexpensive and minimally invasive method of detecting early Alzheimer's disease is needed.

Methods: Longitudinal blood samples were obtained from 253 persons enrolled in the University of Rochester arm of the ADAPT (Alzheimer's Disease Anti-Inflammatory Prevention Trial) Study. At entry, all persons were clinically determined to be cognitively intact. Inclusion criteria were age 70 or greater and having at least one first degree relative who had been diagnosed with Alzheimer's disease or "dementia". 2/7 of study participants were on Naproxen, 2/7 on Celebrex and 3/7 on placebo. Five years after entry into the study 32 persons had phenoconverted to Alzheimer's disease and 10 of these had been on placebo. We formed three groups of age and gender matched cases: (1) Those at risk that had phenoconverted to AD, (2) those at risk that had not phenoconverted to AD and (3) a matched group not at risk for AD. This third group was formed because of evidence indicating that cognitively intact persons who had a first degree relative diagnosed with AD showed changes detected by imaging and other studies. Blood was collected into PaxGene tubes, RNA extracted and expression of selected genes quantified by qPCR. Multivariate analysis of expression of a selected set of transcripts was used to quantify differences among groups in patterns of gene expression. Analysis of data was limited to persons who were on placebo.

Results: Multivariate analysis of gene expression by peripheral blood leukocytes was not convincingly able to distinguish persons at risk who had phenoconverted to AD from persons at risk who had not phenoconverted to AD. We assert that this is because these persons were well along the path toward a clinical diagnosis of AD. However, the distinction of persons not at risk from those at risk was 100% accurate. Thus, we were able to distinguish risk on the basis of having a first degree relative diagnosed with AD or dementia. This finding suggests, but does not formally prove, that the procedure we have developed may be able to determine risk of a future diagnosis of AD that is not based on having a first degree relative that has been diagnosed with AD.

Other data demonstrate the ability of this procedure to distinguish Alzheimer's from Parkinson's disease, thus indicating the specificity of the procedure we have developed.

Conclusions: The present data establish RNA extracted from peripheral blood leukocytes as a promising biomarker of Alzheimer's disease. Although the numbers of cases in the present study is relatively small, the data clearly indicate the potential for development of a minimally invasive, potentially inexpensive blood test for detection of persons at risk for a future diagnosis of Alzheimer's disease. Acknowledgments: Thanks to the ADAPT study, led by John C Breitner. Supported by AG R21AG030429 to PDC and by an Anonymous Donor.

EVIDENCE FOR LYMPHOCYTE INFILTRATION DURING PERIMENOPAUSAL TRANSITION: IMPLICATIONS FOR PRODRONTAL PHASE OF ALZHEIMER'S DISEASE. Desai MK, Yin F, Mao Z, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Menopause or reproductive senescence is characterized by major physiological changes not only in the endocrinological and reproductive system but also in energy metabolism, cognitive function, bone-mineral density and cardiovascular activity which influences susceptibility to diseases. In our aging society, increased morbidity encountered in the menopausal age group makes the study of menopause related changes all the more imperative. Perimenopause is the transition stage during which these changes are initiated. A rat model previously developed to reflect the physiological characteristics of the human menopausal transition included regular and irregular cyclers as well as acyclic female rats of the same age. This model accounts for both chronological and endocrinological changes originating during perimenopause. In the current study we sought to investigate the differential regulation of genes in the hippocampi of the various groups of female rats by sequencing hippocampal total RNA.

Methods: We carried out paired end sequencing of hippocampal RNA with read length of 50 base pairs and a read depth of ~50 million reads per sample using Illumina HiSeq 2500. Raw data files in the FASTQ format underwent QA/QC and trimming procedure in the cloud-based Partek Flow environment (<http://www.partek.com/>). The paired end reads for each sample were then aligned using TopHat to the rat reference genome rn6 (Ensembl 80). Transcript assembly and quantification of aligned reads were carried out using Cufflinks. The Cufflinks output consisted of a list of differentially expressed genes (DEG) for each comparison. The DEG lists were then uploaded into Ingenuity Pathway Analysis (IPA) software to explore differential regulation of critical pathways during the perimenopausal transition.

Results: IPA showed activation of pathways of lymphocytic proliferation and differentiation during the transition from regular to irregular estrus cycling and inactivation of pathways responsible for T cell apoptosis. RNAseq also detected a decrease in platelet-derived growth factor (PDGF) activity, in response to decreased estrogen, indicating increased blood brain barrier permeability in the perimenopausal hippocampus. Analyses of significantly differentially expressed genes (DEG) using PANTHER (<http://pantherdb.org/index.jsp>) revealed enrichment of B and T lymphocyte genes. Interestingly, Interleukin-27 a T lymphocyte regulator was found to be down-regulated during the perimenopausal transition, reinforcing the hypothesis that T lymphocyte dysregulation is an important feature of perimenopausal transition.

Conclusions: Perimenopause is a state of dynamic flux with significant changes occurring in different pathways in the hippocampus resulting from increased blood brain barrier permeability, increased inflammatory T cell infiltration and immune dysregulation which has critical bearing on the cognitive decline experienced during and after menopausal transition and relevant to initiation of the prodromal phase of Alzheimer's disease.

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Poster 14

ENHANCED BETA BAND ACTIVITY IN THE AGED AMYGDALA DURING PROBABILISTIC DECISION MAKING. Duarte L, Samson RD, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: With aging, older adults tend to use strategies that differ from those used by young adults to solve decision making tasks. When compared to young adults, older adults perform better in tasks that are best solved with a win-stay-lose-shift strategy. The amygdala is known to be involved in both the acquisition and maintenance of optimal probabilistic decision making strategies.

Methods: We recorded single units and local field potentials from this structure in young and aged rats for up to fifty days as they learned three versions of a decision making task. Two versions were discrimination tasks in which either the reward magnitude (reward magnitude discrimination) or the probability of receiving a reward (probability discrimination) was manipulated. The third version was a probability discounting task in which rats had a choice between a small/certain reward and a large/uncertain reward (probability discounting).

Results: In aged rats, we found increased oscillatory power in the beta range (20-40Hz, peak ~24 Hz) in the basolateral complex of the amygdala (BLA). These increases occurred in the delay between the chosen lever presses and resulting outcomes, and lasted for ~1 second. Beta band oscillations were not observed in the younger rats. This effect was not present immediately, but developed after an acquisition period of ~ 6 days in aged rats. Furthermore, the effect was only present in the reward magnitude discrimination and probability discounting tasks. It was of higher amplitude during free choice trials, for both tasks. While beta band activity increased in all aged rats, some showed a stronger increase after choosing the uncertain/large reward, while others showed greater increases in beta power after choosing the certain/small reward. This effect was present in spite of the consistent finding that the old animals all became more risk averse over training compared to the younger animals. Beta power did not increase during the probability discrimination task. One possible explanation for this observation is that this task was only administered for 6 days. This may have been too brief a period for the increased beta band power to emerge. Since behavioral performance on the reward magnitude discrimination version of the task was similar between age groups, this suggests the possibility that aging, rather than differences in behavior, impacts BLA networks in a way that promotes the emergence of beta band activity.

Conclusions: Because beta oscillation increases occur in associative learning and motor function, it is possible that our findings reflect a compensatory mechanism in the amygdala of aged rats, which supports the instrumental associations formed during probabilistic decision making.

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Poster 15

CULTURAL BIAS IN MEMORY SCREENING OF AMERICAN INDIAN INDIVIDUALS IN ARIZONA. Ewbank C, Dougherty J, Lomay V. UA College of Medicine Phoenix; Banner Alzheimer's Institute; Salt River Pima Indian Community; Arizona Alzheimer's Consortium.

Background: Purpose: To compare cultural bias in the SWICA (Southwest Indigenous Cognitive Assessment), a novel tool for memory screening AI older adults in Arizona, with the MoCA (Montreal Cognitive Assessment), a validated memory screening tool in common use.

Methods: Retrospective comparison of coded participant responses to 16 questions about their cultural context. Intrasample variation on MoCA and SWICA tests was controlled by using the participants as their own controls. Data were analyzed using a multiple regression general linear model on SPSS software.

Results: Scores on the SWICA test were independently associated with English use in the home (Beta = .396, $p = .026$), years of education (Beta = .335, $p = .027$), and ease of learning (Beta = .361, $p = .029$), but not age (Beta = .366, $p = .054$). Scores on the MoCA test were independently associated with age (Beta = -.491, $p = .001$), English use in the home (Beta = -.320, $p = .039$), and years of education (Beta = -.284, $p = .030$), but not ease of learning (Beta = -.267, $p = .067$).

Conclusions: Scores were similar on both tests ($t=3.934$, $p=.001$), and were independently associated with English use in the home and years of education. SWICA was uniquely associated with ease of learning and MoCA was uniquely associated

Poster 16

IDENTIFICATION OF LEARNING-INDUCED CHANGES IN PROTEIN NETWORKS IN THE HIPPOCAMPI OF 3XTG-AD MICE. Ferreira E, Shaw DM, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Memory loss is the most profound clinical manifestation in Alzheimer's disease (AD); however, the molecular mechanisms underlying these deficits are poorly understood. Identification of the molecular pathways involved in the onset of cognitive deficits may lead to the identification of key events in the pathogenesis of AD

Methods: Using isobaric tags (iTRAQ) and proteomic methods, here we identified learning-induced changes in the hippocampal proteome of non-transgenic (NonTg) and 3xTg-AD mice, a widely used animal model of AD.

Results: We found that the expression of 192 proteins was differentially regulated by learning in NonTg mice. Notably, of these 192 proteins, only 28 were also differentially regulated by learning in 3xTg-AD mice, whereas the levels of 164 proteins were uniquely changed in NonTg mice but not in 3xTg-AD mice. These data suggest that during learning, 3xTg-AD mice fail to differentially regulate 164 proteins.

Conclusions: Gene ontology and protein interaction analyses indicated that these proteins were overrepresented in RNA processing, specifically RNA splicing and mRNA translation initiation pathways. These findings demonstrate that mRNA processing events that take place during learning and memory are significantly affected by AD pathogenesis.

Poster 17

DENSITY ASSESSMENT OF SYNUCLEINOPATHY-AFFECTED NERVE FIBERS IN SUBMANDIBULAR GLAND BIOPSIES OF PARKINSON'S DISEASE SUBJECTS.

Glass M, Adler CH, Serrano G, Intorcchia A, Filon J, Sue LI, Garcia A, Callan M, Walker J, Maarouf C, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Low clinical diagnostic accuracy, particularly at early disease stages, is a critical roadblock to finding new therapies for Parkinson's disease (PD). Brain biopsy has been avoided because of potential risks but biopsy of a peripheral site might provide improved diagnostic accuracy. Previously, we have reported, on the basis of results from a large autopsy survey and two clinical trials of needle core biopsy, that the submandibular gland (SMG) is a promising and safe biopsy site. Lewy-type synucleinopathy (LTS) was found in up to 91% of subjects with Parkinson disease in our autopsy series and 74% in our clinical trials. In addition to being a useful diagnostic biomarker of disease presence or absence, we intend to determine whether SMG biopsies might provide useful prediction of prognosis or be reflective of disease progression. Such information would need to be quantitative, or at least semi-quantitative.

Methods: Here we present pilot data utilizing a semi-quantitative method to assess whether the density of LTS within SMG biopsies correlates with disease duration or clinical severity.

Results: Our results support previous qualitative observations that LTS is present at variable densities between individuals; in some cases only single affected fibers are present while in others LTS affects up to 25% of all fibers.

Conclusions: There is a poor correlation between fiber density and clinical status. However, as total fiber density is quite variable, we will determine whether the ratio of LTS-affected fibers to total nerve fibers is a better predictor of clinical measures. If the method proves promising, it may be incorporated into an ongoing multi-center study of SMG biopsy for PD. Funded by the Michael J. Fox Foundation for Parkinson's Research.

Poster 18

EMOTIONAL MEMORY: A PRE-CLINICAL COGNITIVE MARKER OF ALZHEIMER'S DISEASE? Grilli MD, Woolverton CB, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

Background: The $\epsilon 4$ polymorphism of APOE is associated with increased risk for late-onset Alzheimer's disease (AD). Prior research has established that $\epsilon 4$ carriers exhibit signs of structural and functional brain abnormalities long before the possible expression of mild cognitive impairment or dementia. The identification of cognitive deficits associated with these brain abnormalities could lead to improved diagnosis of AD, and inspire novel therapeutics. Targets of pre-clinical abnormalities in $\epsilon 4$ carriers include the amygdala, prefrontal cortex, and hippocampus. Critically, these brain regions support the emotional memory enhancement effect: the finding that emotional information is remembered better than non-emotional information. Interestingly, although previous research has revealed that older adults with mild cognitive impairment and AD do not demonstrate normal emotional memory enhancement effects, no study has investigated this memory effect in $\epsilon 4$ carriers who have not exhibited clinical signs of cognitive decline. Therefore, the present study investigated whether the emotional memory enhancement effect is attenuated in non-demented older adult $\epsilon 4$ carriers relative to non-carriers.

Methods: 42 community-dwelling, cognitively intact older adults (20 $\epsilon 4$ carriers and 22 non-carriers) participated in this study. Groups were matched on age and education, and there were no group differences on standard neuropsychological measures of memory or executive functioning/working memory capacity. The novel emotional memory test required intentionally studying emotional and non-emotional sentences in three study phases (each with a different encoding strategy). After completing all three study phases, participants were administered a yes-no recognition memory test for the studied sentences and an equal number of new sentences.

Results: Older adult non-carriers demonstrated the typical emotional memory enhancement effect, i.e. better recognition memory for emotional sentences relative to non-emotional sentences (overall proportion correct was .61 for emotional sentences and .52 for non-emotional sentences). In contrast, the emotional memory enhancement effect was virtually abolished in older adult $\epsilon 4$ carriers (overall proportion correct was .49 for emotional sentences and .48 for non-emotional sentences). The memory deficit was specific to recognition memory for emotional sentences, as carriers and non-carriers did not differ in memory for non-emotional sentences.

Conclusions: This study is the first to show that cognitively healthy older adult $\epsilon 4$ carriers do not exhibit the well-established emotional memory enhancement effect. These results indicate that, despite performing within normal limits on standardized neuropsychological tests of learning and memory, $\epsilon 4$ carriers have a striking deficit in emotional memory. This raises the possibility that impairment in emotional memory may be a pre-clinical cognitive marker of AD pathology.

Poster 19

FORMATIVE EVALUATION OF THE NATIONAL FAMILY CAREGIVER OUTREACH PROGRAM. Han E, Park M, Han D, Kim Y, Lee J. Health Insurance Policy Research Institute; Chungnam National University, Daejeon, South Korea; Arizona State University; Ministry of Health & Welfare, KAIST Graduate Program for Future Strategy; Arizona Alzheimer's Consortium.

Background: Family caregivers without support and formal education are vulnerable for social isolation and depressive symptom. Especially, dementia family caregivers are more vulnerable to negative caregiving outcomes. There has been a lack of individualized, home-based intervention since most family caregiver interventions were group based. The purpose of this study was to develop the home based community outreach caregiver program to guide family caregivers' caregiving journey.

Methods: A pilot implementation to assess feasibility of the program was conducted. The evidence based manual for program provider and family caregiver were developed and disseminated across the long term care insurance centers and mental health centers in Korea. The program consisted of 6 visiting, 3 telephone, and 2 group sessions and comprised multi-dimensional components including 12 centers involved and were assigned to the experimental and control group. Family and long-term care recipients dyads completed the intervention. Participants were interviewed at baseline and at the end of sessions. As outcome variables, caregiver's burden, depression, positive aspects of caregiving, quality of life and the patients' neuropsychiatric behavioral inventory (NPI) and other health related characteristics were measured. Satisfaction of the program was assessed after completion of the program.

Results: The program significantly reduced caregiver's depression and burden in experimental group compared to the control group. Family caregivers were satisfied with general program. Caregivers were very satisfied with the contents, the type of activity, and the program provider. Above all, family caregivers showed highest satisfaction in networking with other family caregivers in group activities, social support, and self-health management.

Conclusions: The results indicate that the individualized community outreach home based intervention for family caregivers has positive influences on caregiving related burden and depression. The next objective of this project will be to disseminate it into the community centers at national levels. * This research was supported by research fund by National Health Insurance Service, Health Insurance Policy Research Institute, Ministry of Health and Welfare, and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning(NRF. 2013R1A2A2A01069090).

ALZHEIMER'S PREVENTION REGISTRY: A SHARED RESOURCE TO THE SCIENTIFIC COMMUNITY TO FACILITATE ENROLLMENT IN STUDIES. High N, Gordon D, Nichols J, Aisen PS, Albert MS, Comer M, Cummings JL, Manly JJ, Petersen RC, Sperling RA, Strobel G, Weiner MW, Reiman EM, Tariot PN, Langbaum JB. Banner Alzheimer's Institute; University of California San Diego; Johns Hopkins University School of Medicine; Geoffrey Beene Foundation Alzheimer's Initiative; Cleveland Clinic Lou Ruvo Center for Brain Health; Columbia University; Mayo Clinic; Harvard Medical School; Alzforum; University of California San Francisco; Arizona Alzheimer's Consortium.

Background: Recruitment and enrollment into clinical trials is a major obstacle faced by researchers and study sponsors. It has been estimated that fewer than 10% of Americans participate in clinical trials, mostly due to lack of awareness about study opportunities, resulting in approximately 80% of research studies failing to meet their enrollment goals in the stated timeframes. Given the growing number of preclinical treatment trials being conducted or in the planning stages, we developed a web-based Alzheimer's Prevention Registry ("Registry") to help studies make enrollment more efficient and timely. The Registry is intended to provide a shared resource to the AD scientific community to facilitate enrollment in preclinical studies and to complement and enhance local recruitment efforts.

Methods: Prior to creating the Registry, a national survey of 1,024 adults age 18-75 was conducted for to help guide Registry development and outreach strategy. Interested adults of all ages, with and without memory and thinking problems, are eligible to join at www.endALZnow.org. The Registry was designed to have a low threshold of commitment at entry. At enrollment, individuals are asked to provide their first name, last name, email address, zip code and year of birth; after enrollment they can complete additional contact and demographic information at their convenience and discretion. Enrollees receive regular email communication to keep them apprised of the latest news in Alzheimer's prevention research as well as when study opportunities become available in their communities, with information on whom to contact to explore the possibility of their participation. Beginning in Q3 2016, Registry members will be given the opportunity to share his/her contact information with study site staff in order to be contacted about their study interest. Referrals from the Registry to study sites will be populated on a research referral dashboard that will be used to track referrals and outcomes.

Results: The national survey found that 60% were likely to join the Registry, with the biggest motivators for joining being to prevent themselves (73%) or a loved one (77%) from developing AD and believing that clinical trials are key to medical breakthroughs (72%). As of February 2016, over 212,000 individuals have joined the Registry. Registrants are predominantly women (78%), report a family history of dementia (70%) and have no diagnosis of cognitive impairment (89%). 36% of enrollees are between the ages of 46-60; 40% are between the ages of 61-75.

Conclusion: The Registry is an engaged community of individuals who want to stay abreast of the latest in Alzheimer's news and scientific advances, and to be connected to research studies. Trials such as the ADCS "A4" Trial, the Alzheimer's Prevention Initiative (API) Generation Study as well as early AD trials will utilize the Registry to aid with recruitment. The planned Research Referral Dashboard will enable us to report the success of Registry in facilitating enrollment into these and other studies. We continue to explore novel approaches for increasing enrollment and engagement of enrollees, as well as collaborating with researchers to help promote relevant studies taking place in their catchment areas.

Poster 21

ADDING REFERENCE MEMORY TO A WORKING MEMORY MAZE TASK ALTERS THE PATTERN OF AGE-RELATED IMPAIRMENT IN RATS: ASSOCIATIONS WITH CHOLINE ACETYLTRANSFERASE ACTIVITY IN DISCRETE BRAIN REGIONS. Hiroi R, Prakapenka AV, Poisson M, Kirshner Z, Castaneda AJ, Gibbs RB, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium; Barrow Neurological Institute; University of Pittsburgh School of Pharmacy.

Background: Rodent studies demonstrate that age-related detriments are particularly pronounced for the ability to handle an increasing working memory load in spatial tasks such as the water radial-arm maze (WRAM). However, the extent of age-related cognitive changes may be impacted by the memory domains required to solve the task. Using the WRAM, in young, middle-aged, and aged rats, our laboratory has noted that as working memory load increases, not only do errors in working memory arms increase, but errors into reference memory arms increase as well. This suggests that working and reference memory are linked and that demanding use of both memory types simultaneously can impact performance outcomes.

Methods: Here, we tested whether the addition of a reference memory component impacted working memory performance in young (6 mos) vs aged (21 mos) female rats. Four groups were tested. One young and one aged group were tested on an 8-arm WRAM task requiring working memory only, with 7/8 arms containing platform escape. Another young and another aged group were tested on a 12-arm WRAM task that also had 7/12 arms containing platform escape, plus 5 reference memory arms with no platform. Performance comparison of the mazes enables evaluation of age-related changes in the ability to handle a working memory load with or without distinct reference memory requirements. Because there are critical links between the cholinergic system, aging, and performance, choline acetyltransferase (ChAT) activity was assayed in several brain regions after testing.

Results: Results showed all rats performed worse in the 12-arm vs the 8-arm maze, and there was a larger age effect in the 8-arm, working memory only, version. Trajectories of learning to handle a working memory load differed by age, and this was impacted by whether the distinct reference memory component was present. Moreover, there was an age-related increase in ventral hippocampus and frontal cortex ChAT activity. Analyses to parse out relations between the cholinergic system and memory-specific abilities in young versus aged animals are currently being pursued.

Conclusions: Understanding region-specific relationships between the cholinergic system and prowess for different memory types may unveil distinct neurocircuitries underlying age-related changes in memory.

LONG-TERM STORAGE EFFECTS ON IMMUNOHISTOCHEMICAL AND HISTOCHEMICAL NEURODEGENERATIVE DIAGNOSTIC STAINING OF ARCHIVED PARAFFIN SECTIONS. Intorcía A, García A, Glass M, Filon J, Walker J, Maarouf C, Callan M, Sue LI, Beach TG, Serrano G. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: It is a common practice in histology laboratories to take extra sections at the time of sectioning and store them for possible future usage. There has long been conjecture about whether long-term storage, with exposure of the exposed tissue to oxygen, might alter the staining properties of such tissue, but not many studies confirm such effects.

Methods: In this study we compared the staining in paraffin sections of cerebral cortex that had been stored at room temperature over time periods ranging from months to several years with sections from the same blocks that had been freshly-cut (and hence protected against oxygen exposure as compared to stored sections). Sections were stained with hematoxylin and eosin, thioflavin S and primary antibodies against phosphorylated-tau protein (p-tau; clone AT8; Thermo Scientist), A β peptide (A β ; clone 6E10; Covance), phosphorylated- α -synuclein (p-syn) and phosphorylated TDP-43 (p-TDP; both p-syn and p-TDP were privately obtained from Dr. Haru Akiyama, Tokyo, Japan). The methods used for p-tau, p-syn, A β and pTDP were identical except for the usage of differing epitope exposure methods: 20 minutes in 80% formic acid for p-tau and A β , 20 minutes in boiling 0.1 M sodium citrate for p-TDP, and proteinase K for p-synuclein. Primary antibody concentrations were 1:1,000 for p-tau and A β and 1:10,000 for p-syn and p-TDP.

Results: Initial results of blinded semi-quantitation of staining density suggests that long term storage of paraffin sections has no detectable effects on the staining density of p-tau, p-syn or A β , but staining of p-TDP may be progressively reduced with prolonged storage.

Conclusions: Pathological protein and peptide aggregates in stored tissue sections may be protected from oxidation while unaggregated polypeptides may be exposed and partially degraded. Funded by the Michael J Fox Foundation for Parkinson's Research.

REGULATION OF LXR AND PXR MECHANISMS BY ALLOPREGNANOLONE TO PROMOTE CLEARANCE OF AMYLOID-BETA AND CHOLESTEROL HOMEOSTASIS: THERAPEUTIC POTENTIAL FOR ALZHEIMER'S DISEASE. Irwin RW, Swanson HM, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: We aim to develop Allopregnanolone (Allo) as the first regenerative therapeutic for Alzheimer's disease. Previously we demonstrated that Allo increases expression of two ligand-dependent nuclear receptors, liver-X-receptor (LXR) and pregnane-X-receptor (PXR), coinciding with reduced amyloid-beta ($A\beta$) and neuroinflammatory burden. A series of studies were conducted to evaluate the binding properties of Allo to LXR and to PXR and to determine subsequent *in vivo* effects on specific genes and proteins implicated in Alzheimer's pathology.

Methods: Crystal structures were downloaded from the Protein Data Bank for PXR/RXR α , LXR β , and LXR α /RXR β . Docking calculations were carried out using DockingServer. Lipoprotein Signaling and Cholesterol Metabolism gene array and western blots for protein expression were performed for hippocampus and cortex tissue from 3xTgAD mouse.

Results: The K_i for Allo (LXR β 0.12 μ M, PXR 1.17 μ M) was comparable to known ligands for each receptor indicating that the configuration and composition is compatible for each of the receptors. The free energy of binding for Allo (LXR β -9.44 kcal/mol, PXR -8.49 kcal/mol) signified favorable protein-ligand associations. Allo decreased gene expression of OLR1 and PCSK9 that promote cholesterol efflux and reduce inflammation. Allo also increased the gene expression of CXCL16, LRP6, HMGSC1, and Cyp51 involved in stimulation of the PI3K/Akt/Erk and Wnt pathways and cholesterol synthesis pathway. STAB2 and Idi2 genes were increased suggesting a reduction in neuroinflammation. Allo also decreased PCSK9 and AKR1D1 genes that promote cholesterol efflux while decreased ANGPTL3 provides a mechanism for reducing plasma cholesterol levels. Allo increased LXR β , LDL-R, SORL1, ABCA1, Cyp46a1, and decreased NF- κ B protein expression in 3xTgAD male mice.

Conclusions: The results suggest that Allo directly activates both LXR and PXR to coordinate regulation of important genes and pathways implicated in Alzheimer's pathology. Our studies further support Allo's therapeutic potential to systematically control multiple genes implicated in neuroinflammation, apoptosis, $A\beta$ trafficking, and cholesterol clearance. Taken together, these data provide pre-clinical evidence for allopregnanolone as a multifaceted regenerative therapeutic that may play a significant role in preventing AD pathogenesis. Early phase dose-escalating clinical studies (placebo-controlled) are underway in men and women age 55+ with MCI/earlyAD (NCT02221622) to determine the appropriate dose for Phase 2 trials.

