ANNUAL REPORT

July 1, 2013 to June 30, 2014

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In memory of our dear colleague D. Larry Sparks, PhD,
who passed away on May 12, 2013.

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--Arizona State University, Banner Alzheimer's Institute, Banner Sun Health Research Institute, Barrow Neurological Institute, Mayo Clinic Arizona, Translational Genomics Research Institute (TGen), and 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, and to help address the unmet needs of patients and family caregivers.

The Consortium continues to be recognized inside and outside Arizona as a model of multi-institutional collaboration in biomedical research, capitalizing on complementary resources and expertise from different disciplines and institutions to address scientific problems in a more fundamental 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 many other grants and contracts.

Dr. Eric Reiman is the Director of the Consortium and the NIA-sponsored ADCC, Dr. Richard Caselli is the ADCC's Associate Director, and Dr. Carol Barnes is Chairperson of the Consortium's 25-member Internal Scientific Advisory Committee. Leading officials 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 an annual site visit, review the progress and productivity of the Consortium and the 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 and mathematical analysis of complex data sets, the basic, cognitive and behavioral neurosciences, and clinical, experimental therapeutics, and neuropathology research. It has made critical contributions to the scientific understanding, unusually early detection and tracking of AD, and accelerated evaluation of putative AD prevention therapies. It has provided a national model of multi-institutional research collaboration, and has found new ways for different stakeholders to work together in support of critically important goals.

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. It has also sought to make a difference in the lives of all patients and families affected by or at risk for AD, including Arizona's underserved and understudied Hispanic and Native American communities.

State and institutional matching funds are used 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 competitive NIA grant support for 13 consecutive years. Funds for ADCC's Administrative, Clinical, Data Management and Statistics, Neuropathology, and Education and Information Transfer Cores are used to support a larger number of researchers and projects inside and outside of the state. ADCC's progress, productivity and plans were detailed in our annual report to the NIA, will be reviewed at our advisors' annual site visit on June 6, 2014 and will support the submission of our fourth consecutive competitive five-year ADCC renewal grant in September 2015.

Productivity and Impact

The Arizona Alzheimer's Consortium is the leading statewide AD Center in the nation and among the most impactful AD research programs in the world. To date, its researchers have generated several thousand publications, close to a thousand research grants and contracts, hundreds of millions of dollars in grants, contracts, philanthropy, new research programs and facilities, and numerous jobs. They continue to make pioneering contributions to the scientific fight against AD, related disorders, and the aging brain.

- They have helped clarify several genetic and non-genetic risk factors and disease mechanisms, providing targets at which to aim new AD treatments, and they have proposed promising ways to treat and prevent the disorder.

- They continue to play leadership roles in the earliest detection and tracking of AD and the accelerated evaluation of putative prevention therapies. They have also helped set the stage for the use of amyloid imaging techniques in the clinical setting.

- They continue to clarify how brain cells, regions, and networks, and the mental operations to which they are related, work together to orchestrate memory and other thinking abilities, how they are preferentially affected by AD and by normal aging. They have played leadership roles in the study of normal cognitive aging.

- They continue to develop groundbreaking research methods and strategies to support these and other research endeavors.

- As previously noted, they established an "Alzheimer's Prevention Initiative (API)" to help launch a new era in AD prevention research. API's first trial, which is supported by more than $100M in funding from the NIA, philanthropic funds, and Genentech, began in late 2013. It is intended to evaluate an amyloid antibody therapy in cognitively unimpaired persons at certain risk for autosomal dominant early-onset AD, provide a better understanding of the "amyloid hypothesis," help to establish the biomarker endpoints and accelerated approval pathway needed to rapidly evaluate the range of promising prevention therapies; and provide a public resource of therapeutic trial data and biological samples to the research community after the trial is over. API's second trial, which will be the supported by a recent $33.2M NIA grant award, additional funds from the NIA's Accelerating Medicine's Partnership, philanthropy, and a to-be-determined industry partner will evaluate one or more anti-amyloid agents in cognitively unimpaired persons with two copies of the APOE4 gene, who are at the highest known risk

for developing AD at older ages. Alzheimer's Prevention Registries have been launched in Colombia and in North America (www.endalznow.org) to support enrollment in prevention trials.

- We are pleased to note that Dr. Carol Barnes was the recipient of the 2013 Ralph W. Gerard Prize in Neuroscience from the Society for Neuroscience in recognition of her seminal contributions to the study of the aging brain. The Gerard Prize is the top recognition given by the Society for Neuroscience and it has been reserved for giants in brain research.

More to Do

While we are gratified by the Consortium's productivity, we recognize that there is a lot more to do. During the next few years, we wish to increase the critical mass of productive clinical and basic scientists in Arizona, to launch several new scientific and clinical initiatives, to set a new standard for the care of patients and families, to further assist our understudied and underserved communities, and to help find treatments to prevent the clinical onset of AD as soon as possible.

We wish to express our heartfelt appreciation to the state of Arizona, the NIA, our participating institutions, and all of our partners, supporters and valued research participants. We are especially grateful to our elected officials, the ADHS, and the ABRC for increasing our state funding from $1.15M to $2.375M during the next fiscal year. We are proud of our progress, excited about our plans, and determined to make a transformational difference in the fight against AD.

Arizona Alzheimer's Consortium

16th Annual Conference – Thursday June 5, 2014

Banner Desert Medical Center

1400 S. Dobson Road

Mesa, Arizona 85202

POSTER PRESENTATION SET-UP   7:30 – 9:00AM
CONTINENTAL BREAKFAST

WELCOMING REMARKS & INTRODUCTION   9:00 – 9:15AM
        Eric M. Reiman, M.D.
        Director, Arizona Alzheimer's Consortium

LEON THAL MEMORIAL LECTURE   9:15 – 10:30AM
        "Building a Pipeline to Identify and Validate Novel
        Targets for the Treatment and Prevention of Alzheimer's
        Disease"
        David A. Bennett, M.D.
        Director, Rush Alzheimer's Center
        Robert C. Borwell Professor of Neurological Sciences
        Rush University Medical Center

ORAL RESEARCH PRESENTATIONS – SESSION I   10:30 – 12:00PM

POSTER SESSION I & LUNCH   12:00 – 1:00PM

POSTER SESSION II & LUNCH   1:00 – 2:00PM

ORAL RESEARCH PRESENTATIONS – SESSION II   2:00 – 3:10PM

CLOSING REMARKS   3:10 – 3:30PM
        Eric M. Reiman, M.D.
        Director, Arizona Alzheimer's Consortium

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Oral Research Presentations

SESSION I (Moderator: Dr. Richard Caselli, M.D.)

10:30 - 10:42AM   **mTOR regulates tau phosphorylation and degradation: implications for Alzheimer's disease and other tauopathies.** Salvatore Oddo. Banner Sun Health Research Institute; University of Arizona College of Medicine, Phoenix; Arizona Alzheimer's Consortium.

10:43 - 10:55AM   **PACAP deficit in Alzheimer's disease and protection against beta-amyloid toxicity.** PengCheng Han. Barrow Neurological Institute; The First Hospital of Kunming Medical University; Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

10:56 - 11:08AM   **Protein aggregates as biomarkers for neurodegenerative diseases**. Michael Sierks. Arizona State University; Arizona Alzheimer's Consortium.

11:09 - 11:21AM   **Novel method for behavior-driven molecular and structural investigation in rodent whole brain**. Monica Chawla. University of Arizona; Alzheimer's Consortium.

11:22 - 11:34AM   **Relationships between behavioral declines, hyperexcitability, and inhibitory networks in the medial temporal lobe of aged rhesus macaque**. Daniel Gray. University of Arizona; Arizona Alzheimer's Consortium.

11:35 - 11:47AM   **Improving the power to track fibrillar amyloid-beta PET measurements and evaluate amyloid-modifying treatments using a cerebral white matter region-of-interest**. Kewei Chen. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

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Oral Research Presentations

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

2:00 - 2:12PM   **Reducing delirium in the acute care setting.** William Burke. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

2:13 - 2:25PM   **Short term memory binding in presymptomatic APOE e4 carriers.** Richard Caselli. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

2:26 - 2:38PM   **Development of therapeutic area-specific data standards for Alzheimer's and Parkinson's diseases**. Diane Stephenson. Critical Path Institute; Arizona Alzheimer's Consortium.

2:39 - 2:51PM   **Web-based paired associates testing of over 25,000 individuals demonstrates significant main effects of chronological age, gender, education, and Alzheimer's disease family history on performance**. Lee Ryan. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

2:52 - 3:04PM   **Facebook for seniors: The effects of online social networking on cognitive function in healthy older adults**. Elizabeth Glisky. University of Arizona; Arizona Alzheimer's Consortium.

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Poster Presentations

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1. **Brain-derived neurotrophic factor (BDNF) polymorphisms are associated with differential rates of amyloid accumulation and cognitive decline in cognitively normal older adults.** Acosta JI, Geda YE, Stokin G, Fleisher AS, Reschke C, Bauer R, Thiyyagura P, Lu B, Caselli RJ, Weiner M, Reiman EM, Chen K. Mayo Clinic Scottsdale; Arizona Alzheimer's Consortium; International Clinical Research Center, Brno, Czech Republic; St. Anne's University Hospital Brno, Brno, Czech Republic; Banner Alzheimer's Institute; Tsinghua University; University of California, San Francisco.

2. **Virtually supportive: a feasibility pilot study of an online support group for dementia caregivers in a 3D virtual environment.** Arizmendi B, O'Connor M. University of Arizona; Arizona Alzheimer's Consortium.