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SPECIFICITY OF PAN-FUNGAL PCR PRIMERS FOR DETECTION OF FUNGAL PATHOGENS IN ALZHEIMER'S DISEASE PATIENT TISSUE. Jentarra G, Chavira B, Potter P, Vallejo J, Jones B, Tullot T. Midwestern University; Arizona Alzheimer's Consortium.

Background: Following reports of evidence of fungal infection in the brain tissue of Alzheimer's disease patients by the Carrasco group at the Universidad Autonoma de Madrid (Nature: Scientific Reports 2015, October 15; 5:15015), we decided to attempt to replicate their findings using our own Alzheimer's patient brain tissue samples. A portion of the data presented in multiple publications by the Carrasco group pertained to the detection of the DNA (specifically rRNA genes and their spacer regions) of a variety of different fungi within DNA extracted from brain tissue samples.

Methods: The first step of our project was to acquire the PCR primers and reagents described in the published article, and test them with appropriate positive and negative controls before extracting DNA from our Alzheimer's patient and control tissue samples. This was to confirm that the nested PCR protocol described in their publications functioned as described. We obtained *Candida albicans* DNA from another laboratory for use as a positive control and used various negative controls including a "no DNA" (water or DNA elution buffer) control, 3 samples of DNA from the brain tissue of young adults not known to be affected with Alzheimer's disease, C57BL/6 mouse DNA, and bacterial DNA (*Klebsiella* spp).

Results: Unfortunately, the PCR reactions performed with the non-fungal negative controls, with the exception of the "no DNA" control, produced bands similar in size to those observed in our *Candida albicans* positive control. We have been unable to find any evidence of fungal contamination of any DNA extraction kit reagents, PCR reagents, disposables, or equipment used in our lab. All DNA extractions and PCR reaction preparations have been performed in a biosafety cabinet.

Conclusions: It is likely that the bands we are seeing are non-specific amplifications of regions of homology in rRNA genes common to all of the organisms tested. As we have followed the protocol exactly as described in the publication with the exception of using our standard PCR reagents (PCR reagents were not specified in the publication), we believe that (1) our choice of PCR reagents may have decreased the stringency of the PCR reaction such that bands can be produced from regions of similar sequence in humans and other organisms or (2) the primers are not as specific for fungal DNA as reported. We will show the results of studies of PCR stringency and BLAST analyses. These details will be important for anyone attempting to replicate the published data.

DISPARATE EXPRESSION OF INFLAMMATORY GENES IN CORTEX AND HIPPOCAMPUS OF APOE4-TARGETED REPLACEMENT MICE. Jones TB, Vallejo J, Chavira B, DeVera C, Castro M, Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.

Background: The APOE4 genotype is a significant risk factor for late-onset Alzheimer's disease (AD). Altered neuroinflammatory signaling, especially in microglia, is consistently observed in the AD brain. Previous data from our laboratory indicate that by 4 months of age there is a relative shift toward a pro-inflammatory state in the cortex of APOE4-targeted replacement (TR) mice associated with decreased expression of Triggering Receptor Expressed on Myeloid Cells 2 (*Trem2*). However, the hippocampus appeared to be in a relatively anti-inflammatory state, with increased *Trem2*. Mutations in *Trem2* confer increased risk for AD, suggesting that *Trem2* is protective in the CNS. Together these data demonstrate differences in the inflammatory state between the cortex and the hippocampus related to APOE status which may make the cortex more vulnerable to development of AD. *We hypothesized that the hippocampus of APOE4-TR mice would shift toward a pro-inflammatory state as the mice age in a manner consistent with progression of inflammation in AD brain.*

Methods: Male and female ApoE4-TR and APOE3-TR mice (6 months of age) were transcardially perfused with sterile PBS (pH 7.4). The brain was removed and the cortex and hippocampus dissected from the right hemisphere and snap frozen for qRT-PCR analyses.

Results: Cortical mRNA expression levels were determined in APOE4 versus APOE3 TR mice at 6 months of age. Anti-inflammatory genes Arginase 1 (*Arg1*; p=0.11) and Angiotensin type 2 receptor (*Agtr2*; p=0.10) were decreased while pro-inflammatory Nitric Oxide Synthase 2 (*Nos2*) was unchanged. *Trem2* expression levels were non-significantly increased. In the hippocampus, *Arg1* mRNA increased significantly (p=0.008) and *Nos2* was also increased (p=0.08), while *Trem2* was significantly decreased (p=0.001). Because the overall pattern suggests alterations in inflammatory signaling that are distinct across brain regions and from what was observed at 4 months of age, we chose to measure IL-10, whose expression is independent of microglial phenotype, as an overall index of immunoregulation. There were no overall effects of APOE4 genotype on IL-10 mRNA expression levels in either the cortex or hippocampus. Interestingly, when the data was analyzed by sex, cortical IL-10 expression at 6 months of age was decreased in both males and females (p=0.10), although the decline was most pronounced in males. Within the hippocampus, however, IL-10 expression was increased in males but decreased in females.

Conclusion: In summary, APOE4 genotype appears to modify inflammatory signaling in a distinct manner in the cortex versus the hippocampus. In the cortex, our previous data suggested a pro-inflammatory bias accompanied by decreased *Trem2* expression that was generally similar in older mice with the exception of *Trem2*, which was now not different from APOE3 TR mice. Decreased IL-10 expression in the cortex suggests a diminished ability to regulate inflammation. A distinct inflammatory profile emerged in the hippocampus. The anti-inflammatory bias previously observed was altered in older mice, with expression of microglial genes now indicating a more pro-inflammatory profile. The microglial profile was similar between males and females, but we observed disparate effects of sex on IL-10 expression. The differing inflammatory profiles in these two regions could underlie the distinct temporal progression of symptoms known to occur in AD. *This study was supported by funds obtained through the Midwestern Alzheimer's Advisory Committee (TBJ, JV, BC, MC, GJ).*

Poster 26

OPTICAL CLEARING AND 3D-HISTOLOGY OF MURINE TESTIS. Kaufman JA, Castro MJ, Ruiz SA, Rodriguez-Sosa JR. Midwestern University; Arizona Alzheimer's Consortium.

Optical clearing techniques (e.g., CLARITY, Scale, SeeDB, and 3DISCO) provide unprecedented opportunities to study large tissue samples at histological resolution, eliminating the need for physical sectioning while preserving the three-dimensional structure of intact biological systems. Although these methods have been used primarily to investigate nervous system tissues, there is significant potential for applying optical clearing to reproductive tissues. In testicular biology, for example, the study of spermatogenesis and the use of spermatogonial stem cells offer high-impact applications in fertility medicine and reproductive biotechnology. Therefore, the objective of our study is to apply optical clearing and immunofluorescence to testicular tissue in order to reconstruct its three-dimensional microstructure in intact large samples. We used Triton-X detergent-based clearing in combination with Refractive Index Matching Solution to achieve optical transparency of fixed mouse testes. An antibody against smooth muscle actin (SMA) was used to label peritubular myoid cells of seminiferous tubules while an antibody against ubiquitinC-terminalhydrolase (UCHL1) was used to label Sertoli cells and spermatogonia in the seminiferous epithelium. Specimens were then imaged using confocal fluorescence microscopy. Our results demonstrate that we were able to successfully clear testicular tissue and utilize immunofluorescent probes. Even with a basic confocal microscope and conventional objective lenses, we were able to image through as much as 500 microns of cleared tissue (the mechanical limit of our microscope). Moreover, we successfully visualized the histological compartments of testicular tissue in three-dimensional reconstructions. The anti-SMA antibody labeled the peritubular myoid cells in striking detail and exhibited their characteristic polygonal morphology. The antibody against UCHL1 provided clear visualization of mouse Sertoli cells and spermatogonia. When complemented with DAPI nuclear staining, the progressive stages of spermatogenesis could be observed proceeding from the basal compartment to the adluminal compartment of the seminiferous epithelium. In summary, optical clearing combined with immunofluorescence and confocal imaging offers a powerful new method to analyze the cytoarchitecture of testicular tissue at histological resolution while maintaining the macro-scale perspective of the intact system.

NUCLEAR, BUT NOT MITOCHONDRIAL ENCODED OXPHOS GENES ARE ALTERED IN AGING, MILD COGNITIVE IMPAIRMENT, AND ALZHEIMER'S DISEASE. Khdour OM, Delvaux E, Nolz J, Olsen G, Berchtold N, Cotman C, Hecht SM, Coleman PD, Mastroeni D. Arizona State University; Banner Sun Health Research Institute; University of California, Irvine; Arizona Alzheimer's Consortium.

Introduction: We have comprehensively described the expression profiles of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) gene that encode subunits of the respiratory oxidative phosphorylation (OXPHOS) complexes (I-V) in the hippocampus from young controls, age match, mild cognitively impaired (MCI), and autopsy confirmed AD subjects.

Methods: Frozen unfixed tissue was obtained from 44 non-AD controls (NC), 10 amnesic mild cognitive impaired (MCI) cases and 18 Alzheimer's disease (AD) cases. Total RNA was extracted from hippocampus and hybridized to arrays. Guanine-cytosine robust multi-assay analysis expression values were calculated, and expression differences were analyzed by comparative analysis between individuals, groups and disease status.

Results: The microarray data revealed significant down regulation in many of the respiratory chain complexes in AD, particularly those which were nuclear encoded. In contrast, there was up regulation of the same gene(s) in MCI subjects compared to AD and ND cases. Interestingly, no significant differences were observed in mtDNA genes between AD, ND and MCI subjects. Our results show that complex I and II seem to be about equally affected by age and AD, complex III more by age than AD, and complex IV and V more by AD than age.

Discussion: Our findings suggest that restoration of mitochondrial function in aging could be an impending strategy in blunting AD. Moreover, we have previously proposed a model of Alzheimer pathophysiology in which oligomeric abeta disrupts exchange of molecules between the cell nucleus and the cytoplasm. The present data showing effect of AD on expression of nuclear encoded but not mitochondrial encoded OXPHOS genes complements this model. Furthermore, a detailed analysis of compensatory mechanisms as shown here might be a starting point for further treatment and diagnostic strategies to combat AD.

Acknowledgements: The authors declare no competing financial or conflict of interests. We are grateful to the Banner Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona for the provision of human brain samples. The Brain and Body Donation Program is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium) and the Michael J. Fox Foundation for Parkinson's Research ." This work was supported by NIRG-14-321390 and ADHS14-080000 FY2015 to D.M. Supported by RO1 to C Cotman and 1R01AGO36400 to PDC.

HEAD-TO-HEAD COMPARISON OF SUVR METHODS IN AMYLOID CROSS-SECTIONAL AND LONGITUDINAL STUDIES. Klein G, Sampat M, Staewen D, Lemon C, Suhy J, Reiman EM, Chen K. BioClinica; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Recently, standard uptake value ratio (SUVR) analyses using cerebral white matter reference regions have shown improved power to track florbetapir PET measured longitudinal amyloid- β ($A\beta$) change [Chen2015, Landau2015]. We present a head-to-head comparison between SPM and Freesurfer based methods using white matter and other reference regions, and the Alzheimers Disease Neuroimaging Initiative (ADNI) florbetapir dataset.

Methods: Baseline and 24-m followup data from 399 ADNI subjects (157 Normal, 204 MCI, 32 AD) who also had corresponding MRI scans were included. Apolipoprotein E (APOE) $\epsilon 4$ homozygotes (HM), heterozygotes (HT) and non-carrier status was used to stratify the analysis. Mean-cortical SUVRs were computed using SPM and Freesurfer methods described previously [Chen2015, Landau2015]. The SPM method used a corpus callosum (CC) and centrum semiovale (CS) white matter reference region; the Freesurfer method used reference regions including eroded subcortical white matter, CC, whole cerebellum or cerebellar cortex. Longitudinal Cohen's d effect sizes were computed for AD, MCI and Normal groups, as well as for "likely decliners" defined as baseline $A\beta+$ Normals, APOEHT+HM Normals, $A\beta+$ MCIs, APOEHT+HM MCIs. Cross-sectional effect size was also compared.

Results: Longitudinal effect size was largest across most comparison groups using the SPM (CC and CS reference) and Freesurfer (CC reference) methods. Effect sizes of the SPM and Freesurfer methods were comparable, but only when using the Freesurfer CC reference region. Longitudinal effect sizes of the Freesurfer method for all other reference regions were considerably lower. Freesurfer showed a slightly higher cross-sectional effect size for most reference regions compared to the SPM method, but overall the cross-sectional effect size was very high for all techniques.

Conclusions: SPM and Freesurfer SUVR methodologies can produce similar longitudinal effect size, but only when the Freesurfer method includes a corpus callosum reference region.

MECHANISTIC PATHWAYS LINKING MITOCHONDRIAL OXIDATIVE STRESS AND WHITE MATTER DEGENERATION IN THE AGING MAMMALIAN FEMALE BRAIN. Klosinski LP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) has a complex and progressive pathological phenotype characterized first by a decline in brain glucose metabolism and impaired mitochondrial bioenergetics (Yao et al., 2011). Compromised mitochondrial bioenergetics lead to overproduction and accumulation of β -amyloid, resulting in an increase in hydrogen peroxide (H₂O₂) release from the mitochondria. In parallel, white matter (WM) hyperintensities are an early hallmark of AD followed by late stage WM degeneration. We propose that hyperintensities and WM degeneration are initiated by mitochondrial dysfunction and subsequent H₂O₂ release, leading to phospholipase A2 activation and arachidonic acid release. Increase in arachidonic acid can activate the sphingomyelinase ceramide pathway to catabolize myelin.

Methods: Herein we tested the hypothesis that this cascade leads to catabolism of WM as a source of fatty acids in brain to serve as an alternative fuel. Because aging females are at greatest risk for developing AD, analyses were conducted using aging female mice at 3, 6, 9, 12, and 15 months of age. Western blot, immunohistochemistry and electron microscopy were used to analyze myelin sheath integrity. Phospholipase A2 and sphingomyelinase enzyme activity levels were measured. A hypothesis driven custom low density QT_PCR array was created to investigate WM gene expression across aging transitions in the female brain. Lastly, we conducted lipidomic analyses to investigate levels of fatty acids, ceramides and TCA metabolites during aging.

Results: Evidence for WM degeneration first appeared at 12 months of age indicated by a statistically significant increase in astrocyte immunoreactivity and PLA2 activation. Consistent with increased PLA2 enzyme activity, genes associated with myelin synthesis exhibited a pattern of downregulation between 12 and 15 months of age whereas, myelin degradation genes remained upregulated, indicating potential for long-term activation pathways involved in WM degeneration. Immunohistochemical mapping of myelin basic protein fluorescence indicated that WM area increased in the hippocampal fimbria and anterior commissure between 9 and 12 months, which was followed by a precipitous decline between 12 and 15 months of age. Electron microscopy analysis of WM organization revealed that the expansion of myelin area between 9 and 12 months of age was due to loss of myelin compactness and structural integrity. WM degeneration at 12 and 15 months was further confirmed by lipidomic analysis that revealed an overall increase in myelin's constituent components, ceramides and fatty acids, at 12 and 15 months respectively.

Conclusions: These findings provide a mechanistic pathway and temporal trajectory for progression of WM degeneration observed in aged brain and early Alzheimer's disease. Research supported by NIA P01AG026572 (Project 1 to RDB) and NIA R01AG032236 to RDB.

MENTALLY STIMULATING ACTIVITIES IN LATE-LIFE AND THE RISK OF INCIDENT MILD COGNITIVE IMPAIRMENT: A PROSPECTIVE COHORT STUDY.

Krell-Roesch J, Roberts R, Pink A, Stokin G, Mielke M, Vemuri P, Christianson T, Knopman D, Petersen R, Geda Y. Mayo Clinic Arizona; Mayo Clinic Minnesota; International Clinical Research Center, Brno, Czech Republic; Arizona Alzheimer's Consortium.

Background: We previously reported a cross-sectional association between late-life mentally stimulating activities and decreased odds of having mild cognitive impairment (MCI). However, little is known about the risk of incident MCI as predicted by late-life mentally stimulating activities. Our goal was to test our hypothesis on the association between mentally stimulating activities in late-life and the risk of incident MCI and additionally evaluate the impact of APOE ϵ 4 status.

Methods: We conducted a prospective cohort study derived from the population-based Mayo Clinic Study of Aging in Olmsted County, Minnesota. We followed 1929 cognitively normal participants aged ≥ 70 years to the outcome of incident MCI. Participants provided information about mentally stimulating activities within a year prior to baseline evaluation using a questionnaire. Cognitive diagnosis was made by an expert consensus panel. We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using Cox proportional hazards models after adjusting for age, sex and education.

Results: Over a median follow-up period of 4 years, we observed that playing games (HR [95% CI], 0.78 [0.65-0.95]), reading magazines (0.66 [0.54-0.82]), and engaging in craft activities (0.72 [0.57-0.90]), computer use (0.70 [0.57-0.85]), and social activities (0.77 [0.63-0.94]) were associated with a decreased risk of incident MCI. After stratification by APOE ϵ 4 status, findings remained the same for APOE ϵ 4 noncarriers. However, only computer use (HR [95% CI], 0.65 [0.46-0.92]) and social activities (HR [95% CI], 0.62 [0.43-0.89]) were associated with a decreased risk of incident MCI for APOE ϵ 4 carriers.

Conclusions: Cognitively normal elderly individuals who engage in specific mentally stimulating activities have a decreased risk of incident MCI. The associations may vary with APOE ϵ 4 carrier status.

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PRELIMINARY PATIENT AND PARTNER OUTCOMES IN A RANDOMIZED TRIAL OF TWO COGNITIVE REHABILITATION INTERVENTIONS FOR MILD COGNITIVE IMPAIRMENT. Locke DEC, Cuc AV, Snyder CH, Fields JA, Smith GE, Chandler M. Mayo Clinic Arizona; Mayo Clinic Minnesota; University of Florida; Mayo Clinic Florida; Arizona Alzheimer's Consortium.

Background: This pilot study examined the impact of a restorative strategy (computerized exercises) compared to a compensatory strategy (calendar training) in persons diagnosed Mild Cognitive Impairment (MCI) and a care partner.

Methods: Sixty-four dyads were randomized to calendar training or computer exercises. A standard care control group was used for comparison. This report offers outcomes on measures of adherence, memory-based activities of daily living (mADLs), and memory self-efficacy in those with MCI and outcomes on measures of depression, anxiety, quality of life, and burden in a support partner.

Results: The calendar training group demonstrated significant improvement in mADLs compared to controls, while the computer training group did not. For partners, both treatment groups showed stable depression and anxiety scores over time while the control group showed worsening scores over time. Additional analyses had moderate effect sizes but were non-significant at this sample size.

Conclusions: Calendar training may be more effective in improving mADLs than computerized exercises. However, engaging in either cognitive rehabilitation approach may help prevent increasing depression and anxiety in partners of those with MCI. This study also highlights that behavioral trials with less than 30-50 participants per arm are likely underpowered.

Poster 32

THE EFFECTS OF APOE GENOTYPE ON A β LEVELS IN HUMAN LIVER. Maarouf C, Garcia A, Walker J, Intorcchia A, Filon J, Glass M, Callan M, Walker D, Sue LI, Beach TG, Dugger B, Serrano G. Banner Sun Health Research Institute; Arizona State University; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: It is well known that Apolipoprotein E (APOE) genotype alters the risk of developing Alzheimer's disease (AD), but the molecular mechanism of this effect is still unknown. The most accepted general hypothesis is that the E4 allele-coded form of APOE influences the metabolism of amyloid precursor protein and/or its critical cleavage product, amyloid- β (A β), resulting in brain accumulation of A β as senile plaques. It has also been assumed that the critical molecular events all take place in the brain, but as the liver is a major site for both the synthesis of APOE as well as the metabolism of circulating A β , it is possible that alterations of liver function could affect brain A β levels through changes in blood A β concentration.

Methods: In this study we hypothesized that APOE genotype may affect the rate of A β degradation in the liver. An A β degradation assay was developed using fluorescein-labeled A β 40 and 42 spiked into liver homogenates.

Results: Our preliminary data suggest that A β 42 degradation rates in the liver do not vary between subjects with different APOE alleles, while A β 40 appears to degrade three times faster in individuals with the E4 allele. The expression of potential A β -degrading enzymes presenilin, β -site APP-cleaving enzyme (BACE), cathepsin D and neprilysin were not different in liver samples from E4 carriers, suggesting that other enzymes or mechanisms might be involved.

Conclusions: Identifying such mechanism could be crucial in understanding A β abnormal accumulation in the brain of subjects with AD. Funded by the Arizona Biomedical Research Commission.

THE USE OF RELIABLE CHANGE INDEX TO CHARACTERIZE COGNITIVE COMPOSITE SCORE DECLINE AS AN OUTCOME FOR ALZHEIMER'S DISEASE PREVENTION TRIALS. Malek-Ahmadi M, Chen K. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: The feasibility of Alzheimer's disease (AD) prevention trials was largely based on the successful introduction of composite score, integrating information from multiple cognitive tests. One such score is the Alzheimer's Prevention Cognitive Composite (APCC) [1,2]. The APCC had high sensitivity to detect cognitive changes over time in groups where overt cognitive impairment may not yet be present or is extremely subtle. To account for the intra- and inter-individual variability, practice effects, and measurement error in order to more specifically detect clinically meaningful change, we considered the use of the reliable change index (RCI) to characterize AD-related cognitive decline on the APCC.

Methods: Data for 433 APOE ϵ 4 non-carriers (NCs) and 106 APOE ϵ 4 heterozygotes (HTs) from the Rush Religious Order Study and the Rush Memory and Aging Project were included in this study. The NCs did not convert to MCI over a 5-year period and their data were used to define the APCC change range, based on RCI, beyond which APCC would be deemed clinically meaningful. The clinically meaningful change was then examined in the HTs who were at higher risk for developing AD compared to NCs.

Results: A decline of 7.5 points from Year 1 to Year 5 on the composite score represented clinically meaningful change. 27% of the APOE ϵ 4 HTs demonstrated clinically meaningful decline from Year 1 to Year 5. When analyzed with a logistic regression model, individuals who showed clinically meaningful decline were almost eight times more likely to have converted to amnestic-MCI during the 5-year period [OR = 7.90, 95% CI (2.51, 24.90), $p < 0.001$]. Sample size estimates for a theoretical secondary prevention trial found that RCI-based estimates were substantially lower than those based on the mean APCC change.

Conclusions: The RCI was able to detect clinically meaningful APCC decline in a group at high-risk for developing AD. In addition, RCI-based sample size estimates for a secondary prevention trial were favorable and provide greater interpretation of clinically meaningful change when compared to a standard methodology. It is possible that RCI-based measures of clinically meaningful change can be applied to secondary prevention trials in order to demonstrate treatment efficacy.

1. Langbaum JB, et al. An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease. *Alzheimers Dement* 2014;10(6):666-674.

2. Ayutyanont N, et al. The Alzheimer's Prevention Initiative composite cognitive test score: Sample size estimates for the evaluation of preclinical Alzheimer's disease treatments in presenilin 1 E280A mutation carriers. *J Clin Psychiatry* 2014;75(6): 652-660.

Poster 34

NEURITIC AND DIFFUSE PLAQUE ASSOCIATIONS WITH COGNITION IN ELDERLY PERSONS WITHOUT COGNITIVE IMPAIRMENT. Malek-Ahmadi M, Perez SE, Chen K, Mufson EJ. Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: The presence of Alzheimer's disease (AD)-related neuropathology among cognitively normal individuals has been well-documented. It has been proposed that these individuals may represent a pre-clinical AD population. Previous studies have demonstrated an inverse relationship between the presence of both A β plaques and neurofibrillary tangles with ante-mortem cognitive performance, a relationship that is likely influenced by a number of factors, including age and APOE ϵ 4 carrier status.

Methods: The present study determined whether the presence of neuritic plaques (NPs) and diffuse plaques (DPs) are associated with performance in a number of cognitive domains after accounting for APOE ϵ 4 carrier status and NFT presence in a cohort of 123 older deceased persons with a premortem clinical diagnosis of no cognitive impairment who were participants in the Rush Religious Order Study.

Results: After adjusting for age at death, education, gender, Braak stage, and APOE ϵ 4 carrier status DPs showed no association with cognition, however the absence of NPs was associated with increased performance in the domains of Global Cognition ($p = 0.002$), Episodic Memory ($p = 0.03$), Semantic Memory ($p = 0.009$), and Visuospatial tests ($p = 0.006$).

Conclusions: The results suggest that decreases in cognition are associated with increases in NPs and not DPs when age, education, gender, APOE ϵ 4 status, and Braak stage are taken into consideration.

SEX-DEPENDENT BIOENERGETIC AND METABOLIC GENE EXPRESSION IN THE HIPPOCAMPUS: FEMALE BRAIN AGES DIFFERENTLY FROM MALE BRAIN. Mao Z, Zhao L, Yao J, Ding F, Cadenas E, Brinton RD. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: Women have a higher risk than men in developing Alzheimer's disease (AD). This study examines the impact of age and reproductive status on gene expression in the hippocampus of both female and male brain.

Methods: Total RNA samples extracted from the hippocampal tissues of 6, 9, 12 and 15-month-old female and male mice were comparatively analyzed by qRT-PCR-based Taqman low density arrays for the expression levels of a total of 165 genes involved in mitochondrial bioenergetics, redox, transport, cholesterol homeostasis and amyloid metabolism.

Results: Hippocampal gene expression profiles in female mice were differentially impacted by their age and reproductive status. Transition from pre-menopause to peri-menopause induced most changes, as demonstrated by a total of 69 genes (42%; 20 up & 49 down) significantly differentially expressed from 6-month to 9-month. Among them, genes involved in mitochondrial bioenergetics, redox and transport appeared to be particularly prone to the endocrine status change. Transition from peri-menopause to menopause induced much less changes, with a total of 18 genes (11%; 3 up & 15 down) significantly differentially expressed from 9-month to 12-month. Transition from menopause to post-menopause induced least changes, with a total of 10 genes (6%; 9 up & 1 down) significantly differentially expressed from 12-month to 15-month. In contrast to female brain, there were only 8 genes (5%; 7 up & 1 down) differentially expressed at the transition from 6-month to 9-month. And, an increased number of genes were up-expressed with age progression from 9-month to 15-month in male brain.

Conclusion: Taken together, these results indicate that female brain ages differently from male brain. Peri-menopause may serve as a critical point that switches a female healthy brain to a hypometabolic and oxidative status resulted from deficits in energy production and antioxidant activity that may eventually lead to accelerated neurological aging and increased risk for developing neurodegenerative diseases such as AD. Furthermore, these results suggest that a preventative strategy should be initiated before or at the onset of peri-menopause - much earlier than traditionally thought - in order to reverse or reduce peri-menopause-induced negative impact on neurological health in women.