3. **Age related differences in hippocampal response to increasing difficulty in an associative memory retrieval task: an fMRI investigation of functional compensation in a face-name pairs task.** Baena E, Buckley T, Myhre JW, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

4. **Strategy use in navigating a human radial-arm maze: translating spatial cognition across species.** Baxter LC, Grunfeld IS, Mennenga SE, Camp BW, Patten KJ, Bimonte-Nelson HA*, McBeath MK*. Arizona State University; Arizona Alzheimer's Consortium; Barrow Neurological Institute.

5. **Retinal pathology in Parkinson's and Alzheimer's disease: α-synucleinopathy but not Aβ or tau pathology.** Beach TG, Carew J, Serrano G, Adler CH, Shill HA, Sue LI, Sabbagh MN, Akiyama H, Cuenca N. Banner Sun Health Research Institute; Mayo Clinic Arizona; Tokyo Metropolitan Institute of Medical Science; Universidad de Alicante; Arizona Alzheimer's Consortium.

6. **Theoretical impact of Florbetapir (18f) amyloid imaging on the diagnosis of Alzheimer's dementia and the detection of preclinical cortical amyloid.** Beach TG, Schneider JA, Sue LI, Serrano G, Dugger BN, Monsell SE, Kukull W. Banner Sun Health Research Institute; University of Washington; Arizona Alzheimer's Consortium.

7. **Administration of a selective β2 adrenergic receptor antagonist exacerbates neuropathology and cognitive deficits in a mouse model of Alzheimer's disease.** Branca C, Hartman LK, Shaw DM, Farrell EK, Caccamo A, Oddo S; Banner Sun Health Research Institute; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

8. **An inverse relationship between longitudinal changes in fasting serum glucose and cerebral glucose metabolism in Alzheimer's disease related brain regions.** Burns CM, Kaszniak AW, Chen K, Lee W, Bandy DJ, Reschke C, Caselli RJ, Reiman EM. University of Arizona; Banner Alzheimer's Institute; Mayo Clinic Scottsdale; Arizona Alzheimer's Consortium.

9. **Genetic reduction of mTOR ameliorates Alzheimer's disease-like cognitive and pathological deficits by restoring hippocampal gene expression signature.** Caccamo A, De Pinto V, Messina A, Branca C, Oddo S. Banner Sun Health Research Institute; University of Catania; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

10. **Assessment of geriatric participant's retention of a pharmacist-provided warfarin education class.** Carroll K, Gerber DK. Midwestern University; Arizona Alzheimer's Consortium.

11. **Predictive testing for Alzheimer's disease: suicidal ideation among healthy participants.** Caselli RJ, Langbaum J, Marchant GE, Lindor RA, Hunt KS, Henslin BR, Dueck AC, Robert JS. Mayo Clinic Arizona; Banner Alzheimer Institute; Arizona State University; Arizona Alzheimer's Consortium.

12. **Novel method for behavior-driven molecular and structural investigation in rodent whole brain.** Chawla MK, Gray DT, Comrie AE, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

13. **Improving the power to track fibrillar amyloid PET measurements and evaluate amyloid-modifying treatments using a cerebral white matter reference region-of-interest.** Chen K, Roontiva A, Thiyyagura, P, Lee W, Liu X, Ayutyanont N, Protas H, Landau S, Luo J, Bauer R, Reschke C, Bandy D, Koeppe R, Fleisher AS, Caselli RJ, Jagust WJ, Weiner MW, Reiman EM, and the Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; University of Arizona; Mayo Clinic Arizona; University of California, Berkeley; University of California, San Francisco; Arizona Alzheimer's Consortium.

14. **Differential effects of context shifts on object recognition and source memory in older adults.** Cooke KA, Kawa K, Memel MB, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

15. **An internet-based study of over 25,000 individuals demonstrates significant effects of age, gender, education, and Alzheimer's disease family history in paired associate learning.** Corneveaux J, Schrauwen I, Siniard A, Peden J, Turk M, De Both M, Richholt R, Mueller M, Langbaum J, Reiman EM, Caselli RJ, Coleman P, Barnes C, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University of Arizona; LeaseHawk; Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute.

16. **Sanger sequencing exons of BDNF gene derived from a Latino sample.** Dawit S, Krell-Roesch J, Acosta J, Champion MD, Velgos SN, Shaibi G, Mandarino LJ, Cevette NM, Caselli RJ, Geda YE. University of Kansas Medical Center; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

17. **"Incidental" brain pathologies in prospectively followed normal elderly brain bank volunteers.** Dugger BN, Hentz JG, Adler CH, Sabbagh MN, Shill HA, Jacobson S, Caviness JN, Belden C, Driver-Dunckley E, Davis KJ, Sue LI, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

18. **The presence of total tau in peripheral tissues of Alzheimer's disease.** Dugger B, Whiteside C, Maarouf C, Beach TG, Dunckley T, Meechoovet B, Roher AE. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

19. **Comprehensive profiling of DNA methylation differences in patients with Alzheimer's and Parkinson's disease.** Dunckley T, Meechoovet B, Caselli R, Driver-Dunckley E. Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

20. **Frontal cortical gamma frequency slowing in aging: can C6 rescue cortical synchrony and decision speed?** Espinoza AI, Uprety AR, Lipa P, Thome A, Hindley TR, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

21. **PRAS40 as a novel therapeutic target for Alzheimer's disease.** Farrell EK, Hartman LK, Branca C, Shaw DM, Caccamo A, Oddo S. Banner Sun Health Research Institute; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

22. **Sex differences in anatomical modifications and pathology burden of Alzheimer's disease.** Filon JR, Serrano GE, Intorcia AJ, Carothers K, Carew JJ, Dugger BN, Fornwalt BE, Pullen JC, Saxon-LaBelle MM, Scott S, Scroggins AM, Sue LI, Sabbagh MN, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

23. **Plaques, not tangles related to abdominal circumference at autopsy in elderly brain bank individuals.** Fornwalt BE, Scroggins AM, Saxon-LaBelle MM, Carew JJ, Pullen JC, Filon JR, Intorcia AJ, Scott S, Sue LI, Beach TG, Dugger BN. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

24. **Relationships between behavioral declines, hyperexcitability, and inhibitory networks in the medial temporal lobe of aged rhesus macaque.** Gray DT, Thome A, Erickson CA, Lipa P, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

25. **Pituitary adenylate cyclase activating polypeptide in Alzheimer's disease.** Han P, Baxter LC, Liang WS, Tang Z, Yin J, Beach TG, Caselli RJ, Reiman EM, Shi J. Barrow Neurological Institute; The First Hospital of Kunming Medical University; Translational Genomics Research Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

26. **PACAP deficit in Alzheimer's disease and protection against beta-amyloid toxicity.** Han P, Tang Z, Yin J, Beach T, Reiman E, Shi J. Barrow Neurological Institute; The First Hospital of Kunming Medical University; Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

27. **Genetic suppression of β2-adrenergic receptors ameliorates tau pathology in a mouse model of tauopathies.** Hartman LK, Branca C, Shaw DM, Farrell EK, Caccamo A, Oddo S. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

28. **Relation of MRI white matter hyperintensity severity to nocturnal blood pressure variation and hypertension in healthy cognitive aging.** Haws K, Hishaw GA, Totenhagen JW, Torre GA, Gillespie WL, Reid BA, Nguyen LA, Fitzhugh MC, Lines JW, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

29. **Next-generation profiling to identify the molecular etiology of Parkinson's dementia.** Henderson-Smith A, Phillips L, Corneveaux J, Liang WS, Huentelman M, Beach T, Dunckley T. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

30. **Development of a novel centrifugal-optical diagnostic device for Alzheimer's disease.** Hsia A, Procopio C, Perkins M, Valla J. Midwestern University; Arizona Alzheimer's Consortium.

31. **Altered expression of genes involved in synaptic plasticity and mitochondrial energy metabolism, in the PCC of young-adult APOE4 carriers.** Jentarra G, Chavira B. Midwestern University; Arizona Alzheimer's Consortium.

32. **Cholinergic dysfunction and muscarinic receptor uncoupling in Alzheimer's disease.** Jones DC, Potter PE, Bills M, Killpack L, Hamadan M, Sue L, Beach TG. Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.

33. **Preliminary attempts at replicating the CLARITY method for imaging thick brain specimens.** Kaufman J, Castro M, Chavira B, Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.

34. **The effects of KIBRA, APOE, and hypertension status on measures of memory functioning in older adults.** Kawa K, Stickel A, Walther K, Glisky EL, Hackett N, Huentelman MJ, Ryan L. University of Arizona; Ludwig Maximilians University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

35. **Multifunctional radical quenchers: therapeutic agents for mitochondrial and neurodegenerative diseases.** Khdour OM, Alam MP, Arce PM, Chen Y, Roy B, Dey S, Hecht SM. Arizona State University; Arizona Alzheimer's Consortium.

36. **Physical exercise in midlife versus late-life may have differential impact on the outcome of incident mild cognitive impairment: the Mayo Clinic study of aging.** Krell-Roesch J, Acosta JY, Stokin GB, Bartley MM, Roberts RO, Knopman DS, Christianson TJ, Pankratz VS, Petersen RC, Geda YE. Mayo Clinic Arizona; Mayo Clinic Rochester; International Clinical Research Center and St. Anne's University Hospital Brno; Arizona Alzheimer's Consortium.

37. **Age-related changes in entorhinal-hippocampal dynamics.** Lester AW, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

38. **Multivariate regional network of gray matter volume associated with healthy cognitive aging.** Lines J, Totenhagen J, Haws K, Fitzhugh M, Hishaw G, Torre G, Gillespie W, Chen K, Reiman E, Trouard T, Moeller J, Alexander G. University of Arizona; Arizona Alzheimer's Consortium; Banner Alzheimer's Institute; Columbia University.