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INCREASED 5-HYDROXYMETHYLATION LEVELS IN THE SUB VENTRICULAR ZONE OF THE ALZHEIMER'S BRAIN. Mastroeni D, Chouliaras L, Van den Hove DL, Rutten BPF, Delvaux E, Coleman PD. Arizona State University; Banner Sun Health Research Institute; Maastricht University Medical Centre, Maastricht, The Netherlands; University of Oxford, Oxford, UK; Arizona Alzheimer's Consortium.

Introduction: The subventricular zone (SVZ) is a site of neurogenesis in the aging brain, and epigenetic mechanisms have been implicated in regulating the "normal" distribution of new nerve cells into the existing cellular milieu. Although the existence and biological functions of active methylation (generally mediating gene repression) and de-methylation (generally inducing gene expression) are still in its infancy, 5hmC has been implicated in active DNA de-methylation; particularly in multipotent genes.

Methods: We examined precursor cells from the SVZ in autopsy confirmed AD and ND human subject, both in vivo and in vitro. In order to determine 5hmeC levels we used a wide array of techniques including immunohistochemistry, immunocytochemistry, and slot blots. WST-1 assays were performed in culture to determine proliferation potential in AD and ND subjects.

Results: In a case control study of human primary SVZ cultures and fixed tissue from the same individuals, we have found significant increases in DNA hydroxymethylation levels in the SVZ of Alzheimer's disease (AD) patients compared to Non-diseased (ND) control subjects. We show that this increase in 5-hydroxymethylation directly correlates to an increase in cellular proliferation in AD precursor cells; which implicates the hydroxymethylation tag to a higher degree of cellular proliferation.

Discussion: Although an increase in the number proliferating cells has been reported in AD glial, vascular and neuronal precursor cells none have identified a causal mechanism. It has been previously reported that 5hmeC levels are linked to a higher degree of multipotency and cellular proliferation, and here we provide evidence that the increase in proliferation in AD may be directly linked to the increase in 5hmeC levels.

Acknowledgements: We are grateful to the Banner Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona for the provision of human brain samples. The Brain and Body Donation Program is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium) and the Michael J. Fox Foundation for Parkinson's Research ." This work was supported by NIRG-14-321390 and ADHS14-080000 FY2015 to D.M.

A PARADIGM SHIFT IN MICROGLIAL EXPRESSION PROFILES IN HUMAN BRAIN. Mastroeni D, Sekar S, Delvaux E, Nolz J, Liang W, Coleman PD. Arizona State University; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Introduction: Conventional wisdom holds that brain microglia are similar regardless of brain region. Array expression data from many labs, including our own show large changes in expression of many glial-specific genes in Alzheimer's disease (AD) compared to normal controls (NC). The problem is however; homogenates are often used to obtain these data which introduces un-wanted complication because of the number of cell types analyzed. Although selected glial-specific changes are distinguishable, there are thousands of genes that are not cell class-specific but play major roles in cell function.

Methods: In order to investigate disease and regional effects on gene expression we isolated microglial cells by laser captured micro-dissection from CA1 of hippocampus and substantia nigra (SN) of AD, NC and Parkinson's disease (PD) cases, followed by RNA sequencing.

Results: Laser captured cells allowed more precise definition of relationships between microglia and their expression profiles based on disease and location. In AD CA1 366 significant ($p < .01$) differentially expressed transcripts were observed and 409 in PD CA1. After applying Benjamini-Hochberg-FDR correction $< .1$ (10% false-positives), 66 transcripts were significantly altered in AD and 30 in PD. Of those transcripts (96 total) which were differentially effected, no overlap between AD and PD was found; implying that different neurodegenerative diseases affect microglia differently in the same brain region. Expanding the analysis to brain region (e.g. CA1 vs SN) we show over two-thousand differentially expressed genes. These data indicate that greatest differences in the expression profile within microglial sub-populations are the most significant among brain regions, not within regions or disease.

Discussion: It has been known for more than a decade that microglia have the ability to release neurotoxic inflammatory factors. These pro-inflammatory factors or cytokines, have prompted hundreds of studies and clinical trials to suppress their function, but none have been successful to date. Although there are several explanations listed in the literature on why these clinical studies failed to recapitulate *in vitro* findings, we hypothesize that these studies failed due to the inability to address probable heterogeneity among glial cells as a function of brain region. These findings lay the foundation for future development of therapeutic targets, aid in the pursuit of new research leads, and answer fundamental biological questions regarding the interplay between glial types and their function based on location, and disease.

Acknowledgements: The authors declare no competing financial or conflict of interests. We are grateful to the Banner Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona for the provision of human brain samples. The Brain and Body Donation Program is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium) and the Michael J. Fox Foundation for Parkinson's Research ." This work was supported by NIRG-14-321390 and ADHS14-080000 FY2015 to D.M.

DOES BODY FAT PREDICT COGNITION BETTER THAN BODY MASS INDEX IN A GROUP OF COGNITIVELY HEALTHY OLDER ADULTS? Meyer A, Stickel A, Ryan L.
University of Arizona; Arizona Alzheimer's Consortium.

Background: Obesity has been associated with increased risk for Alzheimer's disease. However, in cognitively healthy populations obesity is linked to poorer executive functioning and is only sometimes linked to poorer memory. Mixed findings may be due, in part, to differences in measuring body fat, especially in older adult populations. Therefore, the present study compared how well two measures of body fat (i.e., percent body fat and body mass index) predicted frontal-based executive functions and temporal lobe-based functions, like semantic fluency and memory.

Methods: Forty older adults between the ages of 60 – 80 completed a neuropsychological battery. Participants had an average 16 years of education and included 19 males. Males and females were matched on age and education. Neuropsychological tests of interest were an inhibition composite, an updating composite, phonemic fluency, semantic fluency, and delayed verbal memory. Body fat was calculated using an impedance scale and body mass index (BMI) was computed using height and scale-measured weight. Using SPSS software, separate general linear models for body fat and BMI were conducted to predict each test of interest, controlling for age and gender. Interactions between body measures and gender were also included in the models because cut-offs for healthy body fat significantly differ between males and females.

Results: The interaction between BMI and gender predicted performance on the semantic fluency task: In males, higher BMI was associated with poorer semantic fluency while the opposite association was found in females. A similar pattern was observed for the body fat by gender interaction: In males, higher body fat was associated with poorer semantic fluency but body fat was unrelated to performance in females. No other tests were significantly predicted by either body measure.

Conclusions: Taken together, these results suggest that neither body measure (BMI or body fat) was better at predicting cognitive performance. Surprisingly, in this small sample neither measure was related to inhibition, updating, or phonemic fluency measures of executive functions. While delayed verbal memory was not associated with body measures, the association of semantic fluency to body fat suggests that body fat affects temporal regions of the brain that may be some of the first regions damaged in Alzheimer's disease. Given that semantic fluency was differentially associated with body measures in males and females, this suggests that the role of body fat in the aging male is in some ways different than in the aging female. Larger samples are needed to confirm such predictions and are needed to look into a possible three-way interaction between age, body fat, and gender.

MEDIN AMYLOID PEPTIDE ENHANCES B-AMYLOID FIBRILLATION AND INDUCES HUMAN ARTERIOLE DYSFUNCTION. Migrino RQ, Davies H, Truran S, Karamanova N, Franco DA, Serrano G, Callan M, Burciu C, Beach TG, Madine J. Phoenix VA Health Care System; University of Arizona College of Medicine-Phoenix; University of Liverpool; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

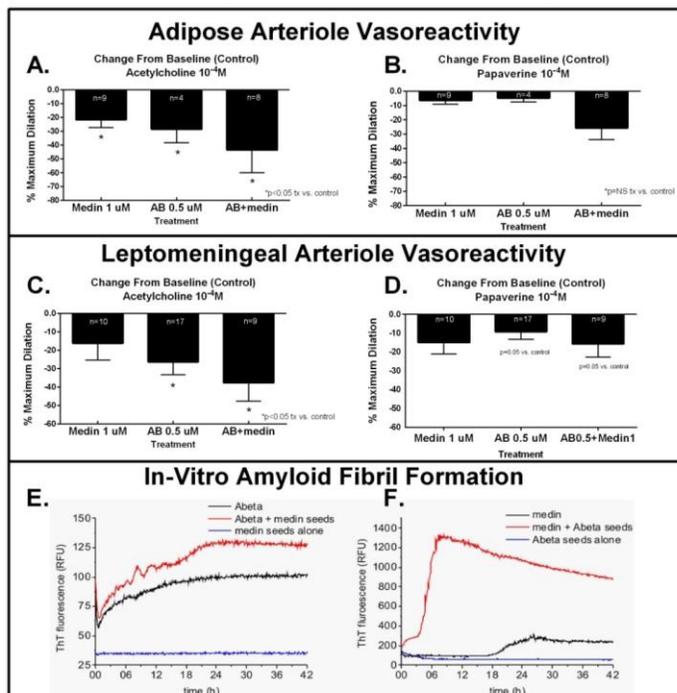
Background: Preclinical, clinical and epidemiologic studies demonstrate the link between vascular disease and dementia from late-onset AD but the mechanistic links between vascular aging and AD are not well-established. Medin, a 50 amino acid peptide, is the most ubiquitous amyloid protein in humans and is present in nearly all individuals >60 years old. It has been implicated in aortic wall degeneration and degenerative vascular changes associated with aging. Our aim is to determine whether presence of medin affects A β 42 fibrillation (and vice-versa) and to assess the effects of medin and A β 42 in ex-vivo human arterioles.

Methods: In-vitro fibrillation of A β 42 using thioflavin-T fluorescence was assessed alone or in the presence of medin seed; similarly, medin fibrillation was assessed alone or in the presence of A β 42 seed. Separately, abdominal adipose fat tissues were collected from human subjects undergoing routine abdominal surgery and the arterioles were isolated, cannulated and pressurized to physiologic pressure. Baseline (control) dilator response to acetylcholine (endothelium-dependent) and papaverine (smooth-muscle dependent) were measured followed by washing and measurement of same response following exposure to 1 hour of medin 1 μ M, A β 42 0.5 μ M or medin+A β . Similar experiments were performed in leptomeningeal arterioles isolated from brain donors undergoing rapid autopsy in the Sun Health Institute Brain Donation program.

Results: See figure. A β 42 caused impaired endothelial, but not smooth muscle dysfunction in adipose and leptomeningeal arterioles. Medin caused impaired endothelial dysfunction in adipose arterioles and a trend towards similar response in leptomeningeal arterioles. The combination of A β 42 and medin caused impaired endothelial function in human arterioles, with a

trend (although not statistically significant) towards additive injury compared to A β 42 or medin alone. In-vitro, A β 42 fibrillation was accelerated in the presence of medin seed and medin fibrillation was accelerated in the presence of A β 42 seed.

Conclusions: Our preliminary results point to potential interaction between A β 42, the amyloid protein implicated in AD and medin, the most common human amyloid protein implicated in vascular aging that could potentially augment vascular toxicity. The pathophysiology of medin needs to be studied as it could provide novel insights into the still unknown link between aging and late onset AD.



AMYLOID-B, NEUROPSYCHIATRIC SYMPTOMS AND THE RISK OF INCIDENT MILD COGNITIVE IMPAIRMENT: A PROSPECTIVE COHORT STUDY. Neureiter J, Krell-Roesch J, Pink A, Stokin G, Roberts R, Mielke M, Christianson T, Spangehl K, Lowe V, Jack C, Knopman D, Boeve B, Petersen R, Geda Y. Paracelus Medical University, Salzburg, Austria; Mayo Clinic Arizona; International Clinical Research Center, Brno, Czech Republic; Mayo Clinic Minnesota; Arizona Alzheimer's Consortium.

Background: Amyloid- β (A β) and neuropsychiatric symptoms (NPS) are independent risk factors for cognitive impairment. However, it remains unclear whether they synergistically interact in further elevating the risk of incident MCI. Our goal was to examine a potential interaction between A β and depression/ anxiety on the outcome of incident mild cognitive impairment (MCI).

Methods: We conducted a prospective cohort study derived from the population-based Mayo Clinic Study of Aging in Olmsted County, Minnesota. We followed 950 cognitively normal participants aged ≥ 50 years for a median of 28 months to the outcome of incident MCI. Participants underwent PiB-PET scans, neuropsychological evaluations and assessments using Beck Depression Inventory II (BDI-II) and Beck Anxiety Inventory (BAI). Cognitive diagnosis was made by an expert consensus panel. We used a global cortical to cerebellar ratio cutpoint to classify participants as PiB+ (≥ 1.4) or PiB- (< 1.4). A BDI-II score ≥ 13 was indicative of depression; and we classified anxiety as BAI score ≥ 10 . We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using Cox proportional hazards models after adjusting for age, sex and education.

Results: Participants who were PiB+ and depressed had a more than 3-fold increased risk of incident MCI (HR [95% CI], 3.56 [1.46, 8.63]) as compared to the reference group (PiB-, non-depressed). Similarly, participants who were PiB+ and anxious had a more than 5-fold increased risk of incident MCI (HR [95% CI], 5.38 [2.35, 12.3]) as compared to the reference group (PiB-, non-anxious). A test of positive interaction was significant for A β and depression at $p=0.032$; and for A β and anxiety at $p=0.034$.

Conclusions: A β and depression or anxiety have a positive synergistic interaction to further elevate the risk of incident MCI. This suggests that interventions that target presymptomatic Alzheimer's disease biomarkers may need to account for depressive and anxiety symptoms.

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THE mTOR/p70S6K PATHWAY PLAYS A KEY ROLE IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE. Oddo S, Caccamo A, Shaw D, Branca C. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging is the major risk factor for Alzheimer's disease (AD); however, little is known as to how the aging process facilitates the development of AD. Changes that occur in the brain as a function of age may facilitate the development of AD. Reducing the activity of the mammalian target of rapamycin (mTOR), and its downstream target p70S6K, increases lifespan and health-span in several genetically different species. mTOR is a protein kinase that plays a key role in regulating protein translation (via p70S6K) and degradation. Therefore, mTOR is key in controlling protein homeostasis, a process that is altered in AD and other proteinopathies. The goal of this work is to assess the role of the mTOR/p70S6K pathways in the pathogenesis of AD.

Methods: Using several mouse models, we employed multidisciplinary approaches to dissect the role of the mTOR/p70S6K signaling in AD.

Results: We will show that genetic and pharmacologic reduction of mTOR and p70S6K signaling reduced amyloid- β and tau pathology and rescued memory deficits. Mechanistically, the reduction in mTOR signaling led to an increase in autophagy induction and restored the hippocampal gene expression signature of the Tg2576 mice to wild type levels.

Conclusions: Given that mTOR and p70S6K regulate lifespan and health span, the data presented here have profound clinical implications for aging and Alzheimer's disease and provide the molecular basis for how aging may contribute to AD pathology. Our results implicate hyperactive mTOR/p70S6K signaling as a previous unidentified signaling pathway underlying gene-expression dysregulation and cognitive deficits in Alzheimer's disease.

DEVELOPING INDIVIDUALIZED WEB BASED DEMENTIA CAREGIVER SUPPORT PROGRAM. Park M. Chungnam National University, Daejeon, South Korea; Arizona State University; Arizona Alzheimer's Consortium.

Background: Recently, web-based interventions to provide education or support to individuals with dementia and to their family caregivers have been actively developed and shown to be effective. In Korea, there has been a lack of online intervention since most family caregivers were offline-based interventions. The purpose of this study was to develop the web-based support program for dementia family caregivers.

Methods: The individualized web-based education and support program was developed using the following processes: analysis stage, designing stage, content framing and development stage, program application stage, and evaluation stage. The program was developed collaboratively by experts including the content experts, a web designer, a website database programmer, and a multimedia designer responsible for animation. The contents were designed to address a various range of issues including understanding dementia stage, treatment of dementia, coping behavioral problem, assisting daily living, and living a pleasant life. Advisory board members reviewed the contents for quality, accuracy, consistency, reading level, and distribution of the program. The selected family caregivers reviewed the storyboards and provided the feedback. These feedbacks were incorporated into the final storyboards. All modules were designed as animation. Core module such as understanding dementia stage was provided to every user who use the website. Optional modules were provided according to the results of family caregiver's need assessment. Formative evaluation to assess usability of the program was conducted. Family caregiver's need and stress were assessed at baseline and satisfaction of the program was evaluated at the end of modules.

Results: Family caregivers were very satisfied with the amount of information, the content of online activity, and the design of website. The use of animation has been shown to improve family caregivers' interest and understanding of the contents.

Conclusions: An active participation of family caregivers with their higher level of satisfaction was gained compared with traditional support programs with written material and group based approach. The use of web-based support program offers users the opportunity to participate support program at their own time and pace. Results from this study demonstrate support to move forward with this web-based program. This programs need to apply to various settings such as home care settings, the physician's office, dementia care centers, and senior centers. * This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning (NRF. 2013R1A2A2A01069090).

GENOME-WIDE EXPRESSION AND METHYLATION PROFILING IN MEDIAL TEMPORAL GYRUS REVEALS CONCORDANT PATTERNS OF DOWNREGULATION/ HYPERMETHYLATION IN KEY MOLECULAR PROCESSES INVOLVED IN THE PATHOGENESIS OF ALZHEIMER'S DISEASES. Piras IS*, Krate J*, Delvaux E, Nolz J, Mastroeni D, Jepsen W, Beach TG, Persico AM, Coleman PD, Huentelman MJ. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona State University; University Campus Bio-Medico, Rome, Italy; University of Arizona; Arizona Alzheimer's Consortium.

* Denotes equal contributions

Background: We analyzed the expression and methylation profiles of Alzheimer's Disease patients (AD) and non-demented matched controls (ND) in order to detect patterns of dysregulation in AD related genes, and whether those corresponding changes can predict site specific methylation.

Methods: Expression profiles were obtained from the Mid Temporal Gyrus (MTG) from 100 AD and 100 ND subjects using the HumanHT-12 BeadChip Array (Illumina). Methylation profiles were analyzed in an overlapping sample of 225 AD and 179 ND using the HM450 BeadChip array (Illumina). Data were processed using R packages Lumi, MethyLumi and Limma, correcting P values with the FDR method. Finally, expression and methylation results were combined using the Fisher's weighted Z-method (FWZ).

Results: We detected 16,947 DEGs, observing a general under-regulation and hypermethylation patterns. Among the top genes we found: RGS4, SYT1, STMN2, CHGB and STXBP1. The gene list was enriched for the Synaptic Vesicle Trafficking and GABAergic transmission pathway. The female samples were specifically enriched for the "L1CAM interaction" pathway including the CHL1 gene, a substrate for BACE1. We combined the expression and methylation results (938 and 36,946 highly significant probes, respectively) detecting 464 genes simultaneously differentially expressed and methylated in AD. 248 of them were characterized by a negative methylation/expression correlation. In particular, the list of genes underexpressed/hypermethylated was enriched for neuronal and synaptic pathways. Among the top genes were PPC3A and NMNAT2, both involved in protein τ phosphorylation. RIMBP2, not previously associated with AD, belongs to the family of RIM-BP genes, which are involved in synaptic transmission.

Conclusions: Using the combined approach, we observed a general pattern of combined downregulation/hypermethylation in several genes involved in key molecular mechanisms of AD pathogenesis (τ phosphorylation or β -amyloid metabolism). However, we detected several genes not directly associated with AD but that could be potential candidates for further investigation because of the molecular mechanisms in which they are involved.

THE MILD COGNITIVE IMPAIRMENT OF PRIMARY PROGRESSIVE APHASIA: A CASE SERIES. Powell J, Lendrum J, Huff R, Belden C, Sabbagh MN, FAAN. Banner Sun Health Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Mild cognitive impairment (MCI) has been characterized potentially as the prodrome of dementia. It has been divided into amnesic and non-amnesic subtypes with the amnesic subtype most commonly progressing to AD. The MCI phase of other dementias such as DLB has also been described. There are very few reports summarizing MCI phase of Primary Progressive Aphasia.

Our aim is to contribute the clinical characterization of MCI and eMCI in the setting of clinically suspect PPA in order to better describe the presenting features and neuropsychological profile.

Methods: This is a cross-sectional case series abstracted from our memory disorders clinic. We retrospectively queried and analyzed the cases of 9 patients with a primary diagnosis of MCI and secondary diagnosis of progressive aphasia. Acquired aphasias (e.g. stroke, mass) were excluded.

Results: Of the 9 cases, 5 were non-amnesic MCI and 4 were amnesic MCI, all with language as the primary domain. All eMCI cases were non-amnesic. Word finding difficulty was observed in 8 of the 9 cases and sentence repetition impairments in 8 of 8 tested.

Conclusions: The prodromal MCI stage of PPA is predominantly characterized by word finding difficulty on observation, sentence repetition impairment on neuropsychological testing, and language as the primary impaired domain ± memory impairment.

RELATIONSHIPS BETWEEN BASELINE BIOMARKERS AND SUBSEQUENT COGNITIVE DECLINE IN COGNITIVELY UNIMPAIRED PSEN1 E280A MUTATION CARRIERS FROM THE COLOMBIAN KINDRED WITH AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE. Quiroz YT, Protas H, Chen K, Roontiva A, Thiyyagura P, Fagan AM, Shah A, Gutierrez M, Londono M, Giraldo M, Munoz C, Tirado V, Velilla L, Garcia G, Jaimes SY, Langbaum JB, Tariot PN, Sperling RA, Lopera F, Reiman EM. Universidad de Antioquia, Medellin, Colombia; Massachusetts General Hospital; Banner Alzheimer's Institute; Washington University School of Medicine; Knight Alzheimer's Disease Research Center; Brigham and Women's Hospital, Harvard Medical School; Athinoula A Martinos Center for Biomedical Imaging; Arizona Alzheimer's Consortium.

Background: While brain imaging and cerebrospinal fluid (CSF) biomarkers have been used in the early detection and tracking of Alzheimer's disease (AD), their ability to predict subsequent clinical decline remains to be defined. In this study, we compared the ability of baseline PET amyloid- β ($A\beta$) and CSF measurements to predict subsequent cognitive decline in unimpaired Presenilin-1 (PSEN1) E280A mutation carriers from the Colombian autosomal dominant AD (ADAD) kindred, up to almost 25 years before the kindred's estimated median age of 44 at the onset of mild cognitive impairment.

Methods: Thirty-seven cognitively unimpaired mutation carriers and non-carriers, aged 20-44 years, were recruited from the Alzheimer's Prevention Initiative (API) Colombia Registry. Baseline cerebral-to-cerebellar florbetapir PET standard-uptake-value ratios (SUVRs) and CSF $A\beta$ 1-42, total-tau and phospho-tau181 levels were related to 2-3 year subsequent decline on the API preclinical ADAD composite cognitive test score, previously found to be associated with preclinical progression. The mixed random effect model was used to estimate the relationship between baseline measures and subsequent cognitive decline in the mutation carriers.

Results: In an independent replication, 2-3 year decline on the composite cognitive test score distinguished between carriers and non-carriers ($p=0.03$). In the carrier group, baseline florbetapir SUVRs and CSF p-tau/ $A\beta$ 1-42 ratios were associated with subsequent decline on the composite cognitive test score ($p=0.008$, 0.04 , respectively). CSF $A\beta$ 1-42, total tau, and p-tau levels alone were not ($p=0.19$, 0.43 and 0.88 , respectively), even after adjusting for age. Florbetapir SUVRs were slightly but not significantly better than CSF p-tau/ $A\beta$ 1-42 ratios ($p=0.09$), and better than CSF $A\beta$ 1-42, total tau, and p-tau levels ($p=0.04$, 0.04 , and 0.06 , respectively) in predicting subsequent cognitive decline.

Conclusions: $A\beta$ PET and, to a lesser extent, CSF p-tau/ $A\beta$ 1-42 measurements may provide prognostic indicators of AD-related cognitive decline in ADAD mutation carriers. Indeed, $A\beta$ PET may be a better prognostic indicator than CSF $A\beta$ and tau levels in the group of mutation carriers assessed up to 25 years before their estimated age at clinical onset. Research is needed to further clarify the prognostic value of these biomarkers in cognitively unimpaired persons at risk for autosomal dominant and late-onset AD.

DIFFERENCES IN RESTING STATE FUNCTIONAL CONNECTIVITY BETWEEN AEROBIC ATHLETES AND SEDENTARY YOUNG ADULTS. Raichlen DA, Bharadwaj PK, Fitzhugh MC, Haws KA, Torre GA, Trouard TP, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Recent studies have shown that aerobic exercise can positively impact brain structure and cognitive function across the lifespan (Kramer et al., 2006). In older adults, physical activity generates the greatest improvements in executive functions, which some have linked to increased functional connectivity in the fronto-parietal resting state network (FPN). Fewer studies have examined the effects of physical activity on young adult brains, a key sample since exercise at young ages may impact the trajectory of brain aging. We compared resting-state functional connectivity in a sample of collegiate cross-country runners and a sample of healthy, sedentary controls to test the hypothesis that aerobic activity affects resting state networks associated with executive control functions in young adults.

Methods: T1 volumetric and resting-state functional connectivity magnetic resonance imaging (MRI) scans were acquired on a 3.0T GE Signa Excite scanner, in 12 adult male cross-country runners (mean±SD age=21.3±2.5) and 11 healthy, sedentary age matched controls (mean±SD age=20.6±1.1). Images were pre-processed, motion scrubbed, denoised and temporal band pass filtered using the CONN functional connectivity toolbox (Whitfield-Gabrieli et al., 2012). Subsequently, the average BOLD signal time course from the bilateral anterior nodes of the FPN was correlated with every other voxel's time course to obtain a brain map of correlation coefficients for each participant, which was used to evaluate group differences with significance for cluster extent taken with FDR, $p < 0.05$.

Results: The athletes had greater average connectivity from the two seed regions of the FPN to a region in the left superior frontal gyrus (SFG) compared to controls, who showed an anti-correlation in this area. The controls also showed a region of anti-correlation in the right precentral gyrus (PCG) that was not observed in the athletes. There were significant positive associations between the correlations at these two regions and self-reported physical activity (left SFG $p=0.003$; right PCG $p<0.00004$) and estimates of maximum aerobic capacity (left SFG $p<0.0002$; right PCG $p<0.00002$).

Conclusions: Our results suggest that differences in aerobic activity observed between endurance athletes and sedentary adults may differentially impact the functional connectivity that link aspects of executive and motor functions. Significant correlations between connectivity and measures of exercise participation and aerobic capacity suggest that time spent in higher intensity activity may play a role in enhancing functional connectivity in young adults. Together these findings suggest that high intensity physical activity, such as running, stresses cognitive domains in ways that lead to altered functional brain connectivity.