39. **A multicomponent intervention for mild cognitive impairment improves mood and cognition in patients and caregivers.** Locke DEC, Fields JA, Cuc AV, Fowler A, Young J, Caselli M, Hoffman Snyder C, Chandler Greenaway M, Smith GE. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

40. **Prioritization of treatment outcomes by partners of patients with mild cognitive impairment.** Locke DEC, Gonzalez P, Smith G. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

41. **Where, not how much. Increased cytoplasmic and decreased nuclear localization of a key epigenetic molecule is an early event in Alzheimer's disease with major implications for gene expression.** Mastroeni D, Delvaux E, Nolz J, Oddo S, Coleman PD. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

42. **Novel coenzyme q10 analogue protects mitochondria from oligomeric Aβ.** Mastroeni D, Khdour OMC, Arcec PM, Hecht SM, Coleman PD. Banner Sun Health Research Institute; Maastricht University Medical Centre; Arizona State University; Arizona Alzheimer's Consortium.

43. **Alzheimer's disease is associated with dysregulated expression of immune response and mitochondrial genes in posterior cingulate astrocytes.** McDonald J*, Sekar S*, Cuyugan L, Aldrich J, Kurdoglu A, Adkins J, Serrano G, Craig DW, Beach TG, Reiman EM, Liang WS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Banner Sun Health Research Institute; Banner Alzheimer's Institute.

44. **A test of the sensitive window for hormone therapy initiation during transitional menopause: conjugated equine estrogens impair memory after, but not before, ovarian follicular depletion.** Mennenga SE, Acosta JI, Garcia AN, Hewitt LT, Kingston ML, Tsang CWS, Camp BW, Mayer L, Dyer C, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium; SenesTech, Inc.

45. **Estradiol only improves performance when working memory load is very high: alternative interpretations of poor performance on an easy task.** Mennenga SE, Gerson JE, Koebele SV, Hewitt LT, Jordan AS, Mousa AA, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

46. **Understanding the cognitive impact of the contraceptive estrogen Ethinyl Estradiol: tonic and cyclic administration impairs memory, and performance correlates with basal forebrain cholinergic neurons.** Mennenga SE, Gerson JE, Koebele SV, Kingston ML, Tsang CWS, Engler-Chiurazzi EB, Baxter LC, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium; Barrow Neurological Institute.

47. **The frequency and distribution of BDNF in a Latino sample in Phoenix, Arizona.** Miller EA, Krell-Roesch J, Acosta JY, Shaibi G, Mandarino LJ, Velgos SN, Cevette NM, Hentz JG, Coletta DK, Caselli RJ, Geda YE. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

48. **Agesist stereotypes about memory may not affect all older adults.** Moseley SA, Edwards CL, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

49. **Aquatic therapy and Alzheimer's disease - a case report.** Myers KW, Capek D, Shill H, Sabbagh M. Midwestern University; Royal Oaks Retirement Community; Banner Sun Health Research Institute; University of Arizona College of Medicine, Phoenix; Arizona Alzheimer's Consortium.

50. **Facebook for seniors: the effects of online social networking on cognitive function in healthy older adults.** Myhre JW, Woolverton C, Robbins R, Polsinelli A, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

51. **Development of therapeutic area-specific data standards for Alzheimer's and Parkinson's diseases.** Neville J, Kopko S, Tolk C, Odenkirchen J, Broadbent S, Romero K, Stafford B, Hartley E, LeRoy B, Avilés E, Stephenson D. Coalition Against Major Diseases**;** Critical Path Institute; Clinical Data Interchange Standards Consortium; National Institute of Neurological Disorders and Stroke.

52. **The relationship between ankle dorsiflexion range of motion and elderly fall risk predictors.** Nithman RW. Midwestern University; Arizona Alzheimer's Consortium.

53. **Mitochondrial abnormalities and nicotine treatment in a familial model of Parkinson's disease.** Odumosu M, Call GB, Buhlman LM. Midwestern University; Arizona Alzheimer's Consortium.

54. **Ketogenic therapy in Alzheimer's disease: potential mechanism for failure in APOE4+ patients.** Pangle P, Shonebarger D, Perkins M, Valla J. Midwestern University; Arizona Alzheimer's Consortium.

55. **Older adults' autobiographical memories suggest importance of social interactions and third person perspective in maintenance of positive affect.** Polsinelli AJ, Rentscher KE, Martinez T, Sherman NC, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

56. **Neuropsychiatric symptoms, APOEe4 and the risk of incident dementia: the Mayo Clinic Study of Aging.** Pink A, Acosta JI, Roberts RO, Mielke MM, Christianson TJ, Pankratz VS, Stokin GB, Boeve BF, Petersen RC, Geda YE. Mayo Clinic Arizona; Mayo Clinic Rochester; International Clinical Research Center and St. Anne's University Hospital Brno; Paracelsus Medical University; Arizona Alzheimer's Consortium.

57. **Is muscarinic receptor uncoupling in Alzheimer's disease related to a decrease in beta-arrestin?** Potter PE, Bills M, Killpack L, Jones D, Hamada M, Sue L, Beach TG. Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.

58. **Early-frame PiB PET perfusion and FDG PET glucose metabolism comparison in cognitively normal persons at three levels of genetic risk for Alzheimer's disease.** Protas HD, Chen K, Luo J, Rausch JT, Bauer III R, Goodwin S, Richter N, Bandy D, Caselli R, Fleisher AS, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Arizona State University; University of California, San Diego; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

59. **Prevalence of age-related peripheral pathologies in Alzheimer's disease and non-demented controls.** Pullen JC, Saxon-LaBelle MM, Serrano GE, Carew JJ, Filon JR, Fornwalt BE, Dugger BN, Intorcia AJ, Scott S, Scroggins AM, Sue LI, Sabbagh MN, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

60. **Brain imaging and blood biomarker abnormalities in children at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred.** Quiroz YT, Schultz A, Chen, K, Brickhouse M, Fleisher AS, Langbaum JBS, Thiyyagura P, Protas H, Fagan AM, Shah AR, Muniz M, Arboleda-Velasquez JF, Munoz C, Velilla L, Tariot PN, Dickerson BC, Lopera F, Sperling RA, Reiman EM. Massachusetts General Hospital and Harvard Medical School; Universidad de Antioquia; Alzheimer's Prevention Initiative; Banner Alzheimer's Institute; Washington University; Boston University; Harvard Medical School; Brigham & Women's Hospital, Boston, MA; Arizona Alzheimer's Consortium.

61. **Gene expression profiling of human astrocytes treated with bexarotene and related compounds.** Richholt RF, Coffey PM, Piras IS, Persico AM, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University Campus Bio-Medico.

62. **Subjective cognitive impairment, APOE ε4 status, and cognitive aging: the Arizona APOE Cohort Study.** Ruider H, Krell-Roesch J, Hentz J, Woodruff B, Nagle C, Stonnington CM, Locke DEC, Acosta JI, Stokin GB, Caselli RJ, Geda YE. Mayo Clinic Arizona; International Clinical Research Center and St. Anne's University Hospital Brno; Paracelsus Medical University; Arizona Alzheimer's Consortium.

63. **Florbetapir PET, FDG PET, and MRI in Down syndrome individuals with and without Alzheimer's dementia.** Sabbagh MN, Chen K, Rogers J, Fleisher AS, Liebsack C, Bandy D, Belden C, Thiyyagura P, Liu X, Roontiva A, Jacobson S, Malek-Ahmadi M, Parks S, Powell J, Reiman EM. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium; Banner Alzheimer's Institute; Arizona State University; SRI International; Translational Genomics Research Institute; University of Arizona.

64. **Banking fibroblast cells from autopsy skin tissue to establish APOE genotype-specific iPSC lines.** Schmitz CT, Serrano G, Sue L, Beach TG, Walker DG, Lue L. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

65. **Changes of TREM2 protein expression with neuropathological features of Alzheimer's disease.** Schmitz CT, Serrano G, Sue L, Beach TG, Walker DG, Lue L. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

66. **Web-based paired associates testing of over 25,000 individuals demonstrates significant main effects of chronological age, gender, education, and Alzheimer's disease family history on performance.** Schrauwen I, Corneveaux J, Siniard A, Peden J, Turk M, De Both M, Richholt R, Mueller M, Langbaum J, Reiman EM, Caselli RJ, Coleman P, Barnes C, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University of Arizona; LeaseHawk; Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute.

67. **mTOR regulates tau phosphorylation and degradation: implications for Alzheimer's disease and other tauopathies.** Shaw DM, Branca C, Hartman LK, Farrell EK, Caccamo A, Oddo S. Banner Sun Health Research Institute; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

68. **Novel FTO inhibitor modulates microRNA and mRNA.** Shen L, Iacoban P, Rowles J, Olsen M. Midwestern University; Arizona Alzheimer's Consortium.

69. **Genetic influence of apolipoprotein e4 genotype on hippocampal surface morphometry.** Shi J, Baxter LC, Caselli RJ, Thompson PM, Wang Y. Arizona State University; Barrow Neurological Institute; Mayo Clinic Arizona; University of California, Los Angeles, School of Medicine; Alzheimer's Disease Neuroimaging Initiative; Arizona Alzheimer's Consortium.

70. **Ventricular morphometry analysis in mild cognitive impairment with hyperbolic ricci flow.** Shi J, Stonnington CM, Thompson PM, Chen K, Gutman B, Reschke C, Baxter LC, Reiman EM, Caselli RJ, Wang Y, the Alzheimer's Disease Neuroimaging Initiative. Arizona State University; Mayo Clinic Arizona; UCLA School of Medicine; Banner Alzheimer's Institute and Banner Good Samaritan PET Center; University of Southern California; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

71. **Alterations in mitochondrial oxidative phosphorylation proteins in young-adult carriers of the Alzheimer's risk factor APOE4.** Shonebarger D, Pangle P, Perkins M, Valla J. Midwestern University; Arizona Alzheimer's Consortium.

72. **The influence of demographic and disease risk factors on paired associates learning in an internet recruited cohort of over 25,000 individuals.** Siniard A, Schrauwen I, Corneveaux J, Peden J, Turk M, De Both M, Richholt R, Mueller M, Langbaum J, Reiman EM, Caselli RJ, Coleman P, Barnes C, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University of Arizona; LeaseHawk; Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute.

73. **Approximate entropy as a metric for quantifying fMRI changes across time.** Steinke K, Braden BB, Frakes D, Baxter LC. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

74. **The Coalition Against Major Diseases: regulatory path to enable targeting the right patients in clinical trials of early stages of Parkinson's disease.** Stephenson D, Cole PE, Comery TA, Gordon M, Grachev I, Hewitt D, Babcock D, Lindstedt K, Meibach R, Matthews D, Romero K, Breen K, Kelly M, Russell D, Stark Y, Imam S, Harbron C, Jimenez T, Marek K. Critical Path Institute/ Coalition Against Major Diseases; Takeda Pharmaceuticals International, Inc; Pfizer; Boehringer Ingelheim; GE; Merck & Co.; NIH/NINDS; Orion; Novartis; ADM Diagnostics, LLC; GlaxoSmithKline; Institute for Neurodegenerative Disorders; Teva; FDA; AstraZeneca.

75. **Resolving the transport kinetics of the corticosterone-sensitive organic cation transporter 3 (OCT3/SLC22A3) in the male rat brain.** Talboom JS, Molinaro J, Lowry CA, Renner KJ, Orchinik M. Arizona State University; University of Colorado Boulder; University of South Dakota; Arizona Alzheimer's Consortium.

76. **Protein aggregates as biomarkers for neurodegenerative diseases.** Tian H, Davidowitz E, Moe J, Sierks M. Arizona State University; Oligomerix. Inc; Arizona Alzheimer's Consortium.

77. **Resting state MRI functional connectivity differences in healthy middle-aged to elderly adults.** Totenhagen JT, Lines JW, Bergfield KL, Fitzhugh MC, Torre GA, Gillespie WL, Haws KA, Reid BA, Nguyen LA, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; Evelyn F. McKnight Brain Institute; Arizona Alzheimer's Consortium.

78. **Rock inhibitor development for cognitive enhancement and blockade of tau phosphorylation.** Turk MN, Adams MD, Wang T, Dunckley T, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Arizona State University; Midwestern University; University of Arizona.

79. **Deficits of synaptic functions in hippocampal slices prepared from aged mice null α7 nicotinic acetylcholine receptors.** Turner D, Gao M, Wu J. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

80. **Interleukin-34, a new player in inflammatory processes of Alzheimer's disease and Parkinson disease.** Walker DG, Whetzel AM, Huentelman MJ, Lue L. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

81. **The Institute for Healthcare Innovation-the heart of one health innovation.** Weingand K, Sidaway B, Fossum T. Midwestern University; Arizona Alzheimer's Consortium.

82. **Using morphology specific reagents to distinguish between different neuro-degenerative diseases.** Williams SM, Sierks MR. Arizona State University; Arizona Alzheimer's Consortium.

83. **What role does the anterior temporal lobe play in sentence-level processing? Neural correlates of syntactic processing in semantic PPA.** Wilson SM, DeMarco AT, Henry ML, Gesierich B, Babiak M, Miller BL, Gorno-Tempini ML. University of Arizona; University of California, San Francisco; Arizona Alzheimer's Consortium.

84. **Absence of a "widowhood effect" on incidence of dementia in cognitively normal research subjects.** Woodruff B, Stonnington C, Locke DEC, Hentz J, Dueck AC, Wojtulewicz L, Caselli RJ, Geda YE. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

85. **Paradoxical impact of widowhood on incidence of dementia in subjects with mild cognitive impairment.** Woodruff B, Stonnington C, Locke DEC, Hentz J, Dueck AC, Wojtulewicz L, Geda YE, Caselli RJ. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

86. **Dynamic brain changes associated with new learning.** Yang S, Nie Z, Braden BB, Morrone-Strupinski J, Steinke K, Ye J, Baxter LC. Arizona State University; Barrow Neurological Institute; Private Practice, Chandler, Arizona; Arizona Alzheimer's Consortium.

2014 Oral Research Presentation

Abstracts

MTOR REGULATES TAU PHOSPHORYLATION AND DEGRADATION: IMPLICATIONS FOR ALZHEIMER'S DISEASE AND OTHER TAUOPATHIES. Shaw DM, Branca C, Hartman LK, Farrell EK, Caccamo A, Oddo S. Banner Sun Health Research Institute; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Accumulation of tau is a critical event in several neurodegenerative disorders, collectively known as tauopathies, which include Alzheimer's disease and frontotemporal dementia. Pathological tau is hyperphosphorylated and aggregates to form neurofibrillary tangles. The molecular mechanisms leading to tau accumulation remain unclear and more needs to be done to elucidate them. Age is a major risk factor for all tauopathies, suggesting that molecular changes contributing to the aging process may facilitate tau accumulation and represent common mechanisms across different tauopathies. Here, we use multiple animal models and complementary genetic and pharmacological approaches to show that the mammalian target of rapamycin (mTOR) regulates tau phosphorylation and degradation. Specifically, we show that genetically increasing mTOR activity elevates endogenous mouse tau levels and phosphorylation. Complementary to it, we further demonstrate that pharmacologically reducing mTOR signaling with rapamycin ameliorates tau pathology and the associated behavioral deficits in a mouse model overexpressing mutant human tau. Mechanistically, we provide compelling evidence that the association between mTOR and tau is linked to GSK3β and autophagy function. In summary, we show that increasing mTOR signaling facilitates tau pathology while reducing mTOR signaling ameliorates tau pathology. Given the overwhelming evidence showing that reducing mTOR signaling increases lifespan and health span, the data presented here have profound clinical implications for aging and tauopathies and provide the molecular basis for how aging may contribute to tau pathology. Additionally, these results provide pre-clinical data indicating that reducing mTOR signaling may be a valid therapeutic approach for tauopathies.

PACAP DEFICIT IN ALZHEIMER'S DISEASE AND PROTECTION AGAINST BETA-AMYLOID TOXICITY. Han P, Tang Z, Yin J, Beach T, Reiman E, Shi J. Barrow Neurological Institute; The First Hospital of Kunming Medical University; Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: This study was aimed to quantify a neuropeptide, pituitary adenylate cyclase activating polypeptide (PACAP) in AD and non-AD brains, to evaluate the protective effects of PACAP against beta-amyloid toxicity, and to provide an insight on the pharmacological mechanism.
PACAP is intrinsically expressed in mammals and is considered to be a potent neurotrophic and neuroprotective peptide. The change of PACAP level in Alzheimer's disease (AD) remains unclear. We quantified the level of PACAP in AD brain to compare it with cognitively normal non-AD brain (CN). We further tested whether PACAP reduced beta-amyloid toxicity in primary cultured neurons, a post-mitotic cell population modeling AD pathological conditions.

Methods: We examined PACAP in human postmortem AD cortex and compared it with CN cortex. We used cultured primary neuron to establish in vitro model of beta-amyloid toxicity, to introduce genetic manipulation to knock down or over-express proteins and to analyze mitochondrial functions.

Results: PACAP expression was reduced in human AD cortex. This deficiency was linked to beta-amyloid plaque burden and Braak Stage. We also observed similar PACAP reduction in the brains of 3T×AD mice. In the cultured neurons, treatment with PACAP effectively protected neurons against beta-amyloid toxicity. PACAP stimulated mitochondrial Sirtuin 3 (SIRT3) production. Similar to PACAP, SIRT3 was reduced in AD and 3T×AD transgenic mice. Knocking down SIRT3 compromised the neuroprotective effect of PACAP, and this was reversed by over-expressing SIRT3.

Conclusions: PACAP is reduced in AD and the reduction is related to the severity of AD pathology. PACAP protects against beta-amyloid induced toxicity. The neuroprotective effects are mediated by SIRT3 and enhanced mitochondrial function. These results suggest that PACAP may be a potentially effective therapeutic approach for AD.

PROTEIN AGGREGATES AS BIOMARKERS FOR NEURODEGENERATIVE DISEASES. Tian H, Davidowitz E, Moe J, Sierks M. Arizona State University; Oligomerix. Inc; Arizona Alzheimer's Consortium.

Background: Aggregation of proteins such as amyloid-beta (Abeta), alpha-synuclein and tau are thought to play a role in the neurodegenerative diseases including Alzheimer's and Parkinson's. During the aggregation process various oligomeric protein species are formed and increasing evidence implicates these oligomeric aggregates in disease onset and progression. Early detection of specific oligomer protein species could facilitate earlier and more accurate diagnoses and targeting these oligomers may also alter the disease manifestations. Our lab focuses on targeting specific oligomeric protein species and identifying their role in different neurodegenerative diseases.

Methods: Using novel technology, our lab isolated single chain antibody fragments (scFvs) that bind to monomeric and different oligomeric forms of Abeta, alpha-synuclein and taufrom a phage display library. We utilized these scFvs in a novel sandwich ELISA to characterize post-mortem human brain tissue representing different neurodegenerative diseases.

Results: The morphology specific scFvs can detect the presence of different oligomeric protein aggregate species in homogenized brain tissue. The presence of different oligomeric aggregates correlates with different neurodegenerative diseases.

Conclusion: Since our scFvs recognizes oligomeric forms of aggregated proteins that occur in Alzheimer's and Parkinson diseases these scFvs may be useful in facilitating early and accurate diagnoses in these diseases. Because the targeted oligomeric proteins are neurotoxic, these scFvs may also be useful as therapies since they could target and remove the oligomers before further damage could occur. Further research is necessary though to establish the role these scFvs can play in managing neurodegenerative diseases.