RELATION BETWEEN SOCIAL INTERACTION AND COGNITIVE FUNCTIONING IN OLDER ADULTS: A FEASIBILITY STUDY USING THE EAR TECHNOLOGY.

Robbins R, Glisky E, Mehl M. University of Arizona; Arizona Alzheimer's Consortium.

Background: In older adults higher levels of social engagement are associated with better cognitive function as measured by intelligence tests, executive functions and memory functioning. Research suggests that it is the quality of interactions instead of the quantity that impacts cognition.

Methods: This pilot study used the Electronically Activated Recorder technology to explore the relation between frontal/executive and memory functioning and social interaction in older adults as measured by type of conversation (substantive talk or small talk) spoken by the participant while with others. The EAR technology was used to collect objective measures of social interaction by recording participants' daily conversations. Participants included 7 females and 3 males with a mean age of 74.5 years (Range=67-80); 17 years of education (Range=14-19); 7 lived alone and 3 lived with a spouse. Neuropsychological tests measured executive functions and memory functioning.

Results: Although small numbers precluded significant findings, a Pearson partial correlation coefficient suggested a positive correlation between memory functioning and substantive talk with others after controlling for living situation (living with a spouse or living alone), $r(8) = .56$, n.s. Results suggested a positive correlation between frontal functioning and percentage of substantive talk with others, $r(10) = .61$, n.s., controlled for living situation. Specifically, the executive function of updating in working memory appears to be correlated with percentage of substantive talk with others, $r(10) = .41$, n.s.

Conclusions: Preliminary findings from this pilot study suggest that social interaction, in the form of substantive talk, is positively associated with frontal functioning and more specifically, updating, in older adults.

AGING WITH TRAUMATIC BRAIN INJURY: AGE AT INJURY EFFECTS ON BEHAVIORAL OUTCOME FOLLOWING DIFFUSE BRAIN INJURY IN RATS. Rowe RK, Ziebell JM, Harrison JL, Law LM, Adelson PD, Lifshitz J. Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona College of Medicine; Arizona State University; Arizona Alzheimer's Consortium.

Background: Development and aging are influenced by external factors with the potential to impact health throughout the life span. Traumatic brain injury (TBI) can initiate and sustain a lifetime of physical and mental health symptoms. Over 1.7 million TBIs occur annually in the United States alone, with epidemiology suggesting higher incidence for young age groups. Additionally, increasing life spans mean more years to age with TBI. While there is ongoing research of experimental pediatric and adult TBI, few studies to date have incorporated animal models of pediatric, adolescent, and adult TBI to understand the role of age-at-injury across the life span. Here, we explore repeated behavioral performance between rats exposed to diffuse TBI at five different ages. Our aim was to follow neurological morbidities across the rodent lifespan, with respect to age-at-injury.

Methods: A single cohort of male Sprague-Dawley rats (n=69) was received at post-natal day (PND) 10. Subgroups of this cohort (n=11-12/group) were subjected to a single moderate midline fluid percussion injury (mFPI) at age PND) 17, PND 35, 2 mo, 4 mo, or 6 mo. A control group of naïve rats (n=12) was assembled from this cohort. The entire cohort was assessed for motor function by beam walk at each 1.5 mo, 3 mo, 5 mo, and 7 mo of age. Anxiety-like behavior was assessed with the open field test at 8 mo of age. Cognitive performance was assessed using the novel object location task at 8 mo, 9 mo, and 10 mo of age. Depression-like behavior was assessed using the forced swim test at 10 mo of age.

Results: Age-at-injury and time since injury differentially influenced motor, cognitive, and affective behavioral outcomes. Motor and cognitive deficits occurred in rats injured at earlier developmental time points, but not in rats injured in adulthood. In contrast, rats injured during adulthood showed increased anxiety-like behavior compared to uninjured control rats. A single diffuse TBI did not result in chronic depression-like behaviors or changes in body weight among any groups.

Conclusions: The interplay of age-at-injury and aging with an injury are translationally important factors that influence behavioral performance as a quality of life metric. More complete understanding of these factors can direct rehabilitative efforts and personalized medicine for TBI survivors.

HISTOPATHOLOGY AND FLORBETABEN PET IN PATIENTS INCORRECTLY DIAGNOSED WITH ALZHEIMER'S DISEASE. Sabbagh MN, Schäuble B, Richards D, Anand K, Beach TG, Murayama S, Akatsu H, Takao M, Rowe CC, Masters CL, Sabri O, Barthel H, Gertz H-J, Peters O, Rasgon N, Booth DR, Schulz-Schaeffer WJ, Seibyl J. Barrow Neurological Institute; Piramal Imaging GmbH, Berlin, Germany; Banner Sun Health Research Institute; Tokyo Metropolitan Geriatric Hospital; Tokyo Metropolitan Institute of Gerontology; Fukushima Hospital, Toyohashi, Japan; Nagoya City University, Aichi, Japan; Mihara Memorial Hospital, Isesaki, Japan; University of Melbourne, VIC, Australia; Florey Institute of Neuroscience and Mental Health, Australia; Leipzig University, Germany; Charité Berlin, Berlin, Germany; Stanford School of Medicine; Bioscript Group, Macclesfield, UK; Georg-August University Göttingen, Germany; Molecular Neuroimaging, New Haven, CT; Arizona Alzheimer's Consortium.

Background: Correct diagnosis in patients with cognitive decline can be challenging, with a high incidence of misdiagnosis and implications for patient management. We describe a series of patients from a Phase 3 study who were found to be negative for amyloid beta (A β) on post-mortem histopathology and florbetaben positron emission tomography (PET) scan, despite a clinical diagnosis of Alzheimer's disease (AD).

Methods: Patients were end-of-life individuals who participated in an open-label Phase 3 study comparing florbetaben PET imaging with post-mortem histopathology (ClinicalTrials.gov: NCT01020838).

Results: Of 74 individuals in the original study, 57 were clinically diagnosed with AD, of whom 13 (23%) were negative for A β on histopathology. These patients presented with memory loss, cognitive dysfunction, behavioural and psychological problems, and inability to carry out activities of daily living. At post-mortem histopathology, a wide range of different non-AD conditions was identified, including frontotemporal dementia (FTD), argyrophilic grain dementia, and dementia with Lewy bodies. Florbetaben PET scans were classified as negative for A β in 11 patients based on visual analysis and in all 12 evaluable cases based on composite standardized uptake value ratios.

Conclusions: The diagnostic accuracy of a clinical diagnosis of AD is 77%. Florbetaben PET can assist physicians in the differential diagnosis of neurodegenerative disorders by reliably excluding amyloid pathology.

ENHANCED SINGLE UNIT FIRING TO UNEXPECTED LARGE REWARDS IN AGED AMYGDALA NEURONS. Samson RD, Duarte L, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: With aging, changes in emotional regulation can lead to biases in decision making towards certain or safe options. In fact, we found that aged rats are more risk averse and will more readily select a small certain reward over a larger probabilistic one.

Methods: The activity of neurons in the basolateral complex of the amygdala (BLA) was examined in young and aged rats during rest and while acquiring and performing a probabilistic decision making task.

Results: The greatest modulation in firing rate occurred following reward, with the largest change occurring after uncertain large rewards, a modest change in firing rate following small/certain rewards and no change when rewards were not delivered. When all neurons that fired at or above 0.1 Hz were analyzed, the variability and amplitude of change following rewards was much larger in old than in young rats. When neurons with a firing rate below 1Hz were excluded from analysis in both age groups, the young and aged rats did not differ in the amplitude of change of their firing rates in response to uncertain/large rewards. To better characterize how BLA neurons change their firing rate to uncertain rewards, BLA cells were separated into four categories: regular, irregular, irregular/bursty and bursty, based on their local variance, which is a measure of the variability between adjacent inter-spike intervals (ISI). Regular firing neurons accounted for only 1-2% of the 10,000 BLA neurons recorded, and had high firing rates at rest, which were reduced following reward delivery in aged rats. In contrast, irregular neurons accounted 20% of the BLA neural population, and showed the greatest increase in firing rate following large rewards, in both age groups. The vast majority of neurons (60%) had a local variance around 1.5 and an ISI distribution indicating that these cells alternated between irregular and burst firing modes. Following rewards, some of these cells displayed increases and others decreases in firing rates. This effect was consistent across age groups. Finally, bursty neurons accounted for the remaining 20% of the BLA population and only in aged rats did these cells show an increase in firing rate following uncertain/large reward delivery.

Conclusions: Thus the change in firing rates of BLA neurons to unexpected rewards appears to be mediated by neurons from all categories, but aging appears to selectively impact low firing rate BLA neurons in a way that allows the aged network to be more responsive to rewards. This effect may contribute to the age-related increases in risk aversion found during probabilistic decision making tasks.

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IDENTIFICATION OF TREM2 AGONISTS AS A THERAPEUTIC AVENUE FOR ALZHEIMER'S DISEASE. Schrauwen I, Sereduk C, Yin H, Huentelman M. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The global prevalence of dementia is projected to increase in the coming decades as the population ages. Alzheimer's disease (AD) is a leading cause of dementia, and current FDA-approved drugs for AD do not prevent or reverse the disease, and provide only modest symptomatic benefits. Alterations in both astrocytes and microglia, reflecting underlying changes in innate immune activation within the brain, are invariant pathological features of AD as well as other neurodegenerative disorders.

Methods: Several studies have demonstrated that genetic variants in triggering receptor expressed on myeloid cells 2 (TREM2), a known regulator of microglial activation and phagocytosis, confer substantial risk to several forms of dementia and neurodegenerative disease. This evidence is further strengthened by the first report of a nonsense mutation we recently identified in a family with behavioral variant frontotemporal lobar degeneration (bvFTLD). TREM2 function may affect AD pathology through the phagocytosis of amyloid plaque deposits and other debris, and recent studies overexpressing TREM2 in vitro and in vivo support this hypothesis. We hypothesize that agonists of TREM2 could increase the clearance of amyloid- β , apoptotic neurons and other debris in the brain and may therefore act to prevent or to slow disease progression when administered during the optimal timeframe.

Results: We have developed a reporter cell line that can detect the activation of TREM2 to identify compounds that can stimulate TREM2 in high throughput. The luciferase reporter cell-line stably expresses TREM2, TYROBP and NFAT Luciferase. We will screen 2,400 compounds from the well characterized Prestwick and LOPAC libraries at two doses (5 and 20 μ M), All positive hits will be further validated using an NFAT-Luc counter-screening approach and TREM2 selective blocking. Results will be presented at the meeting.

Conclusions: This cell-based high throughput assay for TREM2/TYROBP dependent signaling and agonist discovery program are aimed at laying the foundation for the detection of potent and selective compounds for future in vitro and in vivo development to prevent/halt AD progression and other forms of dementia.

TRANSCRIPTIONAL CHANGES IN THE HIPPOCAMPUS RELATED TO AGING AND COGNITION. Siniard AL, De Both MD, Piras IS, Chawla M, Ianov L, Guzman-karlsson M, Kennedy A, Day J, Young J, Blanton S, Wright C, Sweatt D, Foster T, Moroz L, Barnes C, Huentelman MJ. Arizona Alzheimer's Consortium; University of Arizona; Translational Genomics Research Institute; University of Florida; University of Miami; University of Alabama.

Background: Normal cognitive aging results in a wide variance of task performance in humans and rodents. One possible explanation for this variance is the correlation of gene expression patterns with performance and thereby providing a sort of molecular signature to differential cognitive aging. We sought to investigate that here through the use of RNA sequencing of several hippocampal subregions. Comparisons were performed to examine RNA differences associated with aging, spatial memory performance and to hippocampal subregion identity.

Methods: Young (6 month old) and aged (23 month old) rats were tested on a Morris Water Maze task to identify "good" performers and "bad" performers. Hippocampal subregions (CA1, CA3, DG) were isolated, RNA extracted, and RNA sequencing was performed. mRNA and rRNA-depleted whole transcriptome (WT) RNA libraries were sequenced on the Illumina HiSeq 2500 to an average depth of 10 million reads, allowing us to investigate both coding and noncoding RNA. Additionally, mRNA libraries were independently prepared and sequenced on an Ion Proton sequencer as technical validation. Sequencing data was trimmed, aligned to the rn6 reference genome, and summarized at the gene level. Differential expression analysis was performed (DESeq2) to identify genes that correlate with aging or cognitive performance, or are specific to hippocampal subregions. Finally, pathway analysis was conducted to identify significant groups of significant/nearly significant genes.

Results: Using the Illumina mRNA sequencing results as our primary data and subject to validation in the WT and Ion Proton mRNA sequencing, we identified 23 genes associated with aging in the CA1, 12 genes in CA3, and 58 genes in DG. When comparing cognitively good vs cognitively bad age-matched rats, we identified only a single significant gene, MLXIPL in CA1, but pathway analysis uncovers a significant ionotropic glutamate receptor pathway that mediates synaptic transmission. Finally, our study design allowed us to explore subregion-specific expression. For this, we identified 1462 genes with expression significantly unique in CA1 compared to CA3 or DG, 1597 genes significant in CA3, and 4156 genes significant in DG.

Conclusions: RNA sequencing is a powerful approach when profiling small subregions of tissue. Our dual-platform (Illumina & Ion Torrent) and dual-prep (mRNA & whole transcriptome) approach provide confidence that we have accurately sampled the population of RNA and limit our exposure to technique-based false positives. We identify thousands of genes with hippocampal subregion-specific expression, dozens of genes associated with aging, but only one gene significant with cognitive performance, suggesting that the cognitive variance associated with normal aging is likely not occurring at the sub-region level but is more likely associated with differences at the level of the engram.

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THE EFFECT OF STATINS ON RATE OF COGNITIVE DECLINE IN MILD COGNITIVE IMPAIRMENT. Smith KB, Kang P, Sabbagh MN, The Alzheimer's Disease Neuroimaging Initiative. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: This study's aims are to identify whether or not a relationship between statin use and rate of cognitive decline exists. The relationship between statins and MCI has been investigated in the past with the evidence showing mixed results.

Methods: 768 subjects were identified with MCI. Subjects were stratified into 6 possible groups according to ApoE4 status and statin use and assessed for decline in cognitive function.

Results: All cognitive assessments trended towards less decline with statin use. ADAS11 showed the biggest difference in mean change between statin users and non-users (-0.82 vs. -1.22 respectively). Change reached marginal significance on the ADAS11 when stratified by ApoE4 negative subjects.

Conclusions: All cognitive assessments trended towards less decline when subjects were concurrently treated with a statin, supporting the position that statins do not have a net negative effect on cognitive assessment and suggests a potential treatment benefit.

LOWER FRONTAL AMYLOID BURDEN IN ANTIDEPRESSANT USERS: PRELIMINARY FINDINGS FROM PERSONS WITH AND WITHOUT POST-TRAUMATIC STRESS DISORDER IN THE ADNI DOD STUDY. Snyder N, Chen K, Luo J, Thiyyagura P, Devadas V, Chen Y, Bauer III R, Sheline YI, Jagust WJ, Neylan T, Landau SM, Weiner MW, Reiman EM. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of Pennsylvania; University of California Berkeley; University of California San Francisco; Translational Genomics Research Institute; University of Arizona.

Background: Florbetapir PET images were used to compare cerebral amyloid burden in participants with post-traumatic stress disorder (PTSD) and in control subjects without PTSD or history of traumatic brain injury. Since PTSD participants had suggestive evidence of lower (not higher) standard uptake value ratios (SUVRs) than the controls in the frontal cortex, since antidepressants are commonly used in persons with PTSD, and since serotonin reuptake inhibitors (SSRIs) have been shown to be associated with cerebrospinal fluid and PET evidence of lower amyloid accumulation (Cirrito, 2011; Sheline, 2014), post-hoc analyses were performed to investigate the possibility that these findings are attributable to antidepressant use.

Methods: Mean cerebral-to-cerebellar SUVRs, an amyloid positive threshold of 1.18 consistent with moderate-to-severe amyloid plaques (Fleisher, 2011), and statistical brain maps (SPM) were used to compare florbetapir PET scans from 52 male participants with PTSD (68 +/- 4 years old, 4 with mild cognitive impairment [MCI]) and 52 male controls (71 +/- 6 years old, 2 with MCI). Post-hoc analyses were performed to determine whether regional SUVR differences are attributable to antidepressant use in 24 PTSD patients (including 15 on an SSRI) and 3 controls (including 1 on an SSRI).

Results: PTSD and control groups did not differ in their mean cerebral SUVRs corrected for age and education ($P=0.18$; $P=0.04$ without age/education correction). However, the PTSD group had a significantly lower percentage of amyloid positive participants (PTSD: 3.8%, NC: 19.2%; $P=0.01$). Brain maps revealed significantly lower regional SUVRs in the PTSD group, primarily in the frontal cortex ($P<0.005$, corrected for age and education, uncorrected for multiple comparisons). Regional differences were no longer apparent after correction for antidepressant use. Furthermore, antidepressant users were distinguished from non-users by significantly lower frontal SUVRs (uncorrected $P<0.005$), a significantly lower percentage of amyloid positive subjects (users: 0%, non-users: 15.6%; $P=0.03$), and a significantly greater proportion of cerebral voxels with lower SUVRs (Monte-Carlo Simulation, $P<0.001$).

Conclusions: While preliminary, our findings suggest that adults with PTSD have less fibrillar amyloid and that this reduction may be at least partly attributable to antidepressant use. They support the possibility that antidepressants are associated with reduced amyloid plaque burden and with a lower risk of AD.

PREDICTING PROGRESSION TO MILD COGNITIVE IMPAIRMENT IN COGNITIVELY UNIMPAIRED INDIVIDUALS USING NEUROIMAGING BIOMARKERS. Stonnington CM, Lee W, Bauer III RJ, Sharieff S, Chen Y, Caselli RJ, Locke DEC, Reiman EM, Chen K. Mayo Clinic Arizona; Banner Alzheimer's Institute; Midwestern University; Arizona Alzheimer's Consortium.

Background: Neuroimaging biomarkers can detect disease pre-clinically but their prognostic value, alone or in combination, is uncertain.

Methods: Volumetric MRI and FDG-PET data were compared in 18 cognitively unimpaired participants approximately 2 years (1.8 ± 0.8) before the clinical diagnosis of aMCI due to Alzheimer's disease (AD) and 35 participants who were matched for age and sex and remained unimpaired for ≥ 4 years (nonprogressors) after their imaging acquisition. We further compared the 18 pre-MCI participants to 20 nonprogressors who were matched for age, sex, and APOE status. The participants have been followed in the Arizona APOE Cohort, have a reported first degree family history of possible AD dementia, and were enriched for APOE4 gene dose. Voxel-wise analyses were used to characterize reductions in regional gray matter volume and cerebral glucose metabolism in the clinical progressor and non-progressor groups. Binary logistic regression, leave-one-out, and Receiver Operating Curve analyses were performed to characterize the extent to which posterior cingulate glucose metabolism, the AD-related hypometabolic conversion index (HCI), hippocampal volumes (HCV), and entorhinal cortical thickness, alone or in combination, could distinguish between subsequent progressors and non-progressors.

Results: The progressor and non-progressor groups did not differ significantly in their age (68 ± 4), sex, education, or general intelligence, but significantly more APOE e4 carriers appeared in the group who developed aMCI in the group that was not matched for APOE status. The average age of clinical diagnosis was 71 ± 5 . Compared to both nonprogressor groups, those who developed aMCI in approximately 2 years had significant (FWE corrected $p \leq 0.05$) decreases in glucose metabolism, gray matter volume, and cortical thickness in regions known to be preferentially affected by AD. In the groups matched for APOE, the best single predictor of aMCI was right and left HCV, with 79% sensitivity and 78% specificity, and there was no improvement in performance when adding FDG-PET data. For the groups not matched for APOE, the best predictor was left HCV, with 74% sensitivity and 72% specificity, and combining MRI and FDG PET data (Left HCV + right entorhinal thickness + HCI + Posterior Cingulate glucose metabolism) increased the sensitivity and specificity of the predictive model to 77% and 78%. Based on logistic regression models, APOE e4 partially mediated the effect on the left hippocampus.

Conclusion: This study supports the possibility that regional MRI and FDG PET measurements, individually or in combination, could help predict the likelihood of progressing to the clinical stages of AD.

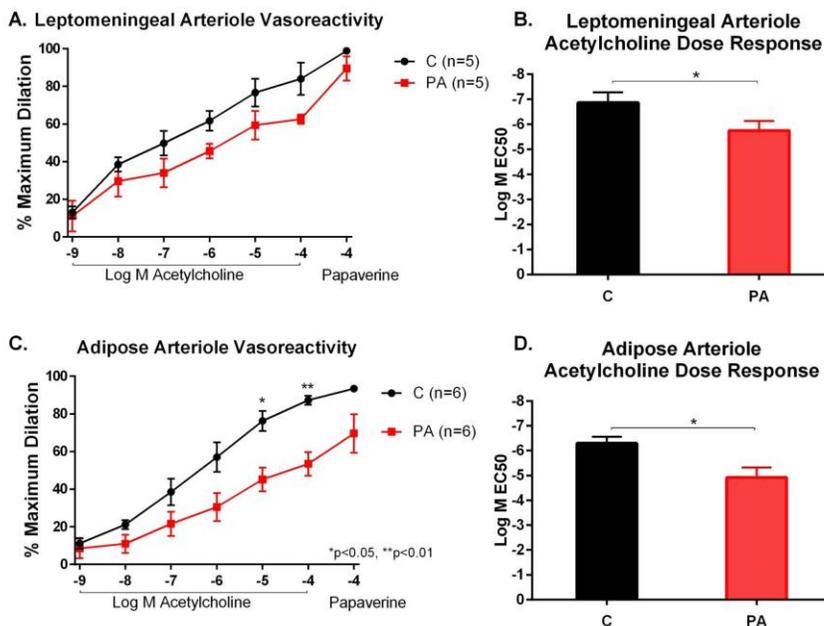
PALMITIC ACID-INDUCED ENDOTHELIAL DYSFUNCTION IN HUMAN LEPTOMENINGEAL AND ADIPOSE ARTERIOLES. Truran S, Karamanova N, Serrano G, Franco D, Burciu C, Beach TG, Roher A, Migrino RQ. Phoenix VA Health Care System; Banner Sun Health Research Institute; University of Arizona College of Medicine Phoenix; Arizona Alzheimer's Consortium.

Background: Epidemiologic data show strong link between Alzheimer's disease (AD) and cardiovascular risk factors with evidence that the earliest changes in AD involve vascular dysfunction. The mechanisms behind vascular impairment in AD remain poorly understood, and lack of a human model to study them impedes progress towards a cure.

Methods: LMA from cadavers of brain donors (post-mortem interval 3.3 ± 0.4 hours) and abdominal subcutaneous AA from living subjects undergoing routine surgery were isolated, cannulated and pressurized. Following precontraction with endothelin-1, baseline (control) dilation response to acetylcholine and papaverine was measured. Arterioles were then exposed to 1 hour of PA ($150 \mu\text{M}$) and a second dilation response was measured.

Results: (see Figure) PA decreased dilator response to acetylcholine in both LMA and AA (change in dilator response to acetylcholine 10-4M: $-28.1 \pm 6.8\%$ for LMA and $-33.8 \pm 7.4\%$ for AA, both $p < 0.05$ versus baseline control). There was no significant reduction in dilator response to papaverine. The changes in dilator response with PA versus control were not different between LMA and AA.

Conclusions: Acute exposure to PA induced endothelial dysfunction in human leptomeningeal arterioles suggesting a potential mechanism for vascular dysfunction that could contribute to AD. Similarity in pathologic response between LMA and AA suggests that AA, which is easier to obtain, may be a novel surrogate human model to study brain microvascular function.



MATERNAL CHOLINE SUPPLEMENTATION AS A PREVENTIVE THERAPEUTIC OPTION WITH TRANSGENERATIONAL ALTERING PROPERTIES FOR ALZHEIMER'S DISEASE PATHOLOGY. Velazquez R, Ferreira E, Tran A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders worldwide. Clinically, AD is characterized by impairments in memory, cognitive and intellectual functions. Over the next few decades, the advancing age of the global population will dramatically increase the prevalence of AD (an estimated 20 million by 2050 in the US alone). Currently, there are no effective treatment options; therefore, there is an urgent need for novel, safe, and efficacious strategies to mitigate this disorder. Recent work in a mouse model of Down syndrome, which develops some aspects of AD-like phenotype, has shown that maternal choline supplementation (MCS), during gestation and lactation leads to an improvement in cognitive function in 12-month-old offspring. Additionally, our preliminary in vitro data provide compelling evidence that MCS reduces A β levels and promotes cell viability in APP/PS1 primary neurons. The main objective of the present experiment was to test the benefits of MCS on learning and memory in APP/PS1 mice, a widely used mouse model of AD.

Methods: 2-month-old APP/PS1 mice were bred with C57Bl/6 mice. We used a balanced number of male and female APP/PS1 mice for breeding. Half of the breeding pairs were kept on a control (CTL) diet, with standard content of 1.1 g/kg choline chloride, while the remaining mice were on a maternal choline supplemented (MCS) diet of 5 g/kg choline chloride, from conception through postnatal day 21. After weaning, mice were kept on the CTL diet throughout the remaining of the experiments. Both APP/PS1 and NonTg male and female offspring were used for testing of spatial reference memory using the Morris water maze task starting at ~ 11 months of age. Animals were sacrificed after testing and tissue was collected to assess AD-related neuropathological markers.

Results: APP/PS1 mice whose mothers were on the MCS diet from gestation through post-natal day 21 performed significantly better than mice whose mother were on the CTL on the Morris water maze task. Specifically, on day 6 probe trial, MCS APP/PS1 mice had a significantly higher number of platform crossings and a shorter latency to reach the platform location compared to CTL APP/PS1 mice. The exact mechanisms behind such long-lasting benefits remains to be determined, although previous work suggest that this may be accomplished through alterations in epigenetic mechanisms. Furthermore, we plan to decipher whether MCS in one generation is capable of reducing AD-neuropathology in a subsequent generation, providing the potential for a preventive therapeutic strategy with transgenerational benefits. To this end, our in vitro data shows that MCS from one generation is capable of increasing cell viability in two subsequent generations.

Conclusions: Collectively, our results suggest that simply modifying the diet of pregnant mothers with additional choline improves cognitive deficits in the offspring late in adulthood. We stipulate that these benefits may be carried over throughout subsequent generations. This work holds a high translational value and serve as a springboard for future clinical trials with the ultimate goal of reducing the estimated increase in AD pathology for future generations.