NOVEL METHOD FOR BEHAVIOR-DRIVEN MOLECULAR AND STRUCTURAL INVESTIGATION IN RODENT WHOLE BRAIN. Chawla MK, Gray DT, Comrie AE, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Currently methods for identifying the regional distribution of neuronal activity within the brain during specific behaviors are not only time consuming, but also labor intensive. To circumvent the need to serial section, stain, obtain confocal images of the tissue, then reconstruct large parts of brain by using algorithms that can montage tissue sections back together, we are currently developing a method that allows behavior-induced activity markers to be imaged in intact brain. This involves combining a recently developed whole brain clarification method (CLARITY; Chung et al., 2013) that provides the capacity to image deep into an intact brain, with a gene expression, cellular activity marker method (catFISH) that labels only those cells active in a given behavioral experience.

Methods: Brain from a young rat was extracted after maximal electro-convulsive shock treatment (that enables rapid transcription of immediate early genes) and quick frozen in isopentane that was cooled in a dry-ice ethanol slurry. The frozen brain was then placed in a 50 ml centrifuge tube containing hydrogel solution for post-fixation which allows cross linkage with formaldehyde in the presence of hydrogel monomers, covalently linking tissue elements to monomers that are then polymerized into a hydrogel mesh. An electric field (25 volts) was applied across the sample in ionic detergent in a electrophoretic chamber which actively transports micelles through the tissue, which removes brain lipids, leaving the fine structure and cross linked biomolecules in place. The cleared brain tissue (~2 mm slab) was then processed for in situ hybridization using full length Arc digoxigenin tagged cRNA probe (Chawla et al., 2005) followed by CY3 TSA amplification. Tissue was counterstained with DAPI and submerged in 85% glycerol for imaging.

Results: Images were collected using an advanced intravital multi-photon microscope and a 3-D rending of the collected images was performed. Cell nuclei with Arc transcription foci and cytoplasmic Arc were clearly visible up to ~300 μm deep in the tissue.

Conclusion: These results provide evidence for the first time that we can combine Arc catFISH with CLARITY methods in a slab of cleared brain. Future experiments will be carried out in whole brain of animals that have undergone exploratory behaviors.

Chawla, M.K., Gray, D.T., Comrie, A.E., and Barnes, C.A. (2014) Novel method for behavior-driven molecular and structural investigation in rodent whole brain. The 2014 Arizona Alzheimer's Consortium Annual Conference, June 2014.

RELATIONSHIPS BETWEEN BEHAVIORAL DECLINES, HYPEREXCITABILITY, AND INHIBITORY NETWORKS IN THE MEDIAL TEMPORAL LOBE OF AGED RHESUS MACAQUE. Gray DT, Thome A, Erickson CA, Lipa P, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Hippocampal neurons have been shown to encode features of episodic memory in multiple animal models. The representation of these scenes relies on complex neural codes, and basic electrophysiological characteristics of neurons in the hippocampus have been suggested to underlie the ability of these networks to encode and retrieve information. In rodent models, activity of neurons in specific subregions of the hippocampus increases with age, and this hyperexcitability correlates with performance deficits in various medial temporal lobe-dependent behaviors. While the origins of this increased neural output remain poorly understood, several studies suggest that inhibitory circuits in select hippocampal regions change with age. It is unknown whether similar age-related alterations occur in non-human primates. Furthermore, no study to date has examined the relationship between the behavioral, electrophysiological, and molecular components of these deficits.

Methods: To address these questions, three middle aged and two aged rhesus macaques were behaviorally characterized in a delayed nonmatching-to-sample task, which has been shown to partially rely on the integrity of the hippocampus. In these same animals, ensemble single unit electrophysiological recordings were obtained from the CA3 region of the hippocampus and perirhinal cortex, along with quantification of the density of parvalbumin- and somatostatin-expressing GABAergic interneurons.

Results: Investigating the interactions between these three levels of analysis revealed hyperexcitability in CA3 neurons which correlated with both a decrease in the density of somatostatin-containing interneurons as well as behavioral deficits. These relationships were not observed in the perirhinal cortex.

Conclusions: Together, these findings are consistent with data suggesting that age-related declines in episodic memory are due, at least in part, to network dysfunction in specific regions of the medial temporal lobe which arise from losses in a specific class of interneuron. This suggests that therapies aimed at restoring or preserving somatostatin-containing interneurons may be a promising intervention for age-related cognitive decline.

Keywords: Geriatric, Aging, Hippocampus, Interneurons, Somatostatin, Parvalbumin, Excitability

Gray, D.T., Thome, A., Erickson, C.A., Lipa, P., and Barnes, C.A. (2014) Relationships between behavioral declines, hyperexcitability, and inhibitory networks in the medial temporal lobe of aged rhesus macaque. The 2014 Arizona Alzheimer's Consortium Annual Conference, June 2014.

IMPROVING THE POWER TO TRACK FIBRILLAR AMYLOID PET MEASUREMENTS AND EVALUATE AMYLOID-MODIFYING TREATMENTS USING A CEREBRAL WHITE MATTER REFERENCE REGION-OF-INTEREST. Chen K, Roontiva A, Thiyyagura, P, Lee W, Liu X, Ayutyanont N, Protas H, Landau S, Luo J, Bauer R, Reschke C, Bandy D, Koeppe R, Fleisher AS, Caselli RJ, Jagust WJ, Weiner MW, Reiman EM, and the Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; University of Arizona; Mayo Clinic Arizona; University of California, Berkeley; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: We postulated that variability in longitudinal positron emission tomography (PET) measurements of fibrillar amyloid-β (Aβ) burden might be partly attributable to the combined effects of between-scan differences in head positioning and the use of inferior reference regions-of-interest (ROIs) in the computation of cerebral-to-reference ROI standard uptake value ratios (SUVRs). We used florbetapir PET images from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to demonstrate improved power to track longitudinal fibrillar Aβ changes and evaluate Aβ-modifying treatments using a cerebral white matter (WM) ROI.

Methods: Baseline and 24-month follow-up florbetapir PET scans from 31 probable Alzheimer's dementia (pAD) patients, 187 mild cognitive impairment (MCI) patients and 113 cognitively normal controls (NCs) were used to compare the power of automatically generated cerebellar, pontine, and WM (eroded corpus callosum/centrum semiovale) reference ROIs to track SUVR changes and evaluate Aβ-modifying treatment effects. Data were analyzed in Aβ+ and Aβ- pAD, MCI, and NC and cognitively normal apolipoprotein E4 (APOE4) carrier and non-carrier sub-groups.

Results: In contrast to use of cerebellar or pontine reference ROIs, the WM reference ROI permitted us to consistently detect significant longitudinal SUVR increases in the Aβ+ pAD, MCI, and NC and normal APOE4 carrier sub-groups, to consistently detect significantly greater SUVR increases in these groups than in their respective Aβ- or non-carrier controls, and to detect an overall correlation between longitudinal SUVR increases and longitudinal Mini-Mental State Examination (MMSE) score declines. Using the WM reference ROI, we estimate the need for far fewer pAD, MCI, Aβ+ NC, and APOE4-carrying NC subjects to detect an amyloid-modifying treatment effect in a 12-month placebo-controlled trial.

Conclusions: A WM white matter reference ROI can help improve the power to track longitudinal fibrillar Aβ increases, relate them to longitudinal cognitive decline, and evaluate Aβ-modifying treatments with improved statistical power.

REDUCING DELIRIUM IN THE ACUTE CARE SETTING. Burke WJ, Balas MC. Banner Alzheimer's Institute; University of Arizona College of Medicine; The Ohio State University College of Nursing; Arizona Alzheimer's Consortium.

Background: Clinical trials aimed at preventing new cases of AD in those at genetic risk of the disease are among the most promising strategies under current study. It should be recognized however that there is another large population at high risk of developing cognitive impairment, those with critical medical illness. More than a quarter of these individuals develop persistent cognitive impairment. Additionally, delirium occurring in the acute care setting accelerates the course of persons with an existing dementia. Delirium prevention then is a very attractive complementary strategy with substantial potential impact. We have conducted a translational trial aimed at reducing the onset of delirium by implementing a bundle of evidence-based, interdisciplinary, clinical practices referred to as the "Awakening, Breathing Coordination, Delirium and Early Mobility" (ABCDE) bundle. The purpose of this study was to evaluate the effectiveness of implementing the ABCDE bundle into everyday practice.

Methods: This prospective, cohort, before-after study included 296 critically ill patients (146 pre- and 150 post-bundle implementation). Regression models were used to quantify the relationship between ABCDE bundle implementation and the prevalence/duration of delirium and coma, early mobilization, mortality, time to discharge, and change in residence. The patients' level of arousal was assessed daily by study staff with the Richmond Agitation and Sedation Scale (RASS). Subjects who had a RASS score of -3 or higher underwent delirium screening by study staff with the Confusion Assessment Method ICU (CAM-ICU).

Results: After adjusting for age, gender, severity of illness, comorbidity, and mechanical ventilation status, patients managed with the ABCDE bundle experienced nearly half the odds of delirium (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.33-0.93; p=0.03) and twice the odds of mobilizing out of bed at least once during an ICU stay (OR, 2.11; 95% CI, 1.29-3.45; p=0.003).

Conclusions: Critically ill patients managed with the ABCDE bundle were much less likely to experience delirium, and were more likely to be mobilized during their ICU stay then patients treated with usual care. Implementation of improved ICU practices has the potential to significantly reduce the number of patients with dementia.

SHORT TERM MEMORY BINDING IN PRESYMPTOMATIC APOE E4 CARRIERS. Caselli RJ, Parra M, Locke DEC. Mayo Clinic Arizona; University of Edinburgh; Arizona Alzheimer's Consortium.

Background: The short term memory binding task (STMB) was shown to be impaired at baseline testing in asymptomatic/preclinical mutation carrier members of autosomal dominant Alzheimer's disease (AD) kindreds (Parra et al, Brain 2010). The apolipoprotein E (APOE) e4 allele is the most prevalent genetic risk factor for AD. We therefore asked whether the STMB might be similarly sensitive to preclinical AD in APOE e4 carriers.

Methods: The STMB is a visual memory paradigm in which patients must detect changes in a target array involving one or multiple (binding) properties. Together with standard neuropsychological tests, the STMB was administered to 50-79 year old members of the Arizona APOE Cohort to encompass the age range of those that previous biomarkers studies have shown to be at risk for harboring preclinical AD but who were cognitively normal at the time of their most recent followup visit.

Results: 97 APOE e4 carriers and 112 noncarriers did not differ in age (65.8+/-6.9 years), education (16.0+/-2.4 years), or gender (69.9% women). Carriers overall performed less well on a measure of shape accuracy (82.4 v 87.7%, p=.0008), as well as on standard memory measures (including the auditory verbal learning test, selective reminding test, logical memory, and complex figure test) and a block design task, among other tests. The differences between noncarriers and heterozygotes (p=.004) and homozygotes (p=.004) were each significant with a significant e4 gene dose effect (p=.003). Additionally shape-color binding accuracy was disrupted in homozygotes (65.0 v 69.7%, p=.038). Within the course of the STMB test epoch, 12 participants met Petersen criteria for mild cognitive impairment (MCI) and showed reduced shape accuracy (74.4 v 85.2%, p=.002) and shape-color binding accuracy (59.9 v 68.4%, p=.007). After excluding these 12 subjects, no comparisons (STMB and otherwise) remained significant, although there remained a trend for reduced shape accuracy among e4 carriers (p=.07).

Conclusions: Shape and shape-color binding accuracy in visual memory are sensitive indicators of early stage MCI, as are other neuropsychological measures, but all were less sensitive to presymptomatic stage AD in APOE e4 carriers.

DEVELOPMENT OF THERAPEUTIC AREA-SPECIFIC DATA STANDARDS FOR ALZHEIMER'S AND PARKINSON'S DISEASES. Neville J, Kopko S, Tolk C, Odenkirchen J, Broadbent S, Romero K, Stafford B, Hartley E, LeRoy B, Avilés E, Stephenson D. Coalition Against Major Diseases; Critical Path Institute; Clinical Data Interchange Standards Consortium; National Institute of Neurological Disorders and Stroke.

Background: Critical Path Institute (C-Path) has played a leadership role in both consensus data standards and precompetitive data sharing for multiple disease areas including Alzheimer's disease (AD) and Parkinson's disease (PD). Both of these factors are key to success of clinical trials in the future. Working with the Clinical Data Interchange Standards Consortium (CDISC), C-Path has successfully developed consensus data standards for AD and PD, and a version 2.0 of the AD CDISC standards has been recently completed aimed at biomarkers and early stages of the AD spectrum. These therapeutic area specific standards represent the preferred format by regulatory agencies for submitting new drug applications. Importantly, CDISC standards will be required by FDA for regulatory submission as early as FY 2017. Thus, these standards serve two main purposes: integration of existing data and the prospective collection of clinical trial data.

Methods: A coalition of industry members, regulatory agencies, academic experts, government agencies and patient groups collectively developed data standards in partnership with the Clinical Data Interchange Standards Consortium (CDISC).
With input from clinical subject matter experts (SMEs), NINDS (for PD) and ADNI (for AD), working groups of data modelers mapped clinical concepts relevant to AD and PD to the CDISC Study Data Tabulation Model (SDTM) and developed controlled terminology to support the construction of standardized databases for research and regulatory submission in AD and PD.

Results: CDISC therapeutic-area data standards implementation guides were developed for AD and PD in collaboration with CDISC as supplements to the CDISC SDTM, a standard recognized by FDA. The AD user guide represents the first ever therapeutic area CDISC standard developed. The remapping of legacy clinical trial data to the AD standard played a critical role in developing an integrated database of legacy clinical trials, which in turn was a key foundation for the development of the first-ever regulatory-endorsed clinical trial simulation tool. Concepts covered by the AD CDISC user guide include CSF biomarkers, ApoE genotype, volumetric MRI, amyloid PET imaging, and more than 10 clinical outcome assessment scales, including ADAS-Cog, MMSE and CDR. Concepts covered by the PD CDISC user guide include MRI, PET-SPECT, Deep Brain Stimulation, Neuropathology, and a variety of clinical outcomes assessments including both UPDRS and MDS-UPDRS.

Conclusions: The use of consensus data standards maximizes efficiency in regulatory review and facilitates analyses across diverse studies. CDISC standards allow for integrating and pooling data across various stakeholders' systems in a platform-independent manner. Implementation of CDISC standards, particularly in the biomarkers arena, promises to facilitate improved efficiencies and harmonization in clinical trials.

WEB-BASED PAIRED ASSOCIATES TESTING OF OVER 25,000 INDIVIDUALS DEMONSTRATES SIGNIFICANT MAIN EFFECTS OF CHRONOLOGICAL AGE, GENDER, EDUCATION, AND ALZHEIMER'S DISEASE FAMILY HISTORY ON PERFORMANCE.

Schrauwen I, Corneveaux J, Siniard A, Peden J, Turk M, De Both M, Richholt R, Mueller M, Langbaum J, Reiman EM, Caselli RJ, Coleman P, Barnes C, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University of Arizona; LeaseHawk; Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute.

Background: Variation in cognitive function across individuals is well documented and is known to be due to a combination of heritable and non-heritable factors. Most studies performed to date have been largely underpowered to detect the changes that significantly influence cognitive performance, especially when such changes exert a subtle effect. To address this, we created a web-based paired associate learning task (PAL) in an attempt to interrogate the largest cohort to date that has been tested on any one cognitive task. Since April 1st 2013, we have had over 66,000 unique visitors on our website and over 25,000 test takers who have completed our entire PAL paradigm and answered our 20 demographic and health / disease risk factor questions. Our large dataset expands most studies involving cognitive testing, and has high power to reveal discrete effects important in human PAL performance.

Methods: Paired associate visual memory and learning test (PAL): Subjects were presented with a list of 12 word pairs sequentially with each pair shown on screen for two seconds. During the recall period, the subject is shown one half of the word pair and must enter the other paired word. This cycle repeats an additional two times for a total of three trials. Data-analysis: Strict filtering criteria were used to clean the data prior to analysis, which lead to a total of 19,202 unique entries. A multiple regression model was fitted with the memory test results as the dependent value and all of the demographic main effects as independent values. Significance of a demographic was tested by comparing the model with and without that demographic by analysis of variance. This allows us to test the main and interaction effects of the demographic of interest, while controlling for the effects of the other demographics. To account for bias during analysis of education level, all analyses regarding education were done on a subset excluding <25 year old participants (N= 15,111). Regression diagnostics and the fit of the models were carried out by visual inspection of several residual plots, testing the presence of high influential data points and/or outliers, and by testing autocorrelation of the residuals and the presence of multicollinearity. Effect sizes (r) were calculated by the regression coefficients and their standard errors.

Results: Our results indicate that Age, Gender, and Education have the highest effect on memory performance ($p < 2.2 \times 10^{-16}$ for each comparison). In addition, we found that having a first-degree relative with Alzheimer's disease also significantly impairs memory performance ($p = 0.002$). Per year, on average we decline 0.16 word pairs (+/- SE 0.005; 0.44%) per year, which equates to a full word pair in performance loss every 6 years (2.8%). Females have an overall better PAL performance than males and the decline in performance with age is significantly pronounced in males (Age:Gender interaction $p < 2.2 \times 10^{-16}$). The difference between men and women is highest during the 50s and 60s, suggesting a performance enhancing effect of the menopause in females. Secondly, we found that individuals with higher education have a better PAL performance, however, the decline in memory performance with increasing age is the same in all education groups (Age:Education interaction $p = 0.902$). Therefore education level doesn't alter the noted age-related PAL performance decline rate. The influence of education on PAL performance is different between males and females (Gender:Education interaction $p = 0.0008$) which means that women with a higher PAL performance are more likely to have a higher education background than men. Lastly, having a first-degree relative diagnosed with Alzheimer's disease significantly influences PAL performance. Interestingly, the effect is most obvious in participants less than 43 years old (Alzheimer's:Age interaction $p = 0.0003$; under 43 years: $p = 4.30 \times 10^{-5}$; r = -4.11% +/-

1.00%). In addition, the effect of having an AD first degree relative is different between males and females (Alzheimer's:Gender interaction p = 0.001), although it is significant in both sexes.

Conclusions: In conclusion, we found that age, gender and education level significantly influence PAL performance. Having a first degree relative with Alzheimer's disease significantly impairs PAL performance, an effect that is most significant in the younger age groups. Our results demonstrate the effectiveness of web-based recruitment for the study of cognition across a diverse cohort. We plan to further investigate the gender and first degree relative findings through the use of on-line questionnaire follow ups with the study participants as well as APOE genotyping.

FACEBOOK FOR SENIORS: THE EFFECTS OF ONLINE SOCIAL NETWORKING ON COGNITIVE FUNCTION IN HEALTHY OLDER ADULTS. Myhre JW, Woolverton C, Robbins R, Polsinelli A, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

Background: Previous research suggests that older adults who remain socially active and cognitively engaged have better cognitive function than older adults who are socially isolated and disengaged. Learning to use an online social network service, like Facebook.com, may tap into both social and cognitive processes, enabling increased social engagement and support, and potentially enhancing cognitive abilities in older adults. This study aimed to examine the efficacy of an online social networking website as an intervention to maintain or enhance cognitive function in older adults.