PIM1 INHIBITION AS A NOVEL THERAPEUTIC STRATEGY FOR ALZHEIMER'S DISEASE. Velazquez R, Shaw DM, Caccamo A, Oddo S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder worldwide. Clinically, AD is characterized by impairments of memory and cognitive functions. Accumulation of amyloid- β ($A\beta$) and neurofibrillary tangles are the prominent neuropathologies in patients with AD. Strong evidence indicates that an imbalance between production and degradation of key proteins contributes to the pathogenesis of AD. The mammalian target of rapamycin (mTOR) plays a key role in maintaining protein homeostasis as it regulates both protein synthesis and degradation. A key regulator of mTOR activity is the proline-rich AKT substrate 40 kDa (PRAS40), which directly binds to mTOR and reduces its activity. Notably, AD patients have elevated levels of phosphorylated PRAS40, which correlate with $A\beta$ and tau pathologies as well as cognitive deficits. Physiologically, PRAS40 phosphorylation is regulated by Pim1, a protein kinases of the proto-oncogene family. Here, we tested the effects of a selective Pim1 inhibitor (Pim1i), on spatial reference and working memory and AD-like pathology in 3xTg-AD mice.

Methods: We have identified a Pim1i that crosses the blood brain barrier and reduces PRAS40 phosphorylation (pPRAS40). Starting at 7 months of age, mice were injected with a 100mg/kg dosage of either the Pim1i or a vehicle (Veh) solution for a total of 28 days. Testing on the radial arm water maze task (RAWM), which probes spatial reference and working memory began at day 26 of treatment and concluded at day 28. Tissue was collected and assayed for pPRAS40 levels, $A\beta$, tau, and protein degradation markers via western blot, ELISA and immunohistochemistry.

Results: Pim1i-treated 3xTg-AD mice performed significantly better than their vehicle treated counterparts as well as non-transgenic mice. Additionally, 3xTg-AD Pim1i-treated mice showed a reduction in soluble and insoluble $A\beta_{40}$ and $A\beta_{42}$ levels, as well as a 45.2% reduction in $A\beta_{42}$ plaques within the hippocampus. Furthermore, phosphorylated tau levels were reduced in Pim1i-treated 3xTg-AD mice by 38%. Mechanistically, these changes were linked with a significant increase in proteasome activity.

Conclusions: These results suggest that reductions in phosphorylated PRAS40 levels via Pim1 inhibition reduce $A\beta$ and Tau pathology and rescue cognitive deficits by increasing proteasome function. Given that Pim1 inhibitors are already being tested in ongoing human clinical trials for cancer, the results presented here may open a new venue of drug discovery for AD by developing more Pim1 inhibitors.

THE QUEST FOR A ROBUST AND RELIABLE REFERENCE REGION (RR). EXPLORING RR STABILITY ACROSS CLINICAL CATEGORIES, ACROSS AB STATUS AND ACROSS TIME FOR FIVE DIFFERENT AB RADIOTRACERS.

Villemagne VL, Bourgeat P, Doré V, Macaulay L, Williams R, Ames D, Martins RN, Salvado O, Chen K, Reiman EM, Masters CL, Rowe CC. Austin Health, Melbourne, Australia; The Florey Institute of Neuroscience and Mental Health, Parkville, Australia; CSIRO, Brisbane, Australia; CSIRO, Melbourne, Australia; The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia; National Ageing Research Institute, Melbourne, Australia; Hollywood Private Hospital, Perth, Australia; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: The reference region (RR) was characterized as having similar cellular and blood flow as target regions (TR) but lacking specific binding, assuming that both nonspecific binding and the volume of distribution of the free compartment are the same as in TR. On account semiquantitative standard uptake value (SUV) ratio (SUVR) being used as outcome measure in anti-A β therapeutic trials we assessed the stability of different RR with five A β imaging tracers and then evaluated the variance in TR derived with stable RR. While several studies have focused on such variance by using different RR, none has focused on assessing if a given RR truly behaves as stable, and if its performance is tracer specific or not.

Methods: 1066 participants were evaluated (327-PiB; 256-flutemetamol -FLUTE-; 189-florbetapir -FBP-; 212-florbetaben -FBB-, and 82-NAV4694), where 496 had longitudinal scans. SUV of either gray matter (GM) or white matter (WM) RR, and their combinations across clinical conditions, A β status, and time was examined. Variance of global A β burden estimates were assessed for stable RR.

Results: Cerebellar GM (CbGM) was the most stable RR for PiB, FBB and NAV. SMMKCER* was the most stable performing RR for FBP, while performing almost identically to SWM-Pons for FLUTE. SMMKCER* and SWM+Pons yielded the lowest variance for longitudinal FBP and FLUTE, respectively. Despite smaller variances in target regions, SWM+WCb+pons was not stable for PiB and FBB across clinical diagnoses, nor for PiB, FLUTE and FBP across A β status. A β burden variances obtained with the stable RR were similar for all tracers.

Conclusions: SWM+pons and SWMKCER for FLUTE, CbGM for PiB, FBB and NAV, and SWMKCER for FBP remained stable across the examined conditions, yielding low variances of the A β burden estimates. To optimize outcomes in ongoing therapeutic trials, tracer-specific RR should be applied.

WHAT ARE ACTIVATED MICROGLIA DOING IN ALZHEIMER'S DISEASE BRAINS?: SEARCH FOR ADDITIONAL FUNCTIONAL MARKERS. Walker DG, Tang T, Tsang A, Lue, LF. Arizona State University; Arizona Alzheimer's Consortium.

Background: It has been 30 years since the studies demonstrating that the major histocompatibility complex (MHC) protein HLA-DR could be a marker to identify "activated" microglia in human brain tissue sections. Increased expression of HLA-DR has been widely observed by microglia associated with neuropathology. In Alzheimer's disease (AD), the most intensely stained microglia were associated with amyloid plaques. The primary function of HLA-DR is antigen presentation to T cells, which does not appear applicable in human brains. HLA-DR has been the most widely used marker to identify activated microglia in human brain tissue sections, followed by ionizing calcium-binding adapter molecule 1 (IBA1). However, there is little understanding of the function of these immunoreactive cells. The identified cells may be classically activated and causing inflammatory damage, or alternatively activated and participating in reparative responses. There are needs for more defined markers of microglia that can designate function. In this report, we describe findings using an antibody to endoglin (CD105), which identifies a subset of activated microglia; an antibody to progranulin, a protein with neuroprotective properties but identifies many plaque-associated microglia. We also revisit findings for CD14 (LPS receptor), a marker of classically activated microglia, and CD206, a marker for alternatively activated microglia.

Methods: This study utilized tissue sections and protein extracts from human brain tissue samples from control, AD and PD cases, and also human microglia cultured from human autopsy brains. Human brain samples were obtained from the Banner Sun Health Research Institute Brain and Body Donation Program. The techniques included immunohistochemistry and western blots utilizing a range of antibodies.

Results: We identified an antibody to endoglin (R &D Systems, MAB1097) that recognized a subset of activated microglia in AD and PD tissues, but with almost no staining in non-pathological tissue. This antibody did not show the expected staining of vascular endothelial cells. Double staining of sections with antibodies to endoglin and HLA-DR or IBA-1 identified colocalization of both markers in microglia. The morphologies of endoglin-positive microglia varied from ramified to highly amoeboid. A similar approach identified that microglia of a range of morphologies from ramified to amoeboid could be stained with an antibody to progranulin. Upregulated expression of progranulin was apparent in microglia around neuritic amyloid plaques. We also reexamined the expression of CD14 by microglia. In normal control cases, strong staining for CD14 was only seen in blood vessel monocytes, while in pathology-rich regions of AD and PD cases, there was a noticeable increase in numbers of CD14-positive microglia. By contrast, no CD206-positive microglia were detected in any human brain sections, only macrophages/monocytes present within cerebral blood vessel. These results expand the range of markers that can be used to describe the microglial populations present in diseased human brains.

Conclusions: Microglia can be contributing to disease pathology or reducing the consequences of pathology by removing and digesting cellular debris included amyloid plaque material. Being able to better distinguish different functions of microglia within tissue sections will aid in developing effective disease modifying therapies. The classical markers of microglia that have been widely used, namely HLA-DR and IBA-1, have limitations in this regard. In conclusion, we have compared results of immunostaining for additional markers, and suggest that they might be useful for subdividing microglia populations in diseased brains.

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THE ALZHEIMER'S PREVENTION REGISTRY GENEMATCH PROGRAM. Walsh T, Langbaum JB*, Karlawish J, Bradbury A, McCarty Wood B, Roberts JS, Kim S, Patrick-Miller L, Blacker D, Caselli RJ, Marchant GE, Zallen D, Langlois C, Gordon D, Reiman EM, Tariot PN. Banner Alzheimer's Institute; University of Pennsylvania; University of Michigan School of Public Health; National Institutes of Health; University of Chicago; Harvard University; Mayo Clinic Arizona; Arizona State University; Virginia Tech University; Arizona Alzheimer's Consortium.

Background: The Alzheimer's Prevention Initiative (API) is a collaborative funded by the NIH, philanthropy, and industry to conduct preclinical Alzheimer's disease (AD) trials in people who, based on age and genetics, are at elevated risk of developing AD symptoms. Given that enrollment is one of the biggest obstacles faced by research studies, there is a need to establish a registry database that includes genetic information in order to more efficiently match interested individuals to studies. The API's Generation Study is currently enrolling apolipoprotein E (APOE) $\epsilon\epsilon$ homozygotes age 60-75. API established a trial-independent APOE genetic testing program, known as GeneMatch, to enrich referrals to the API Generation Study while also serving as the basis for an enduring recruitment infrastructure for the API program.

Methods: GeneMatch is a trial-independent program performing APOE genotyping in individuals age 55-75 to enrich referrals to prevention studies. Participants review a brief, online education video providing an overview of Alzheimer's disease and the APOE gene prior to electronically signing an informed consent. Participants use a buccal swab kit for collection of DNA; APOE genotyping is done by a CLIA-certified lab. Based in part on APOE genotype, participants may be contacted to complete additional online questionnaires, learning modules, surveys, or to notify them about new research studies. GeneMatch does not disclose APOE results to participants, either directly or inadvertently through referral to studies. Recruiting studies, however, may ask or invite individuals to learn their APOE results.

Results: GeneMatch launched in 2015 and aims to enroll tens of thousands of participants. The Generation Study launched in November 2015; enrollment and genetic disclosure are ongoing. Preliminary experience from these GeneMatch will be presented.

Conclusions: GeneMatch is a key element of the API, facilitating enrollment into a range of research studies, including the Generation Study, and serving as a resource to the Alzheimer's scientific community.

RETROSPECTIVE REVIEW OF DEMENTIA SPECIALIST EXPERIENCE WITH AMYLOID PET IMAGING: IMPACT ON CLINICAL DECISION-MAKING IN DIAGNOSIS AND PATIENT MANAGEMENT. Weidman DA, Sabbagh MN, Jacobson SA, Burke A, Belden C, Powell J, Seward J, Roontiva A, Thiyyagura P, Kuang X, Bhalla N, Chen K, Zamrini E, Reiman EM. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

In 2013-2014 a voucher program from the manufacturer of [¹⁸F] florbetapir (Amyvid) was available to dementia specialists at Banner's two memory clinics, Banner Alzheimer's Institute and Banner Sun Health Research Institute, allowing florbetapir-PET scans to be obtained more feasibly, and establish absence or presence of elevated amyloid- β in several patients presenting with objective cognitive impairment, whose diagnosis was not certain after a comprehensive evaluation. A case series review was undertaken, to describe how scan results, negative or positive, impacted on clinical diagnosis, decision-making and patient care. The primary objective was to document how often and in what circumstances amyloid imaging was helpful to the dementia specialist. All 16 patients who underwent amyloid (florbetapir) PET scanning through the memory centers, after (15) or before (1) initial comprehensive evaluation, were included. Patients whose amyloid status was known from screening evaluations in clinical research trials were excluded. Key facts and data from patient medical records were extracted, to determine: when appropriate use criteria (AUC) were met, and if so, which; if a change in diagnosis was made, and if so, what the new diagnosis was; whether diagnostic confidence increased, in cases when the diagnosis didn't change; whether there was a change in drug therapy; and what non-pharmacologic interventions were made after PET results became known. The presence or absence of elevated amyloid-beta by florbetapir-PET altered management of patients in the vast majority of cases, either by helping dementia specialists make a more specific diagnosis, or increasing their confidence. Banner dementia specialists will soon be able to obtain amyloid PET in Medicare beneficiaries who meet AUC, as participants in a multicenter longitudinal cohort study now underway, which aims to assess the impact of amyloid PET results on patient management and outcomes. Our experience with amyloid PET has been encouraging, and in that light we look forward to participating.

HIGHER BMI IS ASSOCIATED WITH GREATER CEREBRAL GLUCOSE METABOLISM IN LATE MIDDLE AGED AND ELDERLY SUBJECTS REGARDLESS OF APOE ϵ 4 GENOTYPE. Weise CM, Chen K, Chen Y, Goradha D, Savage C, Caselli R, Krakoff J, Reiman EM. Klinik und Poliklinik für Neurologie; Universität Leipzig; Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona State University; University of Arizona; Mayo Clinic; NIDDK; Arizona Alzheimer's Consortium.

Background: A number of studies found that higher body mass index (BMI) is associated with reduced risk for future development of Alzheimer's Diseases (AD), particularly in older subjects (Emmerzaal et al., 2015). Since underlying mechanisms remain unknown, we sought to investigate how BMI in late middle aged and elderly subjects relates to regional cerebral metabolic rate of glucose (rCMRgl) and whether this relationship is influenced by the status of APOE ϵ 4 allele, a genetic risk for AD or age.

Methods: A total of 197 cognitively healthy, non-diabetic subjects (59M/138F; age 61.0 ± 6.3 y, BMI 27.3 ± 4.9 kg*m⁻²), including homozygous (n=40) and heterozygous (n=58) carriers of the APOE ϵ 4 allele, underwent positron emission tomography (PET) quantification of rCMRgl using 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG)PET. Voxelwise multiple regression analyses across the whole brain and within specific regions of interest including precuneus, posterior cingulate, parietal, temporal, prefrontal, and occipital brain regions were employed to investigate associations of BMI with rCMRgl and potential interactions with APOE ϵ 4 carrier status and age. Furthermore, we applied the hypometabolic convergence index (HCI; Chen et al., 2011) in order to explore the relationship between BMI and AD typical hypometabolic patterns.

Results: We found extensive and exclusively positive associations of BMI with rCMRgl in regions known to be affected by AD such as occipital, parietal, temporal (including the bilateral hippocampal region), and other regions such as the cerebellum, frontoinsular and subcortical brain regions. Confirmatory results were found for specific ROIs. A significant BMI by gender interaction was observed with stronger associations within the right temporal cortex and the right ventromedial prefrontal cortex in males. However, no significant BMI by APOE ϵ 4 carrier status interaction or BMI by age group interaction was detected. Additionally, BMI was negatively correlated with HCI, indicating less convergence to AD typical hypometabolic patterns in subjects with high BMI measures.

Conclusions: BMI is positively associated with rCMRgl in healthy late middle aged and elderly subjects, including brain regions that are typically affected by AD, thus providing a potential explanation for the proposed beneficial effects of higher BMI with respect to AD development. These associations seem to be modified by gender, possibly as the result of differences in body composition, but not by APOE ϵ 4 genotype or age.

AUTOMATIC PREDICTION OF LINGUISTIC DECLINE FROM WRITINGS OF PATIENTS WITH DEMENTIA. Weissenbacher D, Johnson T, Wojtulewicz L, Dueck A, Locke D, Caselli RJ, Gonzalez G. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Alzheimer's is a brain degenerative disease which is increasing in the world's population due to its general aging. Since no cure is currently known, it is crucial to detect the disease at its earlier stages to develop strategies for reducing the risk of the disease and testing effective drugs. Whereas clinical methods to detect Alzheimer's disease may be costly, unreliable, and tardy, families often notice earlier signs of the disease through their language interactions with their elders.

In this study, we propose to use Natural Language Processing (NLP) to evaluate the quality of patients' writings in order to discriminate decline due to normal aging from decline due to pre-demented conditions. Within the context of the Arizona Alzheimer's Disease Center (ADC), a longitudinal study on Alzheimer's disease, we created a corpus of 201 written descriptions. In the beginning of the year 2015, we added an exercise to the protocol of the study. Patients were asked to describe an image at the end of their annual visit. This image represents a family having a picnic near a lake. The descriptions were manually transcribed and linguistic elements were annotated by several off-the-shelf NLP modules.

We created a classifier to discriminate patients in abnormal decline from patients with normal aging decline. Aside from the exact identities, we had access to all information acquired during the ADC study about the patients enrolled. To label patients with abnormal decline, we used the (1) primary diagnostic made during their last visit, (2) the score measuring their cognitive status, and (3) the Global Clinical Dementia Rating (CDR) scores. If a patient was diagnosed, or presented any signs of a disease or a mild cognitive impairment in one of these three metrics, the patient was labeled as *abnormal decline*. Otherwise, the patient was labeled as *normal*. Our classifier is a Bayesian network that incorporates lexical, stylometric and semantical features proposed by us or found in the literature.

Our experiments confirmed the ability of our classifier to learn the difference between normal patients and patients with abnormal decline. During a leave-one-out cross validation, with an accuracy of 76.6% against 86.1%, our classifier outperformed a baseline classifier which labeled all patients with the majority class label *normal*. Our ablation study showed that our classifier discriminated patients with abnormal decline using lexical and semantical irregularities found in their writings: they failed to convey pertinent information of the image and tended to digress from the initial subject.

PREVALENCE OF AUTISTIC TRAITS IN A COGNITIVELY NORMAL AGING COHORT. Woodruff B, Caselli R, Locke D. Mayo Clinic; Arizona Alzheimer's Consortium.

Background: 1.5% of young children have an autism spectrum disorder (ASD) but not included in such prevalence estimates are individuals with a subclinical “broad autism phenotype” (BAP), which has been found in approximately 4% among adults without a family history of ASD. Individuals with BAP are therefore likely present in most studies of cognitive aging, yet the impact of this is unknown. The Autism Spectrum Quotient (AQ) (Baron-Cohen et al), a validated screening questionnaire, was given to members of a cognitive aging cohort to determine the prevalence of individuals scoring in the BAP range, and to characterize their cognitive, behavioral, and personality profiles.

Methods: The AQ was given during 428 consecutive member visits of the Arizona APOE cohort beginning January 2013, and was completed by 343 members. AQ scores were treated as a dichotomous variable with scores of 23 and higher defining high AQ. Cross-sectional characteristics were compared among groups by using the two-sample t-test / analysis of variance (ANOVA) F-test or Pearson chi-square test.

Results: 35 subjects scored in the BAP range of 23 or higher (AQ+) and included a higher proportion of men, reported history of depression and sleep disturbance but no difference in education, marital status, or estimated income (based on zip code). After adjusting for age, sex and education, the AQ+ group performed less well on most measures of mental speed, working memory and arithmetic. Though behavioral measures remained within a normal range, mean scores on multiple measures including somatization, anxiety, and depression were higher and a measure of personal warmth was lower in the AQ+ group. On the NEO-PI-R five factor personality inventory the AQ+ group exhibited higher neuroticism, and lower extraversion and agreeableness.

Conclusions: In our cognitively normal aging cohort, approximately 10% of subjects completing the AQ scored in the BAP range, and differ from AQ- subjects on multiple cognitive, psychological and personality measures. The impact of the broad autism phenotype on longitudinal cognitive trajectories and outcomes awaits further study.

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HIGHLY MULTIPLEXED SINGLE CELL IN SITU ANALYSIS WITH CLEAVABLE FLUORESCENT PROBES. Xiao L, Mondal M, Liao R, Guo J. Arizona State University; Arizona Alzheimer's Consortium.

Background: The ability to profile the comprehensive molecular states in single cells is crucial for our understanding of cancer, neurobiology, and stem cell biology. However, existing single cell genomics and proteomics technologies are carried out on isolated and amplified biomolecules; thus they conceal the spatial relationships among biomolecules. Meanwhile, other in situ imaging based methods are limited by a small number of parallel analyses.

Methods: To enable highly multiplexed single-cell in situ analysis, we have developed cleavable fluorescent probes (CFP) for comprehensive molecular profiling in single cells in situ. In this method, affinity probes, which can target biomolecules with high efficiency and specificity, are conjugated to fluorophores through a cleavable linker. In each analysis cycle, different probes labeled with varied fluorophores are applied to bind to their molecular targets in single cells. After fluorescence imaging and data storage, all the different fluorophores coupled to affinity probes are efficiently removed simultaneously by cleavage of the linker.

Results: Upon continuous cycles of target binding, fluorescence imaging, and fluorophore cleavage, this approach enables the quantification of the identities, positions and abundances of hundreds of different biomolecules in individual cells in intact tissues.

Conclusions: This highly multiplexed single cell in situ analysis approach will bring new insights into systems biology, cell heterogeneity studies, molecular diagnosis and cellular targeted therapy.

THE PERIMENOPAUSAL BIOENERGETIC TRANSITION IN THE FEMALE BRAIN: IMPLICATIONS FOR PRODROMAL PHASE OF ALZHEIMER'S. Yin F, Yao J, Sancheti H, Feng T, Melcangi RC, Morgan TE, Finch CE, Pike CJ, Mack WJ, Cadenas E, Brinton, RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Perimenopause is a transition state of female aging that proceeds- and leads to reproductive senescence and is associated with multiple neurological symptoms, including those associated with increased Alzheimer's disease (AD) risk, such as depression, insomnia and subjective memory impairment. The current study determined the biological transformations that occur in the aging female brain during the perimenopausal transition and its implications for AD risk.

Methods: A preclinical model of human perimenopause was developed that assessed chronological and endocrine aging in female rats. Levels of key neuroactive steroids in serum and brain were determined by LC-MS/MS. Bioenergetic-, redox-, inflammatory-, and AD pathology-related gene expression was determined by customized low density gene array followed by bioinformatic analysis. The perimenopausal transition state was further characterized by the expression of key metabolic enzymes, the activity of signaling pathways, and mitochondrial respiratory capacity. Functional outcomes were assessed in this model using (a) FDG-microPET for cerebral glucose metabolism, (b) long-term potentiation for synaptic plasticity, and (c) glucose tolerance test for peripheral metabolic status.

Results: Gene expression analyses indicated two distinct aging programs: chronological and endocrine. Modest decline in bioenergetic gene expression occurred with chronological aging. Conversely, a critical period emerged during the endocrine transition from regular to irregular cycling characterized by a down-regulation of genes required for glucose metabolism and mitochondrial function, which were confirmed by declines in brain glucose metabolism, mitochondrial capacity and synaptic plasticity. Bioinformatic and biochemical analyses indicated that bioenergetic profiles were likely regulated by the upstream insulin/IGF1 and AMPK/PGC1 α signaling pathways. The onset of acyclicity was accompanied by a rise in genes required for mitochondrial function, inflammation, and fatty acid metabolism. Subsequent chronological aging resulted in an overall decline in genes involved in mitochondrial function and β -amyloid degradation.

Conclusions: These findings provide novel mechanistic insights into the impact of the aging perimenopausal transition on brain metabolism and synaptic function, which could have implications for identifying phenotypes of AD risk and a critical window for earliest detection in aging females.

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PATCH-BASED SPARSE CODING AND MULTIVARIATE SURFACE MORPHOMETRY FOR PREDICTING AMNESTIC MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE IN COGNITIVELY UNIMPAIRED INDIVIDUALS. Zhang J, Wang Y, Li Q, Shi J, Bauer III RJ, Chen K, Reiman EM, Caselli RJ, Stonnington CM. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Neuroimaging biomarkers in combination with classification methods have shown promise as a tool for predicting progression to the clinical stage of Alzheimer's disease (AD). The hippocampus is affected in late preclinical and early clinical stages of AD. We previously described a method capable of detecting subtle changes in hippocampal surfaces, based on the surface fluid registration and multivariate tensor-based morphometry (mTBM) statistics. We now describe a method for distinguishing between cognitively unimpaired older adults who do or do not subsequently progress to amnesic Mild Cognitive Impairment (aMCI) using our new patch-based sparse-coding system with surface multivariate morphometry statistics (MMS) from the hippocampus.

Methods: From the Arizona APOE cohort, a longitudinal study of cognitively unimpaired persons with two, one and no copies of the apolipoprotein E (APOE4) allele with a reported first degree family history of possible AD dementia, we examined volumetric MRI data from 18 cognitively unimpaired participants approximately 2 (1.8 ± 0.8) years before progression to the clinical diagnosis of aMCI and 35 participants who were matched for age and sex and remained unimpaired for ≥ 4 years. We segmented each individual MRI scan with FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>), parameterized the hippocampal surfaces as described previously, and generated the surface MMS consisting of mTBM and radial distance (RD). We constructed a collection of overlapping patches on the surface as the initial sparse coding dictionary. Stochastic Coordinate Coding was then applied to learn a dictionary and sparse codes. We used the max-pooling algorithm on the newly learned high-dimensional features to obtain a final set of low-dimensional features. Finally, an AdaBoost classifier was applied to categorize aMCI and cognitively unimpaired individuals with 5-fold leave-one-out cross validation adopted to evaluate classification accuracy, sensitivity, specificity, positive and negative predictive values.

Results: The best prediction result of aMCI was achieved with our MMS features, with 96% accuracy, 100% sensitivity, 95% specificity, 86% positive and 100% negative predictive values.

Conclusions: While our findings should be considered preliminary, sparse coding with the sensitivity of surface multivariate morphometry may be applied to volumetric MRIs to predict imminent progression from the preclinical to clinical stages of AD with great accuracy.

STUDENT POSTER PRESENTATIONS

TRANSCRIPTIONAL AND EPIGENOMIC CHANGES ACROSS PERIMENOPAUSE: IMPLICATIONS FOR PRODROMAL PHASE OF ALZHEIMER'S DISEASE. Bacon ER, Desai M, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Transition states represent critical periods during development when systems undergo dramatic and widespread changes. In women, the perimenopause transition spans several years and the resulting loss of estrogen has profound effects in nearly all tissues, including breast, bone, cardiovascular, and brain. Menopause in humans is also marked by an increased risk for stroke, coronary heart disease, and neurological disorders. Although a majority of women have no serious long-term health consequences, many women suffer neurological impairment during and after the perimenopause transition. Heritability of menopause timing is 44-66% and variability is present in monozygotic twins and inbred rat strains, suggesting that epigenetics and environmental factors play a large role in orchestrating timing of events involved in reproductive aging. Individual differences in epigenetic regulation, in addition to individual differences of sex hormone levels may help explain some of the differences seen in menopausal age, risk for cognitive impairment, and response to hormone therapy.