Methods: Participants were 41 older adults (12 male), with a mean age of 79.4 and 16.45 mean years of education. Participants were assigned to learn how to use Facebook (n = 14), an online diary website (active control, n = 13), or placed on a waitlist (no treatment control, n = 14). There were no between group differences on age, education, or gender. Participants assigned to learn a website attended three 2-hour classes over the period of one week. Following the class, participants used the website at home for seven weeks. Two tests previously shown to measure "updating and monitoring of working memory representations" (Miyake et al., 2000) were administered before and after this 8-week period and performance on these two tasks were put into a composite score called "Updating."

Results: A 2 x 3 mixed ANOVA of the composite Updating measure revealed a significant Time x Group interaction, $F(2,37) = 6.482$, $p = .004$. Participants in the Facebook group showed a significant increase in performance compared to no significant change in the other two groups, paired samples t-test for 1) Facebook: $t(12) = 3.517$, $p = .004$, 2) Active Control: $t(12)=.782$, $p>.05$, and 3) Waitlist: $t(13) = -1.91$, $p>.05$. There were no significant group differences at baseline, $F(2,37) = .300$, $p = .743$.

Conclusions: Participants assigned to learn Facebook showed improvements on tasks requiring the dynamic updating of working memory compared to the active and no treatment control group participants. These results suggest that learning and using Facebook may be one way for older adults to bolster specific aspects of cognitive function. Additionally, this study supports the idea that we can maintain or improve cognitive function as we age through continued learning and socializing.

Institutional Information

Research Summaries and Key Personnel

from Each Participating Institution

ARIZONA STATE UNIVERSITY
Institutional Abstract

Over the past decade, ASU has committed to the model of the New American University, focused on academic excellence, inclusiveness to a broad demographic and maximum societal impact. With Alzheimer's disease affecting roughly one in nine people aged 65 and over, and one in three people 85 and up[1], research on Alzheimer's disease exemplifies the type of academic endeavor that ASU seeks to promote.

For the Arizona Alzheimer's Consortium, ASU provides the Data Management and Biostatistics Core and (as of July 1014) the Education and Information Transfer Core for 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 strategies for the diagnosis of Alzheimer's disease and other neurodegenerative diseases (i.e., in the Sierks and Johnson labs), in the development and use experimental animal models to characterize the influence of reproductive hormonal and other influences on brain aging and Alzheimer's disease (in the Bimonte-Nelson lab), in the development of mathematical, computational and image analysis strategies with improved power in the detection, tracking and scientific study of AD (see work by Renaut, Dubey, Xiang, Huang, Li and others, in the additional publications list), and the development of improved care models for patients and family caregivers, including those from Arizona's underserved Latino community (led by David Coon), and emerging strengths and recruitments in the neurosciences, health outcomes research, and other areas that are poised to make a major difference in the scientific fight against AD. These research programs represent the range of colleges and institutes at ASU, and are poised to grow

ASU offers degrees in Statistics and Biomedical Informatics as well as focused programs such as the Undergraduate Behavioral Neuroscience Program[2] and the Cognitive Science Program[3], within the Department of Psychology, as well as an interdisciplinary Graduate Program in Neuroscience[4] which emphasizes approaches that integrate several levels of analysis – molecular, cellular, systems, behavioral, cognitive - to investigate basic, translational and clinical questions about the relationship between brain and behavior, and runs in partnership with Barrow Neurological Institute, College of Medicine - Phoenix - Department of Basic Medical Sciences, Mayo Clinic Scottsdale, Sun Health Research Institute, and the Translational Genomics Research Institute.

A detailed report of the six projects directly funded by the Consortium and ASU for the 2013-2014 period follows.

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[1] http://researchmatters.asu.edu/stories/alzheimers-z-2639#sthash.S5YSQXX4.dpuf
[2] https://psychology.clas.asu.edu/bn
[3] https://psychology.clas.asu.edu/cognitive
[4] http://neuroscience.asu.edu/

ARIZONA STATE UNIVERSITY
Key Personnel

Name (last, first)	Degree	Role in Project
Tahsin, Tasnia	PhD Student	Grad Research Assistant
Furniss, Stephanie	PhD Student	Grad Research Assistant
Lloyd, Buffy	PhD Student	Grad Research Assistant
Ginn, Rachel	MS Student	Grad Research Assistant
Dua, Kanishek	MS Student	Grad Research Assistant
Alam, Mohammad	PhD Student	Grad Research Associate
Chen, Yana	PhD	Postdoctoral Research Associate
Khdour, Omar		Assistant Research Scientist
Felix, Vitae	PhD candidate	Student Worker
Moreno, Alan	MHI Student	Research Specialist
Carbajal, Berta		Research Specialist
Rosas, Victoria	Translation Certificate Student	Research Technician
Gerkin, Richard	PhD	Ass Research Professor
Brackney, Ryan	PhD candidate	
Bimonte-Nelson, Heather	PhD	Investigator
Coon, David	PhD	Investigator
Sierks, Michael	PhD	Investigator
Smith, Brian	PhD	Investigator
Mennenga, Sarah	MS	Graduate student
Gonzalez, Graciela	PhD	Investigator
Hecht, Sidney	PhD	Investigator
Koebele, Stephanie		Graduate student
Prakapenka, Alesia		Graduate student
Castaneda, Arthur		Graduate student
Quihuis, Alicia		Lab manager
Hiroi, Sheri	PhD	Post-doctoral fellow
Hewitt, Lauren		Undergraduate

Mousa, Abeer		Undergraduate
Lavery, Courtney		Undergraduate
Weyrich, Giulia		Undergraduate
Torres, Laura		Undergraduate
Granger, Steven		Undergraduate
Poisson, Mallori		Undergraduate
Patel, Shruti		Undergraduate
Plumley, Zachary		Undergraduate
Stonebarger, Gail		Undergraduate
Carson, Catie		High school student

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. Thus, the BAI is intended to evaluate the effectiveness of promising disease-slowing and prevention therapies in the shortest time and most rigorous and cost-effective way; address both the medical and non-medical needs of patients and families to the fullest extent possible, and demonstrate the value of this new standard of care to third-party payers; and continue to complement, enhance, and benefit from close working relationships with its institutional partners in the Arizona Alzheimer's Consortium (AAC).

The BAI includes a Stead Family Memory Center, which includes the Family and Community Services Program and Clinical Trials Program, an Imaging Center, a Translational Genomics Program (in partnership with TGen), and its own Support Foundation. These resources will be further developed and used to enhance Banner's research activities, eventually evaluate and care for more than 10,000 patients per year and, in conjunction with its partnering institutions, eventually enroll more than 1000 patients and genetically characterized normal volunteers per year in clinical trials.

Through the Alzheimer's Prevention Initiative, the BAI intends to leverage its developing brain imaging, clinical trials, and collaborative resources to conduct preclinical AD treatment trials of promising experimental treatment trials in cognitively normal individuals at increased risk of developing symptomatic AD, along with the registries that support the trials. The first preclinical treatment trial is a public-private partnership between the National Institutes of Health (NIH), BAI, Foundation and Genentech that will capitalize on the world's largest kindred of autosomal dominant early-onset Alzheimer's mutation carriers in Antioquia, Colombia who are within 15 years of their estimated average of clinical onset.. The second preclinical treatment trial, also a public-private partnership between NIH, BAI and a TBN industry partner, will be conducted in cognitively unimpaired adults who carry two copies of the apolipoprotein E (APOE) ε4 allele, the major AD susceptibility gene. In 2012, the API created the web-based Alzheimer's Prevention Registry (www.endALZnow.org) to help overcome one of the biggest anticipated obstacles in the coming years – the engagement and recruitment of people to participate in prevention research. The Registry is an inclusive program that supports enrollment into a variety of Alzheimer's prevention studies now being planned by leading institutions and research groups, including those from the API. Meantime, the BAI will continue to capitalize on subjects and data from its NIH-sponsored longitudinal study of cognitively normal persons with two copies, one copy, and no copies of the APOE ε4 allele; subjects and data from the NIH-sponsored AD Neuroimaging Initiative (ADNI); and improved image-analysis techniques to help in the unusually early detection and tracking of AD, the evaluation of putative genetic and non-genetic AD risk factors, and the development of reasonably likely therapeutic surrogates for the cost-effective evaluation of promising primary prevention therapies.

The research program at BAI has several specific aims:
1. To detect and track the FDG PET, PIB PET and volumetric MRI changes associated with the predisposition to AD, normal aging, and their interaction.
2. To establish the role of brain imaging techniques in the evaluation of promising Alzheimer's disease-slowing and prevention therapies, the evaluation of putative genetic and non-genetic AD risk factors for AD and the differential diagnosis of AD.
3. To conduct presymptomatic treatment trials of promising experimental treatments.
4. To develop, test, and apply improved image-analysis techniques for these endeavors.

5. To provide subjects and data for collaborative research studies of cognitively normal persons with two copies, one copy, and no copies of the APOE ε4 allele.
6. To conduct genome-wide association studies of AD and memory in conjunction with our partners at TGen.
7. To establish the cost-effectiveness of our care model.
8. To establish, maintain and capitalize on a clinical research registry to help the consortium fulfill its ambitious clinical research and clinical trials enrollment goals.
9. To support the clinical and minority outreach goals of the Arizona ADCC.
10. To establish an extraordinarily productive clinical research site for the evaluation of promising disease-slowing, risk-reducing and primary prevention therapies.