Methods: Ovarian cycles were assessed by vaginal lavages for proportions of leukocytes, nucleated epithelia, and cornified epithelia [Nelson et al. 1981]. Regular cyclers (RCs) were selected by 3 consecutive 4- or 5-day cycles; irregular cyclers (IRs) were selected by their loss of consecutive cycling. Acyclic animals (AC) were selected by 8 or more days of constant estrus. Because stages of reproductive aging in rodents are driven by ovarian senescence as in women, rodents are a model for a subset of perimenopausal changes according to the updated Stages of Reproductive Aging Workshop (STRAW) criteria [Harlow et al. 2012; Finch 2014]. RNA-seq libraries of hippocampal and hypothalamic tissues were generated and sequenced. Resulting data was analyzed by Qiagen's Ingenuity Pathway Analysis (IPA), with a focus on genes related to epigenetic regulation.

Results: Duration of the perimenopause transition (time spent cycling irregularly before anestrus) can be separated into three groups: short, average, long. All animals begin to cycle irregularly around the same time (9-10mo), however animals complete the perimenopause transition at different ages. Older ages are correlated with longer overall durations of transition. Changes in genes related to epigenetic regulation were observed across all perimenopause groups (RC, IR, AC). IPA upstream analysis identified key players one-carbon metabolism (which is involved in the maintenance of the epigenome) as likely regulators of endocrine aging.

Conclusions: Duration of perimenopause is correlated with age of exiting the transition, and early perimenopause is not due to early initiation of transition but rather, early completion. Hypothalamic aging and changes in epigenetic regulation begin before the onset of irregular cycling, between 6 and 9 months. Impaired one-carbon metabolism that occurs during the transition to irregular cycling may contribute to increased risk for neurodegenerative diseases after menopause.

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EFFECTS OF MULTIBAND ACCELERATION ON HIGH ANGULAR RESOLUTION DIFFUSION IMAGING DATA COLLECTION, PROCESSING, AND ANALYSIS.
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University of Arizona; Arizona Alzheimer's Consortium.

Background: One of the largest obstacles preventing high angular resolution diffusion imaging (HARDI) and multi shell diffusion-weighted imaging from being incorporated into standard diffusion MRI (DMRI) protocols is the large time burden required to collect sufficient numbers of images with different direction encodings directions and b-values. Recently, multi-band techniques 1,2, which excite and collect data from multiple slices simultaneously, have greatly increased the speed of acquisition and hold tremendous potential for extending the range of DMRI sequences that can be carried out within research or clinical protocols. To date, however, there has been little validation of the techniques in terms of the effects of multiband acceleration on resulting diffusion parameters. In this study, we have explored the differences of DMRI data collected with and without MB acceleration, and investigate the effects that MB acceleration has on resulting DMRI parameters.

Methods: Seven healthy subjects were scanned on a 3T Siemens Skyra with a 72 direction, b=1000 s/mm² protocol. Without MB acceleration, TR/TE = 9600/88 ms. With a MB acceleration of 2, TR/TE = 5000/102 ms and with MB acceleration of 3, TR/TE = 4000/102 ms. Six b=0 images were obtained in each of the studies and two additional b=0 images were collected with reverse phase encoding direction to correct EPI distortions using the TOPUP routine within FSL. Images were also corrected for eddy currents using the EDDY routine in FSL. LPCA denoising was implemented in MATLAB. MRTrix was used to generate FOD maps as well as to perform probabilistic tractography and track density image formation. MATLAB 2015a was used for statistical analysis and calculation of FOD coefficients for constrained spherical deconvolution.

Results: The diffusion images produced after preprocessing steps are quite similar across all levels of acceleration, but it should be noted that there are subtle differences throughout the dataset that distinguish images collected without multiband acceleration and those collected with it. Differences in the data become more apparent when the parameters, such as FA, are compared. The values of FA are similar, but not identical when Multiband acceleration is implemented. The fiber orientation distribution functions generated using the constrained spherical deconvolution technique also vary. Of note, the primary diffusion directions seem to remain intact in both Multiband and non multiband images, but the FODs in the region of crossing fibers appear to lose some of their angular resolution as the multiband acceleration increases. Lower order FOD coefficients are very similar for all levels of multiband acceleration, but begin to deviate from each other as the order increases. Finally, the results of probabilistic tractography appear to remain largely intact despite some of the differences discussed above in earlier processing steps. While there are some minor variations between the tractography results, all of the major, and most minor pathways appear to be intact. Track density imaging results indicate that as more tracts are traced out, the more similar the tractography results are.

Conclusions: While there are subtle differences between data collected with and without multiband acceleration throughout all stages of data processing and analysis, it is difficult to determine how these differences truly affect the results of a diffusion study, given that there is no gold standard other than a sequence without multiband imaging. Despite some visually apparent differences in FODs calculated at some locations in the brain, tractography results seem to remain intact.

USING HUMAN INDUCED PLURIPOTENT STEM CELLS TO INVESTIGATE THE CONTRIBUTION OF RISK VARIANTS AND AGING TO THE ONSET AND PROGRESSION OF ALZHEIMER'S DISEASE. Brookhouser N, Brafman D. Arizona State University; 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: We are generating a diverse set of human induced pluripotent stem cell (hiPSC) lines from AD and non-demented control (NDC) patients with no (i.e. APOE 3/3) and two (i.e. APOE 4/4) copies of the E4 allele. We are using these hiPSCs to elucidate the potential genetic, molecular, and cellular mechanisms by which the APOE 4 allele contributes to AD onset and age-related disease progression.

Results: By using a novel 3D 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 age-related progression.

Conclusions: 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.

SEX DIFFERENCES IN BRAIN METABOLISM AND THERAPEUTIC RESPONSE IN 3xTgAD MOUSE MODEL. Caldwell CC, Wong K, Stefanko D, Yin F, Mao Z, Deng Q, Jakowec M, Cadenas E, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: We aim to develop a novel nutraceutical formulation that contains non-feminizing estrogenic compounds and mitochondrial enhancer substrates to promote brain metabolic activity. We predict this unique combination will counterbalance the bioenergetic system decline in the 3xTgAD Alzheimer's mouse model.

Alzheimer's disease (AD) is a national and global epidemic. The disease population can be divided into two subsets; familial (FAD) and late-onset (LOAD). Familial AD cases make up only 5% of the AD patient population. LOAD affects a larger population and its causes are not fully understood; but likely include a combination of environmental, genetic, and lifestyle factors. LOAD patients are largely associated with having phosphorylated Tau and Amyloid beta plaque pathology, this make the 3xTgAD mouse an appropriate model for study.

Alzheimer's disease (AD) has a complex and progressive neurodegenerative phenotype, with hypometabolism and impaired mitochondrial bioenergetics among the earliest pathogenic events. Bioenergetic deficits are well documented in preclinical models of mammalian aging and AD, emerge early in the prodromal phase of AD, and in those at risk for AD.

Understanding the bioenergetic adaptations that occur during aging and AD led us to focus on a systems biology approach that targets the bioenergetic system rather than a single component of this system. Bioenergetic system-level therapeutics personalized to bioenergetic phenotype would target bioenergetic deficits across the prodromal and clinical stages to prevent and delay progression of AD. We introduce a novel therapeutic formulation that acts on the multifaceted bioenergetic system to help reduce cognitive and brain metabolic decline in the 3xTgAD mouse model.

Additionally, little is understood regarding the possible differences between genders amongst the same phenotype in the 3xTgAD model. This study hopes to illuminate some of the characteristic variances between the two genders in baseline and in response to treatment.

Methods: Dosing- Animals were fed with one of 4 diets for 9 months starting at 3months of age. AIN-93M control, formulation diet #1 (R+Lipoic Acid and Acetyl-L-Carnitine), formulation diet #2 (Genistein, Daidzein, S-Equol), or formulation #3 (R+Lipoic Acid, Acetyl-L-Carnitine Genistein, Daidzein, and S-Equol). Mitochondrial Metabolism- Isolated mitochondria from the brain were analyzed using the Seahorse Biosciences Flux Analyzer to measure mitochondrial respiration. Isolated mitochondria were used in test kits for complex I and IV activity. Additionally mitochondrial DNA copy number was determined to control for mitochondria volume. Peripheral Blood Markers- Suborbital blood taken from the animals was tested for triglycerides, ketone bodies, and insulin. Glucose tolerance testing was preformed throughout the study. Imaging and Behavior- Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) images were taken of the brain to determine glucose uptake activity. Animal cognition was tested using the Novel object recognition (NOR) test.

Results: Significant gender differences were detected at baseline and in response to treatment in mitochondrial respiration (RCR), peripheral blood markers (triglycerides, ketones, insulin, GTT), FDG-PET scans, and improvements in NOR test performance.

Conclusions: Two main conclusions have developed from this study. First gender differences need to be accounted for in all studies using models for Alzheimer's disease with a therapeutic treatment. Second, using a combined multi-system therapeutic approach is preferred for preventing the negative bioenergetic and cognitive decline in Alzheimer's disease.

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A NOVEL DROSOPHILA MODEL OF ALZHEIMER'S DISEASE BASED ON TDP-43. Chaung M, Kraft R, Zarnescu DC. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's is a deadly disease that affects ~ 5 million Americans and is projected to grow in subsequent decades. The features of Alzheimer's are known including the development of neurofibrillary tau tangles and the accumulation of beta amyloid plaques, but there is currently no treatment or means of slowing down the progression of the disease. In an effort to catalyze the process of finding therapeutic strategies, we have been working to develop a novel *Drosophila* (fruit fly) model of Frontotemporal dementia (FTD). Flies have emerged as a powerful model organism for the study of genetic and neurological disorders including other forms of dementia beyond Alzheimer's. To accomplish this we generated transgenic flies, and using the bipartite Gal4-UAS system, we expressed human TDP-43 protein (wild-type or disease associated mutant, TDP^{G298S}) in the mushroom body, the center for learning and memory in the insect brain. We then aged these transgenic flies and used courtship assays to quantify learning and memory in adult males. Preliminary data suggests that TDP-43 expression in the mushroom body neurons using the 201Y mushroom body driver, impacts learning. In addition, preliminary confocal microscopy experiments showed that TDP-43 severely alters the structure of mushroom bodies in the brain and spreads beyond its expression domain. These findings suggest that TDP-43 expression in mushroom bodies results in morphological and functional phenotypes that mimic adult onset dementia in patients with Alzheimer's or related neurodegenerative disorders. Funding was provided in part by NIH grant P30 AG019610.

Methods: Experimental transgenic flies were created by crossing OK107 and 201Y virgin females with TDP* (*= WT or G298S) and w¹¹¹⁸ males.

Results: In both the 201Y>TDP^{G298S} and OK107>TDP^{G298S} males we see extensive spreading of the human protein beyond the cells in which it is being expressed in mutants but less so with the wildtype protein. In addition, there are frequent mushroom body morphological defects. To measure behavioral deficits, learning and memory assays are ongoing.

Conclusions: TDP-43 dependent morphology defects and spreading phenotypes are amenable to large scale genetic and drug screens that will allow us to gain mechanistic insights into neurodegeneration. Complementing these assays with learning and memory studies will help establish a novel model for studying the molecular mechanisms of dementia.

SPECIES- AND AGE-RELATED DIFFERENCES IN LEARNING AND PERFORMANCE ON WORKING MEMORY TASKS IN TWO SPECIES OF MACAQUE MONKEYS. Comrie AE, Gray DT, Burke SN, Smith AC, Barnes CA. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.

Background: Deficits in executive function, such as working memory, are characteristic of human aging. Because of similar aging phenotypes and homology in the organization of the lateral prefrontal cortex, nonhuman primate research continues to be especially informative for understanding the underlying mechanisms of normal cognitive brain aging. Two nonhuman primate models that have been used for studying such age-related changes include the rhesus macaque (*Macaca mulatta*) and the bonnet macaque (*Macaca radiata*). It is unknown how these two macaque species compare in their abilities to learn and perform working memory tasks, and how these skills change throughout healthy aging.

Methods: We employed state-space modeling algorithms (Smith et al., 2004) to analyze behavioral data from young and aged rhesus and bonnet macaques from two separate colonies in order to characterize any possible species or age-related differences in task acquisition and levels of performance. The macaques were trained on two behavioral tasks that engage working memory systems for optimal performance. These tasks include the delayed response (DR) and delayed nonmatching-to-sample (DNMS) tests, which have been shown to be dependent on different association areas of the brain, including the hippocampus and prefrontal cortex.

Results: The data suggest that, although performance on the tasks after reaching criterion is comparable across age and species, bonnet macaques appear to learn working memory tasks faster than do rhesus macaques and also show smaller age-related differences in performance than do rhesus. This finding occurred even though the ages at which the animals were tested were comparable between the two species (i.e., mean rhesus old = 24 years, bonnet old = 25 years; mean rhesus young = 11 years, bonnet young = 11 years). To obtain human equivalent ages from macaque ages, Tigges et al. (1988) have suggested that the age conversion of 3 human years for every one macaque year is a good approximation. Thus these data reflect animals that range in age from 21 to 90 human equivalent years - a significant portion of the lifespan.

Conclusions: These data suggest that bonnet macaques are more resistant to age-related declines in working memory function compare to rhesus macaques. An understanding of the differences in cognitive aging between these species may inform future choices in selecting models of normal aging for experiments, and should help to connect respective bodies of primate literature using each species.

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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 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.

CEREBELLAR DIFFERENCES ASSOCIATED WITH FINE MOTOR DYSFUNCTION IN AGING AUTISM COHORT. Deatherage BR, Braden BB, McBeath MK, Baxter LC. Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; Arizona State University; Arizona Alzheimer's Consortium.

Background: Gait disturbance, clumsiness, and other mild movement problems are often observed in Autism spectrum disorder (ASD; Rinehart et al., 2006). This study focused on brain changes that may indicate the neural basis for these motor symptoms that are common although not ubiquitous among ASD individuals. As the brain ages, these ASD-related symptoms may be exacerbated. Using magnetic resonance imaging (MRI), we examined cerebellar volumes and white matter integrity in a cross-sectional study comparing aging ASD and healthy controls (n=33). We hypothesized that elderly ASD subjects would exhibit smaller cerebellar volumes along with decreased white matter integrity that would be related to fine motor dysfunction, as compared to their typically developing (TD) age-matched counterparts.

Methods: All images were collected using a Phillips 3T scanner. 3D T1 and diffusion tensor images were obtained to measure gray and white matter volume and white matter integrity. Freesurfer, a volumetric measurement software, was used to determine group cerebellar volume differences. In order to determine white-matter integrity with automated segmentation, we used Voxel-Based Morphometry. A finger oscillation (Finger Tapping) test was administered as a behavioral measure to determine if cerebellar differences predict fine motor performance.

Results: 16 ASD and 17 TD participants were matched according to age and similar for IQ and level of education. Smaller white matter volume and reduced integrity was found in the ASD group within the bilateral cortico-ponto-cerebellar white matter tracts as compared to TD. ASD individuals' finger tapping speed exhibited a trend of being slower compared to TDs. Cerebellar white matter predicted finger tap scores in the ASD participants. There were no differences between ASD and TD participants for cerebellar cortical volume (gray matter).

Conclusions: A measure of cerebellar white matter correlated with reduced fine motor function in ASD subjects. Cerebellar atrophy, specifically in the white matter, in patients diagnosed with ASD may account for the prominence of fine motor dysfunction in this group. Previous studies have found anatomical differences in younger ASD subjects (Courchesne et al., 2011). This cross-sectional study extends those findings to aging adults, with novel results that correlates cerebellar white matter with fine motor speed, suggesting that these cerebellar changes, especially white matter is related to decreased motor functioning. Longitudinal assessments (every two years) are planned to determine whether ASD older individuals show an exacerbation in atrophy and behavioral change over time.

BEHAVIORAL EVIDENCE FOR ENHANCED INTERFERENCE DURING WORKING MEMORY AND ASSOCIATIVE LEARNING TASKS IN AGED MACAQUES. Gray DT, Ashford SL, Pyon W, Burke SN, Smith AC, Barnes CA. University of Arizona; University of Florida; Arizona Alzheimer's Consortium.

Background: The ability to protect ongoing cognitive processes from distracting stimuli is known as interference control. Human studies investigating this phenomenon have revealed that despite impressive flexibility in most cognitive domains, there is a severe capacity limitation in the ability to perform multiple tasks simultaneously. Efforts to develop behavioral paradigms for animal models to study interference control at the single-neuron level have recently led to insights into the neuronal mechanisms behind these limitations. For example, Wantanabe and Funahashi (2014) demonstrated that during a spatial attention task, neurons in the lateral prefrontal cortex show a decreased ability to represent task-relevant information proportional to the cognitive demand of a competing task. During normal aging this capacity limit is further reduced, but our understanding of the neural basis underlying these age-related declines is minimal.

Methods: A colony of young and aged bonnet macaques performed two behavioral paradigms that test different forms of memory interference. The first paradigm is a novel computer-controlled associative learning task with varying levels of interference, and the second is a manually-presented working memory interference task (adapted from Clapp et al., 2009). Learning of these tasks are characterized using a state-space modeling algorithm (Smith et al., 2004).

Results: In the associative learning interference task, the ability of monkeys to form associations between novel images and rewards was significantly reduced as the number of associations to simultaneously learn increased. This interference effect was proportionally greater in aged than in young monkeys. During the working memory interference task, interruptions presented in the delay period of a delayed nonmatching-to-sample task decreased the performance of aged monkeys significantly more so than young monkeys.

Conclusions: Together these data suggest that older macaque monkeys, like older humans, exhibit age-related deficits in interference control. As with the associative learning paradigm, the working memory interference task is currently being implemented under computer control to facilitate the temporal precision required to monitor behavior in relation to electrophysiological recordings, which will provide a novel opportunity to study age-related deficits in interference control at the single-neuron level.

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AN ORDERLY INTERACTION? MAZE ORDER IMPACTS THE OUTCOME OF ESTROGEN EFFECTS ON MEMORY. Koebele SV, Quihuis AM, Lavery CN, Plumley ZMT, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging and the loss of ovarian hormones are each associated with memory decline for spatial navigation. In females, there is evidence that estrogen administration during a critical window of opportunity during middle-age may attenuate age-related memory decline. This beneficial effect of estrogens is thought to be dependent upon a variety of factors, including dose, timing, and route of administration. Additionally, the order in which animals experience a battery of maze tasks may impact performance and flexibility to shift from one task to another. Indeed, our laboratory has shown that female rats with prior maze experience transfer the benefits of practice to a novel spatial memory task. Here, we evaluated the effect of 17-beta estradiol treatment and maze task learning order on spatial memory performance during middle-age.

Methods: Eleven-month-old Fischer-344-CDF female rats were ovariectomized and received a tonic dose of Vehicle, low 17-beta estradiol, or high 17-beta estradiol via a subcutaneous miniosmotic Alzet pump. Animals were trained on the delayed-matching-to-sample water maze (DMS), a low-cognitive demand spatial working and recent memory task, and the water radial-arm maze, a spatial working and reference memory task that involves increasing working memory load capacity as trials progress and is considered to be a more taxing memory task (i.e. high-cognitive demand). Half of the animals were trained on DMS first, and the other half was trained on WRAM first, before each group learned the second task.

Results: Results indicate that 17-beta estradiol-treated animals that experienced WRAM first learned DMS better than animals without prior maze experience, such that animals with prior maze experience treated with tonic 17-beta-estradiol made fewer errors on DMS compared to 17-beta estradiol-treated animals without prior experience. Divergent memory effects were revealed with respect to WRAM performance. Previous maze experience on DMS did not impart the same beneficial effects of enhanced performance on WRAM compared to animals that had no prior maze experience.

Conclusions: Overall, these data indicate that the order in which maze batteries are administered matters, and that 17-beta estradiol treatment while learning a complex cognitive task confers an enhanced capacity for learning a novel spatial memory task; however, previous experience on a less cognitively demanding memory task does not enhance learning and memory performance on a novel task to the same extent. Results suggest that 17-beta estradiol exposure and high-memory demand performance are important factors for cognitive flexibility to transfer learning skills to novel tasks and attenuating age-related memory impairments.

BEHAVIORAL IMPACT OF LONG-TERM CHRONIC IMPLANTATION OF NEURAL RECORDING DEVICES IN THE RHESUS MACAQUE. Kyle CT, Permenter MR, Vogt JA, Barnes CA. University of Arizona; University of California, Davis; Arizona Alzheimer's Consortium.

Background: Although ensemble recording methods are pervasive throughout neuroscience, little is known about how chronic electrode implants affect behavioral performance. Here we investigate the effect of chronic hippocampal tetrode array implants on recognition memory in a delayed nonmatching-to-sample (DNMS) task.

Methods: Five female rhesus macaques were tested (mean age: 16 yrs (+/-) 7.7, ranging 7 – 26 yrs) prior to implant, and re-tested (mean age: 21 yrs (+/-) 6.9, ranging 15-31 yrs) after implant (mean elapsed time between tests: 5.1 yrs (+/-) 1.5). DNMS testing was conducted using the Wisconsin general testing apparatus. Pre-implant measures of trials to criterion, recognition memory (percent correct), and reaction time were compared to post-implant scores. To distinguish between the effects of normal aging-related behavior changes and those related to the hyperdrive implants, we employed an additional group of 90 rhesus macaques. These 90 control animals were tested on the same apparatus at ages ranging from young to old. Quantile regression analysis estimated trends for age related behavioral changes on the 90 control animals. These trend lines were then used to correct for normal aging related effects of the 5 implanted animals.

Results: Analysis on the control animals suggest that trials to reach criterion increases with age ($r^2(93) = .7, p \ll .01$) and recognition memory significantly decreases with age ($r^2(93) = -.5, p \ll .01$), replicating canonical aging-related effects on DNMS performance. Analysis on the 5 implanted animals suggests that neither uncorrected nor corrected behavioral measures (via quantile regression) are significantly affected by our hyperdrive implants.

Conclusions: Here we introduce quantile regression as an effective approach for distinguishing between normal age-related behavioral effects and effects of an experimental manipulation. Our results suggest that chronic hippocampal hyperdrive implants do not significantly impede performance on DNMS behavior.

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RECOGNITION MEMORY CONTEXT EFFECTS IN AGING. Lawrence A. Ryan L.
University of Arizona; Arizona Alzheimer's Consortium.

Research suggests that recognition memory performance declines with age (Yassa et al., 2011). However, recent work in our laboratory indicates that although older adults perform more poorly at object recognition, their recognition is boosted to the same degree as younger adults when the object is presented in the same context at study and test. Older adults may be using relatively spared scene recognition processing to boost recognition of objects presented in a scene. We predicted that older adults will be impaired at object recognition, relatively intact in scene recognition, and that when identifying objects in scenes they will be able to utilize the scene to boost performance. Young adults ($n=15$, mean age=19) and older adults ($n=15$, mean age= 71) were given three continuous recognition tasks consisting of objects, scenes, and objects in scenes. Participants indicated whether each image in the series was either the same as, similar to, or different from an image they had seen previously. Older adults performed more poorly on all three continuous recognition tasks ($t= -2.584$, $p< .01$). However, there were no differences in older adult's performance across tasks (n.s.). Interestingly, individual differences in performance on the scenes only recognition task were related to false positive errors on the objects in scenes recognition task for both younger and older adults ($t=2.47$, $p< .05$). These findings suggest that individuals who are better at recognizing scenes may be biased by scene information to falsely recognize an object presented in a scene.

AGE-RELATED CHANGES IN EXTERNAL CUE-BASED NAVIGATION IN THE MEDIAL ENTORHINAL-HIPPOCAMPAL NETWORK. Lester AW, Koutia AJ, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: The hippocampus and entorhinal cortex are critical for spatial navigation and are highly susceptible to age-associated brain changes. As with older adults, aged rats are impaired in many spatial navigation tasks. These impairments are accompanied by changes in the degree to which the spatial tuning properties of hippocampal place fields are influenced by external visual cues in an environment. Such alterations may arise from circuit disruptions caused by known age-related functional and anatomical changes in the hippocampal processing pathway, which could have the effect of either slowing external cue processing or weakening the ability of these cues to influence firing field alignment.

Methods: To address these possibilities, a novel behavioral apparatus has been developed that allows for complete and immediate control of all visual cues in the environment. The apparatus is composed of a 1.4 m diameter circular track. Projectors arranged around the outside of the apparatus project a 360 degree panorama of visual cues on 68 cm tall cylindrical walls that enclose the track. There are 36 identical feeders evenly spaced along the perimeter of the track and animals learn to run to only one of them for food reward. The projected cues around the rewarded feeder are identical for 50 degrees to either side which eliminates any local visual cue information, forcing the rat to use the full panorama of cues to navigate to the rewarded feeder. By instantaneously rotating the cues we can precisely characterize when and to what degree animals update their internal representation of space to realign to the rotated external cues. In this context, we can: 1) investigate how spatial representations are updated both at very short time-scales of tens of milliseconds and over longer time intervals of seconds to minutes; 2) identify how different processing stages within the hippocampal formation are affected by age.

Results: Behavioral pilot data collected from three young (9 – 13 months old) and two aged (24 month old) animals show that immediately following a 40 degree rotation of the projected cues, animals typically visited feeders that were offset from the learned feeder by a comparable distance (i.e., 20 – 40 degrees).

Conclusions: These findings suggest that rats rapidly update their behavior to maintain alignment with the orienting cues in an environment. The next step of the study will be to perform simultaneous high density recordings from both medial entorhinal cortex and the CA1 region of the hippocampus as rats perform the task. With these measurements we hope to more precisely characterize the loci, timing and effect of age-related functional changes within the medial entorhinal-hippocampal network.

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USING BIOENGINEERING APPROACHES TO GENERATE A THREE-DIMENSIONAL (3-D) HUMAN INDUCED PLURIPOTENT STEM CELL (hiPSC)-BASED MODEL OF ALZHEIMER'S DISEASE (AD). Lundeen R, Petty F, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: The pathophysiology of neurodegenerative diseases remain difficult to precisely ascertain in part because animal models fail to fully recapitulate the complex pathophysiology of these diseases. In vitro models of Alzheimer's disease (AD) generated with patient derived human induced pluripotent stem cells (hiPSCs) could provide new insight into disease mechanisms. Although many protocols exist to differentiate hiPSCs to neurons, standard practice relies on two dimensional (2-D) systems which do not accurately mimic the complexity and architecture of the in vivo brain microenvironment. The proposed research aims to create three dimensional models of AD using hiPSCs which will enhance our understanding of AD pathophysiology thereby enabling the generation of more effective therapeutics.

Methods: We have developed two protocols that allows for the generation of 3-D cultures of neurons from hiPSCs. In the first protocol, hiPSC-derived neural progenitor cells (hNPCs) were plated in a suspension of Matrigel before terminal differentiation of neurons. In the second protocol, hiPSC are placed in suspension cultures and forced into aggregates called embryoid bodies (EBs) and differentiated to neural lineage through dual SMAD inhibition. Culture conditions are then changed to expand putative hNPC populations and then finally differentiated to neuronal spheroids. The 3-D hiPSC-derived neural cultures were compared to standard 2-D uses cellular, biochemical, genetic, and electrophysiological methods.

Results: Our ongoing analysis has revealed that these 3-D neuronal cultures express high levels of mature pan-neuronal markers (e.g. MAP2, β 3T) and neural transmitter subtype specific markers. Future genome wide expression and electrophysiological analysis will reveal the extent to which hiPSC-derived 3-D neuronal cultures recapitulate native brain tissue.

Conclusions: In the future, we will generate 3-D cultures of neurons from hiPSC lines derived from patients with familial and sporadic AD. As such, these 3-D culture systems will serve as the basis for more mechanistic studies to elucidate the molecular underpinnings of AD

EPIGENETIC AND ENDOSOMAL-LYSOSOMAL DYSFUNCTION IN THE BASAL FOREBRAIN DURING THE PROGRESSION OF ALZHEIMER'S DISEASE. Mahady L, Nadeem M, He B, Perez SE, Mufson EJ. Barrow Neurological Institute; Rush University; Arizona State University; Arizona Alzheimer's Consortium.

Background: Basal forebrain neuronal degeneration occurs during the progression of Alzheimer's disease (AD). However, the factors underlying the onset of basal forebrain cellular dysfunction remains unclear. Recent findings indicate that endosomal-lysosomal (E-L)/autophagic dysregulation occur prior to β -amyloid ($A\beta$) plaque and tau tangle pathology and may play a role in neuronal selective vulnerability during the progression of AD. However, E-L alterations likely act in concert with other factors to drive neuronal degeneration. In fact, epigenetic factors regulate E-L gene transcription and function. For example, histone deacetylases (HDAC6 and HDAC2) and methylated histone H3 lysine 9 (H3K9) are implicated in the pathogenesis of AD. Whether E-L/autophagic and epigenetic changes co-occur in the basal forebrain during the onset of AD remains unknown.

Methods: Here we quantified changes in the E-L/autophagic proteins cathepsin D (Cat D), rab5, respectively, and the epigenetic markers HDAC2, HDAC6, and H3K9 using frozen basal forebrain tissue obtained from subjects who died with a premortem clinical diagnosis of NCI (n=7; mean age=87; mean MMSE=28), MCI (n=7; mean age=91; mean MMSE=24), mild/moderate AD (n=8; mean age=90; mean MMSE=20) and severe AD (n=8; mean age=75; mean MMSE=6.7) from the Rush Religious Orders Study (RROS) and the Rush RADC, respectively. Groups were matched by age and postmortem interval (PMI=5 hr) and underwent detailed postmortem neuropathologic evaluations. Western blot analysis of tissue homogenates revealed stable levels of HDAC2 and HDAC6 across the four clinical groups examined.

Results: Increased levels of dimethylated H3K9, Cat D, and rab5 were found in severe AD compared to NCI, MCI and mild/moderate AD. We also observed a strong positive correlation between both H3K9 and Cat D ($r=0.73$), and H3K9 and rab5 ($r=0.65$), suggesting that epigenetic factors play a role in the regulation of E-L systems in AD.

Conclusions: In summary, these results indicate that the basal forebrain is resilient to E-L disturbances early in the disease process. Since, E-L and epigenetic dysregulation occur late in the disease process, this molecular interaction may exacerbate neuronal degeneration in severe AD.

TRANSITIONS IN THE INFLAMMATORY PHENOTYPE DURING THE PERIMENOPAUSE: IMPLICATIONS FOR PRODROMAL PHASE OF ALZHEIMER'S DISEASE. Mishra A, Brinton, RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is known to have a long latent prodromal stage, before the symptoms and the pathology actually manifest. The etiology of the disease, obscured by the multifactorial nature of the disease, poses a challenge in isolating the effects of each risk factor and studying the mechanism involved in the development of Late Onset Alzheimer's disease (LOAD). The perimenopausal transition is considered a "tipping point" leading to the development of the AD phenotype. Estrogen is a potent anti-inflammatory agent, and as perimenopause is marked by the lack of this hormone, causing a consequent rise in inflammation in the brain as well as periphery. Inflammation is evident by enhanced microgliosis and secretion of proinflammatory cytokines at the endpoint of Alzheimer's disease. Characterization of the inflammatory phenotype with the progression of the disease and especially during the prodromal phase of the disease largely remains unknown. Characterization of the inflammatory phenotype is crucial in understanding the timing of anti-inflammatory drug treatments. The disparate results from the ADAPT trial, highlighting the beneficial effects of NSAIDs at an early stage and the treatment worsening the pathology at later stages, are indicative of the changing course and function of inflammation with the disease. Both age and menopause are causative factors that affect inflammation. This study addresses activation of the inflammatory system across the perimenopausal transition.

Methods: Multiplex assay was performed to measure cytokine levels in serum isolated from female - 6 month old regular cycling rats, 9-10 month old regular cycling, irregular cycling, and acyclic rats, 16 month old acyclic rats and 9-10 month ovariectomized regular and irregular cycling rats. RNA-seq analysis was also conducted on RNA isolated from tissue homogenates of hippocampus and hypothalamus 6 month old regular cycling, 9-10 month old regular cycling, irregular cycling and acyclic rats and 16 month old acyclic rats.

Results: In our preliminary study in the perimenopausal rat model, which isolates endocrine aging from chronological aging, the gene expression profiling of hippocampus and cortex indicated an upregulation of genes involved in the NFkB pathway. Serum cytokine profiling in the same rats indicated a significant increase of IL-12 and IL-1A in acyclic rats as compared to regular cycling rats of the same age. RNA seq analysis, in the hypothalamus as well as hippocampus, revealed that expression of major histocompatibility complex-I (MHC-I) and Major Histocompatibility Complex-II (MHC-II) molecules (specifically HLA-DR, HLA-DQ) changed during the perimenopause. The increase in expression of MHC-I and MHC-II molecules is indicative of age related priming and reactivity of microglia. While during the perimenopause itself, the expression of both MHC-I and MHC-II reduced significantly.

Conclusion: Reduction in the expression of MHC-I and MHC-II molecules in the hippocampus during the perimenopause as compared to the chronological aging both pre and post menopause, is indicative of the transition of antigen presentation pathway and possibly, the microglial reactivity. These findings provide early evidence relevant to transition to prodromal phase of Alzheimer's disease.

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RELATION OF WHITE MATTER HYPERINTENSITY VOLUME TO COGNITIVE PERFORMANCE IN OLDER ADULTS. Nguyen LA, Bharadwaj PK, Haws KA, Fitzhugh MC, Trouard TP, Hishaw GA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Greater prevalence of cerebral white matter abnormalities, which appear as hyperintense regions in T2 FLAIR magnetic resonance imaging (MRI) scans, have been associated with increasing age, diminished cognitive performance, and cardiovascular risk factors, such as hypertension. We investigated the relation between white matter hyperintensity (WMH) volume and cognitive performance in a group of community-dwelling, elderly adults with and without histories of hypertension to further evaluate the role of WMH in cognitive aging.

Methods: A sample of 74 neurologically healthy older adults, 75-89 years of age, with treated hypertension (N = 32) and without hypertension diagnosis or treatment (N = 42) completed a battery of neuropsychological tests. T1-weighted volumetric and T2 FLAIR MRI scans were acquired on a 3T GE Signa Excite scanner. The volumes of WMHs were computed with a multispectral, automated lesion segmentation method to produce probability maps using Statistical Parametric Mapping (SPM8) and a lesion segmentation toolbox (LST; Schmidt et al., 2012).

Results: The results indicated that greater WMH volume was related to poorer performance ($0.001 \leq p \leq 0.018$) on several measures of memory (Selective Reminding Test: Sum Recall, Long-Term Storage, Long-Term Retrieval, and 30-minute Delayed Recall), executive functions (Paced Auditory Serial Addition Test, Trail Making Test - part B, and Wisconsin Card Sorting Test categories completed), and visuo/psycho-motor processing speed (Trail Making Test - part A and Grooved Pegboard), but was not related to performance on general measures of intellectual function (Wechsler Adult Intelligence Scale-IV - Full Scale IQ). After individually controlling for age ($0.006 \leq p \leq 0.049$) and the combination of age and hypertension status ($0.007 \leq p \leq 0.048$) in the cohort, these specific associations with cognitive performance remained significant.

Conclusions: In a sample of generally healthy, community-dwelling older adults, having greater WMH volume is associated with poorer memory, executive functions, and processing speed, even after controlling for age and hypertension status. Together these findings suggest that WMH volume may be an important factor contributing to the individual differences observed in cognitive aging. Further research is needed to evaluate the longitudinal impact of white matter lesion volumes on cognitive decline in the context of healthy aging.

GENERATION OF ISOGENIC APOE VARIANTS TO INVESTIGATE ALZHEIMER'S DISEASE RISK AND PROGRESSION. Potts C, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: According to current trends, by the year 2050, dementia will cost the United States over a trillion dollars a year, and the most common cause of dementia is Alzheimer's disease. Effective diagnosis and treatment remain elusive, although several familial varieties exist which arise from mutations in Presenilin 1, Presenilin 2, and Amyloid Precursor Protein (APP), these only account for 1-5% of known cases. A much more prevalent, but less understood genetic factor is Apolipoprotein E (APOE), of which there are three isotypes, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. APOE $\epsilon 4$ has been strongly correlated with an increased risk of Alzheimer's disease in the general population, with a 15 fold increase for homozygotes and a 3 fold increase for heterozygotes with the wild type $\epsilon 3$ allele. Human induced pluripotent stem cells (HiPSCs) offer a unique opportunity to study the mechanism through which APOE leads to increased risk as they can be generated from non-neuronal tissue, and APOE activity can be studied during each stage of development in becoming a neuronal cell.

Methods: Our group is seeking to generate isogenic cell lines of these three APOE variations using the CRISPR/Cas-9 genome editing system in order to better model and study this mechanism. These isogenic lines will be useful in minimizing the expression "noise" which can arise from the innate genetic differences between patients. We will be generating HiPSCs derived from a homozygous $\epsilon 4/\epsilon 4$ patient and seek to create isogenic $\epsilon 3/\epsilon 4$ and $\epsilon 3/\epsilon 3$ lines to see if this results in the elimination of the Alzheimer's phenotype when these are differentiated to neurons. We will also generate HiPSCs from a healthy $\epsilon 3/\epsilon 3$ donor and seek to generate an $\epsilon 4/\epsilon 4$ isogenic cell line, monitoring for the manifestation of any Alzheimer's phenotypes. The isogenic cell lines will be primarily compared through genome-wide expression analysis (RNA-seq) and qPCR profiling of key Alzheimer's related genes.

Results: Once the cell lines have been generated, the cells will be analyzed for off target modifications, and then differentiated into neurons to most effectively model the expression environment through which APOE is affecting Alzheimer's disease. APOE $\epsilon 4$ is the strongest correlated genetic risk factor for acquiring non-familial Alzheimer's disease, however due to the variable nature of this pathway due to individual genetic variation, the mechanism through which these effects are conferred has remained elusive, we seek to generate isogenic cell line for each APOE variant to better study and elucidate this mechanism.

Conclusions: There are currently no effective treatments for slowing or reversing Alzheimer's disease, partially because of the lack of mechanistic knowledge of the disease, here we seek to provide insight into part of that mechanism, and potentially highlight effective areas for future treatment.

GENERATION OF HIPSC-BASED MODEL OF PROGERIN-INDUCED AGING. Raman S, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: The use of AD human induced pluripotent stem cell (hiPSC)-derived neurons has provided new opportunities to study this disease in a simplified and accessible system. However, neurons generated from these hiPSCs showed some, but not all, of the early molecular and cellular hallmarks associated with the disease. Additionally, phenotypes associated with late onset in humans, such as synaptic and neuronal loss, were not observed in these studies. Moreover, neurons generated from only some SAD patients showed phenotypes similar to neurons generated from the FAD lines. We hypothesize that hiPSC-derived neurons may be too immature to accurately mimic the degenerative phase of the disease that is often observed in aging adults.

Methods: We have established a method that uses the overexpression of progerin, a truncated form of lamin A associated with premature aging, to induce aging-related phenotypes in hiPSC-derived neurons. Specifically, we have developed a lentiviral-based system to engineer clonal hiPSC lines from patients with FAD, SAD, and non-demented control individuals (NDC) that overexpress progerin. The effect of progerin overexpression on the induction of age-related phenotypes such as abnormal nuclear morphology, loss of nuclear lamina-associated proteins and heterochromatin markers, and increased mitochondrial reactive oxygen species is currently being analyzed in undifferentiated hiPSCs as well as hiPSC-derived neurons.

Results: We have confirmed using gene expression and immunofluorescence analysis that our lentiviral system allows for overexpression of progerin in undifferentiated NDC and AD hiPSCs. We are currently using biochemical, cellular, and genetic methods to determine if the overexpression of progerin in AD iPSC-derived neurons induces the manifestation or augmentation of AD-related phenotypes. In particular, we are interested in determining if progerin overexpression leads to the induction of AD-related phenotypes in SAD hiPSC lines where no phenotypes were previously observed.

Conclusions: To date, studies of human neuronal cells have been restricted to experiments with cadaveric tissue samples, which are limited in supply, rapidly lose disease phenotypes with extensive ex vivo culture, and only provide an end stage view of the disease. By comparison, the progerin-induced aging of AD hiPSC neurons will allow us to track in real-time the onset and progression of the disease in an age-dependent manner, thereby mimicking the disease progression that is observed in aging adults.

RELATION BETWEEN SOCIAL INTERACTION AND COGNITIVE FUNCTIONING IN OLDER ADULTS: A FEASIBILITY STUDY USING THE EAR TECHNOLOGY.

Robbins R, Glisky E, Mehl M. University of Arizona; Arizona Alzheimer's Consortium.

Background: In older adults higher levels of social engagement are associated with better cognitive function as measured by intelligence tests, executive functions and memory functioning. Research suggests that it is the quality of interactions instead of the quantity that impacts cognition.

Methods: This pilot study used the Electronically Activated Recorder technology to explore the relation between frontal/executive and memory functioning and social interaction in older adults as measured by type of conversation (substantive talk or small talk) spoken by the participant while with others. The EAR technology was used to collect objective measures of social interaction by recording participants' daily conversations. Participants included 7 females and 3 males with a mean age of 74.5 years (Range=67-80); 17 years of education (Range=14-19); 7 lived alone and 3 lived with a spouse. Neuropsychological tests measured executive functions and memory functioning.

Results: Although small numbers precluded significant findings, a Pearson partial correlation coefficient suggested a positive correlation between memory functioning and substantive talk with others after controlling for living situation (living with a spouse or living alone), $r(8) = .56$, n.s. Results suggested a positive correlation between frontal functioning and percentage of substantive talk with others, $r(10) = .61$, n.s., controlled for living situation. Specifically, the executive function of updating in working memory appears to be correlated with percentage of substantive talk with others, $r(10) = .41$, n.s.

Conclusions: Preliminary findings from this pilot study suggest that social interaction, in the form of substantive talk, is positively associated with frontal functioning and more specifically, updating, in older adults.

CHARACTERIZATION OF CIRCULAR RNAs IN THE POSTERIOR CINGULATE IN ALZHEIMER'S DISEASE. Sekar S, McDonald J, Cuyugan L, Craig DW, Liang WS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: 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. In the current study, we hypothesize that Alzheimer's disease (AD) affected tissues demonstrate differences in the abundance and expression of circRNAs when compared to healthy controls.

Methods: We laser capture micro-dissected healthy astrocytes from the posterior cingulate (PC) of late onset AD (LOAD) patients (n=10) and healthy elderly controls (n=10), and prepared RNA sequencing libraries from total RNA isolated from these cells. We then performed paired end next generation sequencing on the Illumina HiSeq. The raw fastq files generated were aligned (hg19) using either bwa or Bowtie2 and run through two circular RNA detection algorithms - Circular RNA Identifier (CIRI, v2) and find_circ. CIRI takes the bwa-aligned sequence alignment files (SAM) to look for segments of a read that align to the genome in chiasitic order. Paired end mapping and GT-AG splicing signals are used as filtering criteria to reduce the false positive rate. Find_circ first filters out reads that align contiguously and full length to the genome, since such reads are representative of linear splicing. From the remaining reads, 20-mers are extracted from both ends and aligned individually to the reference to find unique anchor positions within spliced exons. Anchors aligning in the reverse orientation indicate circular splicing and are picked up by the tool. Using Cytoscape, we also performed gene ontology enrichment analysis on the genes from which the identified circRNAs arise.

Results: We generated over 5.22 billion total reads and over 295 Gb of Q30 sequencing data. An average of 123,214,013 mapped reads were sequenced per sample. Following circRNA detection, find_circ identified 1335 circRNAs that were unique to the AD samples and 1705 circRNAs unique to the control tissues. On the same dataset, CIRI was able to identify 1459 circRNAs unique to the disease affected tissues and 1454 circRNAs unique to the controls. GO enrichment analysis of the circRNAs identified in the AD samples revealed significant enrichment of ontology terms such as regulation of neuron differentiation, nervous system development, neuron projection development/morphogenesis and synaptic vesicle cycle.

Conclusions: In this study, we evaluate the abundance of circRNAs in LOAD PC samples compared to controls, and thus demonstrate the feasibility of performing circRNA detection in whole transcriptome data using bioinformatics algorithms. Though further optimizations are needed in our wet lab and informatics workflows to identify circRNAs, our preliminary results demonstrate that there may be an abundance of circRNAs in LOAD PC samples. In our next set of experiments, we will be performing circRNA enrichment using Ribonuclease R (RNaseR) treatment prior to sequencing. Such a biochemical enrichment step will help improve our ability to detect circRNAs and subsequently understand the pathological relevance of circRNAs in the context of AD.

CONFORMAL INVARIANTS FOR SHAPE ANALYSIS IN BRAIN MORPHOMETRY STUDY. Shi J, Zhang W, Tang M, Caselli RJ, Wang Y (Alzheimer's Disease Neuroimaging Initiative). Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Shape space has been widely studied in computer vision and medical imaging. Two shapes are conformally equivalent if they can be conformally mapped to each other. All conformally equivalent surfaces form the Teichmüller shape space. The coordinate of a surface in the Teichmüller space is invariant under conformal maps, so it may provide a simple and refined index to represent a unique shape. This work proposes a novel method to compute conformal invariants for genus-0 surfaces with multiple (more than 2) open boundaries. We applied these conformal invariants to analyze abnormalities in brain morphometry associated with Alzheimer's disease (AD).

Method: First, given a 3D MR image, we segment it and reconstruct the cortical surfaces with the FreeSurfer software package. Second, we automatically label six landmark curves on each cortical surface using the Caret tool. The landmarks include Central Sulcus, Anterior Half of the Superior Temporal Gyrus, Sylvian Fissure, Calcarine Sulcus, Medial Wall Ventral Segment, and Medial Wall Dorsal Segment. Third, with topology optimization, we convert each cortical surface to a genus-0 surface with six open boundaries. As a result, the cortical surfaces admit hyperbolic background geometry and their hyperbolic uniformization metric, which is conformal to the original Euclidean metric, can be computed with the hyperbolic Ricci flow algorithm. Finally, the conformal invariants of each cortical surface are defined as lengths of the six boundaries in the hyperbolic space.

Results: We applied our conformal invariants to perform the group-wise statistical analysis between AD and control subjects. The dataset consisted of 60 left hemispherical cortical surfaces, which were randomly selected from the ADNI baseline database, including 30 AD patients and 30 matching control subjects. We used Hotelling's T^2 test to measure group mean difference and permutation test to correct for multiple comparisons. With the conformal invariants, the statistical p -value of the group comparison was 0.0133, indicating significant differences in cortical surfaces between AD patients and healthy people. We also compared with two other standard surface features, surface volume and area, whose statistical p -values were 0.1152 and 0.5888, respectively. This experiment demonstrated the feasibility of the proposed conformal invariants as a succinct shape index to characterize the brain morphometry in AD.

Discussion and Conclusion: We introduced a stable and efficient method to compute conformal invariants for genus-0 surfaces that have multiple open boundaries. The proposed method can reliably detect shape differences, at the group level, between control subjects and patients. In future, we will validate the potential of our algorithm to be applied in disease diagnosis and prediction.

DEVELOPMENT OF iPSC-BASED BIOMARKERS TO IDENTIFY THE PATIENT POPULATION RESPONSIVE TO ALLOPREGNANOLONE. Solinsky CM, Hennes V, Park JA, Chui HC, Blurton-Jones M, Ichida JK, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a national and global epidemic with complex pathoetiology including compromised brain metabolic activity and decreased regenerative capacity. Allopregnanolone (Allo) is an investigational neuroregenerative therapeutic, currently in Phase 1b clinical trial for AD (NCT02221622, <https://clinicaltrials.gov/ct2/show/NCT02221622?term=NCT02221622&rank=1>). In rodent pre-clinical models, Allo promotes neural stem cell (NSC) proliferation and neural differentiation and improves mitochondrial function. To develop biomarkers to predict regenerative response to Allo, we have initiated proof of concept analyses to determine the impact of Allo on human induced pluripotent stem cells (iPSCs) and iPSC-derived neural cells.

Methods: T-cells from a patient with familial AD due to the A431E presenilin-1 point mutation were reprogrammed via a non-integrating, non-viral method, to iPSCs. Additional iPSCs were provided by the University of California Irvine Alzheimer's Disease Research Center (UCI-ADRC) and the Institute for Memory Impairments and Neurological Disorders. Isogenic iPSCs were generated using CRISPR-Cas9. Using dual inhibition of SMAD signaling, iPSCs were differentiated to NSCs. Mitochondrial respiration and regenerative capacity were determined using metabolic analyzer and FACS.

Results: Mitochondrial respiration and proliferation analyses were conducted in AD-derived and healthy control iPSCs and NSCs. Initial data indicates that AD iPSCs have similar proliferation rates, but altered bioenergetics compared to healthy controls. Analyses were conducted to determine the regenerative and bioenergetic effect of Allo. In iPSC-derived NSCs, Allo increased basal mitochondrial respiration by 78% and maximal mitochondrial respiratory capacity by 35%.

Conclusion: Initial data demonstrate that iPSCs derived from AD patient lymphocytes can be generated, differentiated to NSCs, and their metabolic and neurogenic phenotype determined. Data indicate that Allo can increase mitochondrial respiration and promote regeneration of human-derived NSCs. Going forward, this approach will be used to evaluate the effect of Allo on the regenerative capacity and metabolic phenotype of clinical trial participant iPSC-derived NSCs. These data will form the foundation for developing the first regenerative biomarker to determine and monitor response to therapeutics.

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WHITE MATTER INTEGRITY IN YOUNG AND AGED BONNET MACAQUES ASSESSED USING DIFFUSION MRI. Umaphy L, Burke SN, Thome A, Plange K, Engle JR, Bernstein A, Do L, Trouard TP, Gothard KM, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: The orbitofrontal cortex and amygdala are both necessary for decisions based on expected outcomes. With age, cognitive processes tend to decline. Aging disrupts the function of OFC to support reward guided behavior. Prior anatomical MRI studies have been performed on young and aged bonnet macaque monkeys that measured volume losses in the orbital frontal cortex (OFC) with advanced age, which suggests there are impairments in stimulus associated reward devaluation, which could result in a reduced connectivity between the OFC and amygdala. This idea supports the finding that long range projecting white matter tracts are particularly vulnerable to normative aging process.

As a follow up to these observations, we have carried out diffusion MRI investigations to quantitatively assess the integrity of white matter tracts between Orbitofrontal cortex (OFC) and amygdala to relate these variables to reward devaluation and OFC volume.

Methods: Diffusion MRI scans were performed on seven young (mean±SD: 13±1.8708) and six old (mean±SD: 26±2.9155) bonnet macaques monkeys using a single-shot echo planar imaging (EPI) sequence with a diffusion weighting of $b=1000$ s/mm² in 57 directions. Anatomical T1 (MPRAGE) images and T2 weighted images were also acquired.

A pre-processing pipeline was established that included corrections for distortions due to eddy current, and B0 field inhomogeneity. This was followed by a denoising step that was based on principle component analysis [Manjón, Coupe´ et al] to improve SNR. Diffusion images were co-registered with the T1 scans using the FSL software. Tissue Probability masks (TPM) were generated using the anatomical T1 reference from the subjects. SPM12 was used to segment each subject's T1 to an average space using the TPMs to generate deformation fields, which were then applied to the corresponding DWI scans to move them to the average space for intra-subject analysis.

Results: Inclusion of denoising steps in the pre-processing pipeline significantly improved the quality of diffusion datasets and provided higher quality parameter maps. DTI-based techniques as well as constrained spherical deconvolution (CSD) based techniques for tractography were both employed in the analysis. Whole brain probabilistic/streamlined tractography were performed on a small subset of bonnet macaques using the Mrtrix3 software. White matter tracts connecting orbitofrontal cortex and amygdala were clearly identified. These will be used in future studies to calculate track density imaging (TDI) maps to compare the track strengths between these ROIs across the subjects and to determine how the results from diffusion MRI correlate with previous findings.

Conclusions: Using high-angular resolution diffusion MRI, white matter integrity along the tracts connecting the OFC and amygdala have been quantitatively measured in young and old bonnet macaques. Ongoing work will be to determine if these metrics can explain age related cognitive impairment observed in reward devaluation and object reversal tasks observed in young and aged bonnet macaques.

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ENHANCEMENT OF DELIVERY TO THE BRAIN USING ULTRASOUND. Valdez M, Fernandez E, Matsunaga T, Witte R, Furenlid L, Romanowski M, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Background: Treatment of neurological disorders is often hampered by the inability of therapeutics to cross the blood-brain barrier (BBB). Over the last several years, novel techniques have been developed that use focused ultrasound (FUS) energy in combination with microbubble (μ B) contrast agents to temporarily open up the BBB. Foundational studies have been carried out in animal models where BBB opening is clearly visible via contrast-enhanced MRI. While MRI allows assessment of BBB opening to contrast agents, it does not directly show the distribution of therapeutics within the brain. In this work, MRI, SPECT, and fluorescence are used to compare the distribution of contrast agents and model therapeutics in mice following BBB opening.

Methods: BBB opening was carried out in anesthetized mice with the following procedure: Mice were placed in a supine position on a custom-made cradle which held a FUS transducer such that the focal spot was targeted to the midbrain. A 0.2 μ L/g diluted dose of μ Bs was injected IV. FUS was immediately applied for 2 min (10ms pulse at 1 Hz). Following an IP injection of Gd-DTPA, mice were imaged using T1-weighted MRI on a 7T Bruker BioSpec MRI system. Mice were then injected with pertechnetate and imaged on a custom dual-modality SPECT/CT imaging system. Other mice underwent the same BBB-opening and MRI procedures followed by IV injection of 1 mg each of 3, 70, and 500 kD dextrans with different fluorescent labels, then perfused with PBS and PFA. Brains were cryosectioned then imaged with an Olympus MVX10 fluorescence microscope. Safety was evaluated by opening the BBB with various FUS pressures in mice (214, 120 and 72 kPa peak negative pressures). The brains were H&E-stained and imaged to quantify tissue damage. Liposome-coated μ Bs were made by conjugating carboxyfluorescein-loaded liposomes using maleimide-SPDP linkers, and imaged with an Olympus IX71 microscope.

Results: MRI and fluorescence microscopy images following BBB opening show a strong co-localization of MRI signal enhancement with the fluorescent dextrans. The volume of brain with Gd-enhancement and dye increased with pressure and decreased with dextran size. 120 kPa demonstrated significant opening of the BBB with no visible damage. Higher pressures showed damage, and lower pressures showed little to no BBB-opening. SPECT/CT images of the same mouse following an injection of pertechnetate demonstrated a slight uptake of radiotracer into the brain that is co-localized with MRI enhancement.

Conclusions: These results demonstrate FUS can safely open the BBB, allow molecules of various sizes to enter the brain, and the effect of molecular weight. They also emphasize the need to develop more efficient methods with which to introduce drugs to the specific site of BBB opening without exposing the rest of the body to excessively high concentrations of drug. Drug-loaded liposomes conjugated to μ Bs could prove useful in this regard. While the BBB opening technique described herein is intended to increase drug delivery to the brain for neurological disorders (e.g. Alzheimer's and Parkinson's), these imaging experiments could also be utilized to evaluate the loss of BBB integrity caused by other pathologies such as brain tumors, TBI, and viral infections.

A ROBUST VITRONECTIN-DERIVED PEPTIDE (VDP) SUBSTRATE FOR THE SCALABLE LONG-TERM EXPANSION AND NEURONAL DIFFERENTIATION OF HUMAN PLURIPOTENT STEM CELL (HPSC)-DERIVED NEURAL PROGENITOR CELLS (HNPCS). Varun D, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Several debilitating neurological disorders, such as Alzheimer's disease, stroke, and spinal cord injury, are characterized by the damage or loss of neurons and supporting cell types in the central nervous system (CNS). Human neural progenitor cells (hNPCs) derived from human pluripotent stem cells can proliferate extensively and differentiate into the various neuronal subtypes and supporting cells that comprise the central nervous system. As such, hNPCs have tremendous potential for disease modeling, drug screening, and regenerative medicine applications. However, to use hNPCs for the treatment of neurological disorders and diseases many challenges need to be addressed such as (i) lack of well-defined, xeno-free conditions for the long-term expansion of hNPCs and their neuronal differentiation, (ii) insufficient systematic control over the conditions that regulate hNPC behavior, and (iii) inability to produce hNPCs on a large scale (~1 billion cells) under defined conditions.

Methods: We have developed a vitronectin-derived peptide (VDP)-based substrate to support the growth and neuronal differentiation of hNPCs in conventional two-dimensional (2-D) culture and large-scale microcarrier (MC)-based suspension culture. HNPCs were expanded on VDP in 2-D or suspension culture for up to 10 passages. HNPCs grown in both culture systems were also differentiated into neurons on the VDP substrate. HNPC expansion or neuronal differentiation on VDP was validated by RT-qPCR, immunofluorescence, and flow cytometry and comparison to standard extracellular matrix protein (ECMP)-based cultures.

Results: Compared to hNPCs cultured on ECMP-based substrates, hNPCs grown on VDP-coated surfaces displayed similar morphologies, growth rates, and high expression levels of hNPC multipotency markers. Furthermore, VDP surfaces supported the directed differentiation of hNPCs to neurons at similar level to cells differentiated on ECMP substrates. We also demonstrated that VDP is a robust growth and differentiation matrix, as demonstrated by its ability to support the expansions and neuronal differentiation of hNPCs derived from three hESC (H9, HUES9, and HSF4) and one hiPSC (RiPSC) cell lines. Finally, we show that VDP allows for the theoretical expansion or neuronal differentiation of hNPCs to quantities (>1010) necessary for drug screening or regenerative medicine purposes.

Conclusions: In this study, we developed a completely defined, scalable, and robust peptide-based substrate that allows for the long-term growth and directed neuronal differentiation of hNPCs. Compared to cells grown on standard ECMP-based substrates, hNPCs grown on VDP maintained their characteristic morphology, expressed high levels of hNPC multipotency markers, and retained their neuronal differentiation potential. In the future, the use of VDP as a defined culture substrate will significantly advance the clinical application of hNPCs and their derivatives as it will enable the large-scale expansion and neuronal differentiation of hNPCs in quantities necessary for disease modeling, drug screening, and regenerative medicine applications.

MITOCHONDRIAL GENE EXPRESSION DURING PERIMENOPAUSE AND CHRONOLOGICAL AGING: IMPLICATIONS FOR PRODROMAL STAGE OF ALZHEIMER'S DISEASE. Wang Y, Brinton RD. University of Southern California; University of Arizona; Arizona Alzheimer's Consortium.

Background: Human mitochondrial genome contains 37 genes, including 13 protein-encoding genes, which are all core subunits belonging to complexes I, III, IV, or V of the electron transport chain. Alterations in gene expression can lead to changes in cellular respiration and bioenergetics, which are implicated in multiple neurodegenerative diseases including Alzheimer's disease. Compared to males, females over 60 years old are at greater risk for Alzheimer's disease. Here we present the effects of endocrine transition during perimenopause and chronological aging on mitochondrial gene expression in female brain.

Methods: We used a rat model recapitulating fundamental characteristics of the human perimenopause. Specifically, female Sprague-Dawley rats between 9-10 months old were classified as either regular cycling, irregular cycling, or acyclic based on their estrus status. 6-month-old regular cycling and 16-month-old acyclic rats were included to distinguish the effects of chronological aging from endocrine aging. Changes in gene and protein expression were assessed using rtPCR and western blot respectively, and potential upstream regulators and signaling pathways were identified by RNAseq.

Results: We observed that in the hippocampus, MT-ND3 (complex I), MT-CYB (complex III), and MT-ATP6 (complex V) had significantly lower expression in both irregular and acyclic 9-month-old animals comparing to regular cyclic 9 month ones, and MT-CO1, MT-CO2, and MT-CO3 had significantly lower expression in acyclic 9-month old animals compared to regular cyclers. Although other protein coding genes did not show statistically significant differences, they did share a similar trend in decreased gene expression. In terms of chronological aging, relative to 6 month old female rats 9 month old animals exhibited mitochondrial genes were generally up-regulated in hippocampus, whereas a decline in mitochondrial gene expression occurred by 16 months of age. In contrast, the cerebral cortex exhibited a different pattern of gene expression. During perimenopause, mitochondrial gene expression patterns in irregular cycling and acyclic rats were not significantly different from regular cyclers. Rather than have a surge in expression at 9 month as seen in hippocampus, mitochondrial gene expression in cortex continuously decreased as animals aged, and at 16-month-old, 8 out of 13 protein coding genes spanning electron transport chain complexes I, III, IV, and V were significantly lower level compared to 6-month-old animals.

Conclusions: Our data suggest that in the hippocampus, mitochondrial gene expression is sensitive to both endocrine and chronological aging. We have also shown regional differences in mitochondrial gene expression between the chronological and endocrine programs with the hippocampus exhibiting both chronological and endocrine aging whereas the cerebral cortex exhibited only chronological aging.

TIME-DEPENDENT DECREASE IN THE PEAK FREQUENCY AND POWER OF HIPPOCAMPAL SHARP-WAVE RIPPLES AND HIGH-GAMMA EVENTS DURING POST-BEHAVIOR SLEEP IN AGED AND YOUNG RATS. Wiegand J-P, Gray DT, Schimanski LA, Lipa P, Barnes CA, Cowen SL. University of Arizona; Arizona Alzheimer's Consortium.

Background: Sharp-wave ripples (SPW-Rs) are brief (20-150 ms), high-frequency (130-180 Hz) oscillations in the hippocampus (Buzsaki et al., 1992) linked to the process of memory consolidation. Previous work has demonstrated that neural activity associated with recent experience is reactivated during SPW-Rs (e.g., Wilson and McNaughton, 1994) and that the strength of this reactivation decreases to approximately 20% of original levels within 30 minutes after behavior (Kudrimoti et al., 1998).

Methods: We investigated the general hypothesis that the rapid decrease in reactivation strength is correlated with a time-dependent reduction in frequency and power of the ripple oscillation. Given the association between age and memory decline, we also investigated whether the time course of such change differs between aged and young animals. CA1 local field potentials (LFPs) were recorded in aged (n = 5) and young (n = 6) male F344 rats during rest periods following a place-dependent eyeblink-conditioning task. To examine the time course of the probability of occurrence of high frequency LFP events during the 20 minutes following the behavior experience, we bandpass filtered between 80-300Hz, rectified the data, set a power threshold, and then found the onset and offset of these events throughout this time period.

Results: Peak frequency and power at higher frequencies were reduced in aged rats compared to young, and both frequency and power decreased gradually during the first 20 minutes to ~90% of initial levels in both age groups (unpaired t-test, $p < 0.05$). In the older animals, the entire probability distribution of peak frequency oscillatory events was significantly shifted downward.

Conclusions: This reduction could reflect an increase in the proportion of fast gamma to ripple events, or age-associated changes in the CA1 network that limit the maintenance of high-frequency oscillatory activity. Given that high gamma activity is associated with increased entorhinal input to CA1 (Colgin et al., 2009), these results suggest that CA1 may receive increasing input from entorhinal cortex throughout the course of sleep, and that this effect may be particularly strong in aged animals.

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PATCH ANALYSIS BASED SPARSE-CODING SYSTEM FOR PREDICTING FUTURE COGNITIVE DECLINE. Zhang J, Stonnington CM, Li Q, Shi J, Bauer III RJ, Gutman BA, Chen K, Reiman EM, Caselli RJ, Thompson PM, Ye J, Wang Y. Arizona State University; Mayo Clinic Arizona; University of Southern California; Banner Alzheimer's Institute; University of Michigan; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive brain disease. Accurate diagnosis of its prodromal stage is crucial for clinical trial design. Here we introduce a patch-based sparse coding method to classify different stages of AD based on hippocampal morphometry.

Methods: We studied longitudinal MRI from the Alzheimer's Disease Neuroimaging Initiative (ADNI). In our experiments, we analyzed a baseline dataset, including 228 elderly healthy controls (CTL), 388 participants with mild cognitive impairment (MCI) and 194 AD patients. First, we analyzed the same 3D brain MRI dataset as our previous work and segmented each individual MRI scan with FSL, and parameterized the hippocampal surfaces with our prior surface fluid registration method. Our surface multivariate morphometry statistics (MMS) consisted of multivariate tensor-based morphometry (mTBM) and radial distance (RD). Then, we constructed a collection of overlapping patches on the hippocampal surface to build an initial sparse coding dictionary. After that, Stochastic Coordinate Coding (SCC) was applied to learn a dictionary and sparse codes on the selected patches. Finally, we used the pooling algorithm on the newly learned high-dimensional features to obtain a final set of low-dimensional features. An AdaBoost classifier was then applied to classify different stages of AD. Meanwhile, we also studied five different classification problems, listed below.

Results: We tested our new framework on five classification experiments, including: (1) AD vs. CTL, (2) AD vs. MCI, (3) MCI vs. CTL, (4) MCI-converters vs. MCI-stable and (5) CTL-converters vs. CTL-stable. For the third task, to make the classification fair and not confounded, we selected 73 stable subjects with matched sex, age and initial memory scores. Ten-fold leave-one-out cross-validation was adopted to estimate classification accuracy. With our PASS, we achieved an accuracy of 81%, 77%, 77%, 77%, and 73% in five experiments, respectively. Our new approach also achieved high sensitivity: 83%, 83%, 83%, 82%, and 80%, and reasonable specificity 78%, 83%, 82%, 82%, 76%.

Conclusion: We combined the efficiency of sparse coding with the sensitivity of surface multivariate morphometry, to boost classification performance in a range of problems in AD neuroimaging.

STUDYING VENTRICULAR ABNORMALITIES IN MILD COGNITIVE IMPAIRMENT WITH SPARSE CODING ON HYPERBOLIC SPACE. Zhang J, Stonnington CM, Shi J, Li Q, Gutman BA, Chen K, Reiman EM, Caselli RJ, Thompson PM, Ye J, Wang Y. Arizona State University; Mayo Clinic Arizona; University of Southern California; Banner Alzheimer's Institute; University of Michigan; Arizona Alzheimer's Consortium.

Background: Mild Cognitive Impairment (MCI) describes individuals who cognitively lie between normal aging and dementia. Here we introduce a hyperbolic space based patch-selection sparse coding method to predict future progression of MCI patients based on ventricular morphometry.

Method: The dataset we used was downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. We selected 133 subjects from the MCI group in the ADNI baseline dataset, including 71 subjects who developed AD and 62 subjects who did not convert to AD, which were chosen on the basis of having 36 months of longitudinal data.

We propose a new framework based on hyperbolic geometry with sparse coding. First, we generates a one-to-one diffeomorphic mapping between ventricular surfaces with consistent boundary matching conditions and morphometric statistics was computed on the hyperbolic space [1]. Second, geodesic farthest point sampling with breadth-first search was proposed to select ring patches from hyperbolic domain to construct the initial original dictionary for sparse coding [2]. Then, Stochastic Coordinate Coding (SCC) [3] was applied to learn a dictionary and sparse codes on the selected patches. Finally, we used the pooling algorithm to obtain a final set of low-dimensional features. An AdaBoost classifier [4] was then applied to predict future MCI progression based on their baseline ventricular morphometry features.

Results: For testing, five-fold leave-one-out cross-validation was adopted to estimate classification accuracy. Five standard performance measures were computed to evaluate the classification - Accuracy, Sensitivity, Specificity, and Positive and Negative predictive values. For comparison purposes, we computed ventricular volumes and surface areas within the MNI space model in each side of brain hemispheres [5]. In our experimental results, we achieved the best accuracy (96.7%), best specificity (100%) and best positive position value (100%) by using our new system.

Conclusion: The results show the novel sparse coding based on ventricular morphometry method may offer a new and more sensitive approach to study preclinical and early symptomatic stage AD.

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COGNITIVE DECLINE AFFECTS THE MORPHOMETRIC PROPERTIES OF HIPPOCAMPUS AND LATERAL VENTRICLE. Zhang W, Shi J, Stonnington C, Bauer III RJ, Gutman BA, Chen K, Thompson PM, Reiman EM, Caselli RJ, Wang Y. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer's Institute; University of Southern California; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease most prevalent in the elderly. Distinguishing disease-related memory decline from normal age-related memory decline has been clinically difficult due to the subtlety of cognitive change during the preclinical stage of AD. In contrast, sensitive biomarkers derived from in vivo neuroimaging data could improve the early identification of AD. In this study, we employed a morphometric analysis of the hippocampus and lateral ventricle. We applied our brain surface morphometry pipeline to analyze brain MRIs obtained from the well-characterized Arizona APOE cohort of presymptomatic individuals. We hypothesized that our surface multivariate statistics may identify subtle shape difference on both hippocampus and lateral ventricle on presymptomatic subjects. The results showed that our new method identified significant regional differences between stable and declining participants.

Methods: 1. Segmentation of Hippocampus and Lateral Ventricle. The hippocampus was segmented from T1 images by using FSL software package. For ventricular segmentation, in this research, we used a novel pipeline that computed a group-wised ventricular template and used it to accurately segment continuous ventricular structures.

2. Surface Multivariate Tensor-based Morphometry. Based on segmented binary volume masks, we extracted hippocampal and ventricular boundaries with a topology preserving level-set method and constructed triangular surface meshes with marching cubes algorithm. Later, the surfaces were further smoothed using a two steps mesh smoothing method.

3. Group Difference Study. All subjects were cognitively unimpaired when the baseline images were acquired. 18 subjects with presymptomatic imaging studies developed MCI or AD an average of 2 years after their last imaging visits and were the decline group. 35 subjects matched for sex and age who remained cognitively unimpaired for at least 4 years were selected as the comparison stable group. Baseline high-resolution T1 MRI scans were used in this study. We used the Mahalanobis distance to measure the difference between the mean morphometry feature vectors between these two groups. The Hotelling's T2 test was performed to evaluate the morphometric variations of hippocampal and ventricular surfaces between two groups of subjects, declining vs stable on each vertex.

Results: P-maps computed by Hotelling's T2 test and corrected for multiple comparisons were shown in Figure 2. With $p < 0.05$ as the threshold, the global significance levels for both hippocampus and lateral ventricle reached significance bilaterally (hippocampus, left $p = 0.0135$, right $p = 0.0367$; ventricle, left $p = 0.0131$, right $p = 0.0461$).

Conclusions: We identified significant differences between cognitively stable and declining subjects. Hippocampal and ventricular morphometry may be useful as imaging biomarkers to predict impending cognitive decline in asymptomatic, cognitively unimpaired subjects. Future work will focus on developing advanced machine learning algorithms which make use of our surface mTBM features to advance the preclinical AD research.

Additional Abstracts

IMPACT OF WHITE MATTER HYPERINTENSITY VOLUME ON CORTICAL BRAIN MORPHOLOGY IN HEALTHY COGNITIVE AGING. Alexander GE, Bharadwaj PK, Haws KA, Nguyen LA, Fitzhugh MC, Trouard TP, Hishaw GA. University of Arizona; Arizona Alzheimer's Consortium.

Background: White matter hyperintensities on T2 FLAIR magnetic resonance imaging (MRI) scans are often observed in healthy aging and to a greater extent in those with cerebrovascular risk factors, like hypertension. We sought to evaluate the effects of WMH lesion volume on cortical brain morphology and cognitive performance in a sample of 79 healthy, community-dwelling adults, 50 to 89 years of age without hypertension to determine whether the presence of white matter lesions in this healthy elderly cohort have an impact on the course of cognitive and brain aging.

Methods: Participants (33M/46F; mean \pm sd age = 65.7 ± 10.0 ; mean \pm sd Mini-Mental State Exam = 29.3 ± 1.0) completed a battery of neuropsychological tests and were medically screened to exclude neurological, psychiatric, and medical illnesses that could affect cognitive function, including any hypertension diagnosis and clinic systolic blood pressures greater than 140 mmHg. Regional patterns of cortical brain thickness and area were assessed using Freesurfer software with T1-weighted 3T volumetric MRI scans (GE Signa Excite system) and logWMH volumes were computed from T1 and T2 FLAIR images using a multispectral, automated lesion segmentation method to produce probability maps with a lesion segmentation toolbox (SPM8 LST). The relations between logWMH and cortical morphology were evaluated using Monte Carlo correction with 10,000 iterations for clusters with $p < 0.05$.

Results: The results showed that after controlling for the effects of age in the cohort, greater logWMH volume was associated with greater reductions in cortical thickness in medial frontal and right inferior temporal regions. In contrast, cortical area showed greater increases in lateral orbital and superior frontal and inferior parietal regions in relation to greater logWMH volumes. Greater logWMH volumes were also associated with poorer performance on several measures of executive cognitive functions, assessing aspects of inhibition and set-shifting abilities ($0.016 \leq p \leq 0.041$).

Conclusions: Together, these findings suggest that in healthy community-dwelling, normotensive older adults, greater WMH volume leads to diminished cortical thickness, as well as poorer cognitive performance involving brain regions often impacted by cognitive aging, but is also associated with corresponding increases in cortical area. This areal expansion may reflect a compensatory response in these healthy older adults that could serve to enhance brain connectivity when faced with increasing WHM lesion load.

RAPID, FULLY AUTOMATED METHOD FOR QUANTITATIVE ANALYSIS OF PET AMYLOID SCANS IN ALZHEIMER'S DISEASE. Kuo PH, Bharadwaj PK, Krafft WP, Fitzhugh MC, Alexander GE, Zubal G. University of Arizona College of Medicine; University of Arizona; Arizona Alzheimer's Consortium; Z-Concepts LLC.

Background: Amyloid imaging by positron emission tomography (PET) plays a critical role in patient selection for clinical trials for Alzheimer's disease (AD) and is also poised for more routine clinical use. The ADNI database provides quantitative analyses of amyloid imaging with the application of a method using Freesurfer (FS) which can often require hours to analyze a PET amyloid scan (Jagust et al., 2008; Mormino et al., 2009). In contrast, the Alzheimer's Disease Evaluation of Radiotracers (ADER) software is a fully automated program that yields quantitative, reproducible results of regional amyloid deposition in less than a minute using a standard laptop computer. We report initial results using ADNI data to compare ADER and the FS based method using a discriminant analysis to determine classification accuracy between patients with AD and controls.

Methods: The study population comprised of participants from ADNI-2 and included 93 controls and 64 AD patients. The fully automated ADER, evaluates a beta-amyloid whole brain PET image by geometrically normalizing the scan to templates with varying beta-amyloid burden, masking the white matter tissue and CSF (without relying on co-registered MRI scans), placing standardized ROIs onto the transverse slices, to report the SUV_r from different ROIs relative to the cerebellum. The diagnostic classification accuracy of the composite mean SUV_r of the frontal, parietal, anterior cingulate, and precuneus regions is compared with that of the mean SUV_r from similarly located regions produced by the FS based method using a discriminant analysis. The correspondence between the SUV_r values from the two methods is further evaluated by a linear regression analysis.

Results: Discriminant analysis using the mean of 4 regions calculated by ADER produced an overall classification accuracy of 80%, controls' classification accuracy of 88% and AD classification of 67%. Discriminant analysis using the mean of 4 regions calculated by the FS based method resulted in an overall classification accuracy of 82%, controls' classification accuracy of 89% and AD classification of 72%. A linear regression analysis comparing the two methods showed good agreement (adjusted R² = 0.71).

Conclusions: The comparable overall and control subject classification accuracies and the strong correlation between the ADER generated AV45 SUV_r values and the Freesurfer based method, though showing some variability across scans, provide preliminary support for utilizing ADER to quantify the beta-amyloid load in PET images of the human brain. The low processing time and modest computational resource requirements makes ADER a promising high-throughput and objective alternative to visual ratings. Further validation studies focusing on other disease stages, potential scanning site differences, and longitudinal data are needed to further optimize the algorithm.

PERIPHERAL APOE LEVELS ARE ASSOCIATED WITH REGIONAL GRAY MATTER VOLUME, CEREBRAL GLUCOSE METABOLISM AND COGNITIVE PERFORMANCE IN COGNITIVELY NORMAL APOE ϵ 3/4 CARRIERS. Nielsen HM, Chen K, Bauer III RJ, Reiman EM, Caselli R, Bu G. Mayo Clinic College of Medicine, Jacksonville FL; Stockholm University, 10691 Stockholm, Sweden; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Carriers of the APOE ϵ 4 allele are at increased risk of developing Alzheimer's disease (AD). Endophenotypes of APOE ϵ 4 include reduced cerebral metabolic rate of glucose (CMRgl) in the same brain areas known to be affected by AD, and reduced plasma total apolipoprotein E (apoE) levels attributed to a specific decrease in the apoE4 isoform concentrations. Whether low plasma apoE levels are associated with structural and functional brain measurements remains to be investigated. Here we quantified plasma total apoE and the individual apoE3 and apoE4 isoforms in n=25 cognitively healthy APOE ϵ 3/4 individuals who had completed an extensive cognitive test battery and undergone FDG-PET and MRI to determine CMRgl and regional gray matter volume (GMV). In addition to negative associations of total plasma apoE, apoE3 and apoE4 each with GMV or CMRgl in the frontal, occipital and temporal areas (uncorrected p=0.005), an increase in relative ratio of apoE4 over apoE3 was associated with reductions of GMV in the right posterior cingulate, and CMRgl bilaterally in the anterior cingulate and in the right hippocampal area. Interestingly, this isoform ratio was also correlated with more preservative errors on the Wisconsin Card Sorting Test. To assess whether the association between the apoE4/apoE3 ratio and prefrontal executive functions could be replicated in a larger cohort we expanded our analysis to include in total n=128 cognitively healthy APOE ϵ 3/4 individuals from whom plasma samples were analyzed for total apoE and apoE isoforms. Our results show that total apoE levels differed between sexes and in females, apoE3 but not apoE4 levels increased with age. Also, performance on cognitive tests assessing executive and language functions was positively associated with total apoE levels in females only. We conclude that peripheral apoE levels and specifically the relative apoE4/3 isoform ratio are associated with GMV, CMRgl and cognitive performance in cognitively healthy individuals with a genetic predisposition to neurodegenerative disease.

TARGETING OLIGOMERIC A-SYN AGGREGATES AS A THERAPEUTIC FOR PARKINSON'S DISEASE. Spencer B, Williams S, Rockenstein E, Valera E, Mante M, Florio J, Adame A, Masliah E, Sierks MR. University of California, San Diego; Arizona State University; Arizona Alzheimer's Consortium.

Background: Progressive accumulation of alpha-synuclein (a-syn) has been associated with Parkinson's Disease (PD) and Dementia with Lewy Body (DLB). The mechanisms through which a-syn leads to neurodegeneration are not completely clear; however formation of various oligomeric species has been proposed to play a role. Antibody therapy has shown effectiveness at reducing a-syn accumulation in the CNS; however, most of these studies have been conducted utilizing antibodies that recognize both monomeric and higher molecular weight a-syn. In this context, the main objective of this study was to investigate the efficacy of immunotherapy with single chain antibodies (scFVs) against specific conformational forms of a-syn fused to a novel brain penetrating sequence.

Methods: For this purpose we screened various scFVs against a-syn expressed from lentiviral vectors by intracerebral injections in an a-syn Tg model. The most effective scFVs were fused to the cell penetrating peptide penetratin to enhance transport across the blood-brain barrier, and lentiviral vectors were constructed and tested for efficacy following systemic delivery (IP) into a-syn Tg mice.

Results: Two scFVs (D5 and 10H) selectively targeted different a-syn oligomers and reduced the accumulation of a-syn and ameliorated functional deficits when delivered late in disease development; however, only one of the antibodies (D5) was also effective when delivered early in disease development. These scFVs were also utilized in an ELISA assay to monitor the effects of immunotherapy on a-syn oligomers in brain and plasma.

Conclusions: The design and targeting of antibodies for specific species of a-syn oligomers is crucial for therapeutic immunotherapy.