Our brain imaging research program was founded on the use of PET and MRI in the study of cognitively normal persons 20-80 years of age with two copies, one copy, and no copies of the APOE ε4 allele and image-analysis techniques with improved power to characterize subtle brain changes over time. AARC funds complement research activities supported by competitive grant awards from several NIA-sponsored ADCC and R01 grants, the ADNI, private foundation grants, and clinical trials. In conjunction with our NIA-sponsored ADCC, subjects, images, other data, and image-analysis techniques from our study of cognitively normal APOE ε4 carriers and non-carriers provide a core resource for interested investigators inside and outside of Arizona.

BANNER ALZHEIMER'S INSTITUTE
Key Personnel

Name (last, first)	Degree	Role on project
Reiman, Eric	MD	Executive Director, Banner Alzheimer's Institute (BAI) Director, Arizona Alzheimer's Consortium (AAC)
Tariot, Pierre	MD	Director, BAI Director, AAC Clinical Therapeutics Core
Anderson, Darin		Operations Director
Aguilar, Pat		Study Coordinator and Office Coordinator
Ayutyanont, Napatkamon	PhD	Staff Scientist
Bandy, Dan	MS, CNMT	PET Technical Director
Brand, Helle	PA	Physician's Assistant, Memory Disorders Center
Burke, Anna	MD	Dementia Specialist
Burke, Bill	MD	Director, Stead Family Memory Center
Chen, Kewei	PhD	Director, Computational Brain Imaging Director Biomathematician
Dougherty, Jan	RN, MS	Director, Family & Community Services
Goodwin, Sandy	CNMT	Senior PET Technologist
Hall, Geri	PhD, ARNT, CS, FAAN	Clinical Nurse Specialist, Family & Community Services
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	Research Project Coordinator
Lee, Wendy	MS	Assistant Director, Computational Brain Imaging
Lomay, Nicole		Native American Outreach Representative
Medina-Rodriguez, Sarah	MD	Clinical Trials Operations Director
Perrin, Allison	MD	Physician Dementia Specialist
Protas, Hillary	PhD	Associate Scientist
Seward, Jim	PhD	Neuropsychologist

BANNER SUN HEALTH RESEARCH INSTITUTE
Institutional Abstract

The Banner Sun Health Research Institute (BSHRI) research program capitalizes on A) its faculty, which comprises the state's largest group of scientists directly engaged in Alzheimer's research, B) its major core resources in brain banking, tissue banking and recruitment of clinical subjects suitable for enrollment into the cores and for clinical trials, and C) the manifold collaborative possibilities afforded by the AARC, where BSHRI has major, funded collaborative projects with virtually every other AARC institution.

Banner Sun Health Research Institute (BSHRI) plays a key role in the Arizona Alzheimer's Research Center (AARC) in several different areas, from tissue banking to basic research and from basic research to clinical trials. In 2013, the BSHRI Brain and Body Donation Program, which functions as the brain bank for the Arizona Alzheimer's Disease Center (ADC) and the AARC, enrolled 113 subjects (96 from BSHRI) performed 90 autopsies, the vast majority of which were antemortem-evaluated under ADC guidelines, and continued its track record of 2 hours 50 minutes average postmortem interval. In that same year, the BSHRI Clinical Center logged over 7200 patient visits, and was engaged in 19 Alzheimer's-related protocols. BSHRI scientists published over 50 basic and clinical research papers related to Alzheimer's.

BSHRI's research program has several specific aims:
1. Underlying mechanisms of Alzheimer's disease pathogenesis. Major areas of emphasis include vascular changes in Alzheimer's, epigenetics, soluble RAGE, Aβ metabolism and clearance, transgenic mouse models, BACE1 detection, genomics of tangle-bearing neurons, tau splicing, development of pharmacological treatments for AD and neuroinflammation. Dr Walker received an NIH R21 investigating neuroinflammation (Toll-Like Receptor 3 Signaling in AD). Dr Oddo was recruited in 2013 and has expanded vivarium activity with multiple TG models for AD.
2. Development of culture models and neuronal progenitor cells from rapid autopsies of Alzheimer's and control patients. Methods to differentiate the progeny of neuronal progenitors into functional, neurotransmitter-specific neurons are now underway.
3. Alzheimer's diagnostics. Major areas of emphasis include CSF and serum proteomics, blood assays of complement-adherent erythrocyte Aβ, and lymphocyte markers using a highly sophisticated canonical multivariate statistical approach. . This was also developed under the purview of ADNI. Many investigators at BSHRI including DeCourt, Coleman, Lue, and Walker, receive samples to develop and test novel diagnostics.
4. Clinical trials. New Alzheimer's therapeutics, including multiple Alzheimer's Disease Cooperative Study (RI, DHA, homocysteine, HBA) and industry protocols, are being pursued through some 22 different protocols. Two investigator initiated studies were completed. These include a phase IV study assessing the safety and tolerability of switching from rivastigmine patch to 23mg donepezil and a phase II study assessing the safety and tolerability and biomarker effect of thalidomide in the treatment of AD. There are several prevention (Takeda, A4) and treatment studies (BACC, insulin, Neuronix TMS, Avanir, Elan D5, Avid A18) starting.
5. Neuroimaging. Imaging capabilities are being exploited through the Alzheimer's Disease Neuroimaging Initiative. This project takes advantage of the large, highly research-motivated elderly population in the BSHRI service area. Several imaging protocols have been conducted including Avid, Bayer, GE, and MNI. Recently, an imaging study of Down syndrome was completed with results submitted to JAMA Neurology. Another phase III trial of an amyloid imaging compound has been secured (Navidea).

6.   Outreach. Student and minority outreach projects are being pursued. For example, BSHRI's Student Intern program, now in its 14th year, provided two months hands-on research training for 20 high school and college students who are interested in biomedical careers. Registration and evaluation of a large aging cohort, the Longevity study, to be comprised of normal subjects each at every decade from 50 to 100 years old, is underway and has enrolled 1100 subjects. This cohort should become an invaluable resource not simply for studies of aging, but also for studies of the antecedents of age-related disorders such as Alzheimer's. The BSHRI faculties in 2011-2012 were featured in multiple media events including BBC, Huffington Post, Parade Magazine, the Arizona Republic, Yahoo News and local television.

BANNER SUN HEALTH RESEARCH INSTITUTE
Key Personnel

Name (last, first)	Degree	Role on project
Sabbagh, Marwan	MD	Director BSHRI, Clinical Core Site PI, Principal Investigator,
Beach, Thomas	MD, PhD	Neuropathology Core Director, Principal Investigator Senior Scientist
Belden, Christine	PsyD	Neuropsychologist
Coleman, Paul	PhD	Principal Investigator Senior Scientist
Dugger, Brittany	PhD	Principal Investigator Associate Scientist
Davis, Kathryn	BA, CSP, CRC	BSHRI Site Clinical Core Coordinator
Decourt, Boris	PhD	Principal Investigator Staff Scientist
Jacobson, Sandra	MD	Geriatric Neuropsychiatrist
Lue, Lih-Fen	PhD	Principal Investigator Senior Scientist
Macias, MiMi	PhD	Principal Investigator Post-Doctoral Fellow
Mastroeni, Diego	PhD	Principal Investigator Associate Scientist
Nieri, Walter	MD	Director, Center for Healthy Aging
Oddo, Salvatore	PhD	Principal Investigator Senior Scientist
Roher, Alex	MD, PhD	Principal Investigator Senior Scientist
Schmitt, Andrea	BS	ADCC Administrative Director
Serrano, Geidy	PhD	Anatomist
Shill, Holly	MD	Parkinson's Research Director
Sue, Lucia	BS	Neuropathology Core Coordinator
Walker, Douglas	PhD	Principal Investigator Senior Scientist

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. Using magnetic resonance imaging protocols in the BNI's Keller Center for Imaging Innovation and cognitive tests, the Human Brain Imaging Lab (Dr. Leslie Baxter) investigates of the earliest signs of pathological brain changes and imaging indicators of brain health that could be causing these changes. Additionally, BNI focuses on developing and fostering collaborative relationships between disciplines and institutes to further studies in disease and aging. BNI capitalizes on the integration within the Consortium institutes through ongoing Consortium collaborations allowing us to combine genetic, neuropsychological, neurological, and basic science data to assess changes in neural integrity over time. A summary of ongoing efforts includes:

Cellular Metabolism Studies: The Cellular Metabolism laboratory studies the role of energy metabolism and, more specifically, mitochondrial function, in brain aging and age-related neurological disorders, including Alzheimer's disease. Normal cerebral metabolism requires large quantities of energy and mitochondria, the main source of cellular energy, are particularly affected in older brains. PET imaging studies have revealed regional specific metabolic deficits in AD. Impaired mitochondria generate less energy while emitting toxic byproducts that further harm the brain. Within this context, we have discovered that ketones, a group of physiological compounds produced by the liver following fasting or consumption of the low-carbohydrate, high-fat ketogenic diet, protect neurons in various models of neurological disease by enhancing mitochondrial function. Presently, our efforts are aimed at understanding the role of the PACAP-AMPK-Sirtuin3 pathway in the pathogenesis of Alzheimer's disease, characterizing the neuroprotective properties, and 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.

Human Studies of Brain Functioning: The aim of studies within the Human Brain Mapping Lab is to assess brain-behavior changes associated with disease. We study age-related changes in brain regions associated with memory and other cognitive declines during normal and pathological aging, such as Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). We have focused on developing non-invasive functional and structural imaging paradigms that can help elucidate differences between normal aging and AD in order to better understand mechanism of change in at risk individuals. Of special interest to us is a major genetic risk factor of AD, the apolipoprotein variant (APOE ε4). We have established collaborations with others within the Consortium and introduce potential new partners in research to Alzheimer's related research in order to better describe brain changes.

Cognitive Disorders Program: We are an active contributor to the Arizona Alzheimer's Disease Core Center study. The focus of the BNI is to provide clinical services and referrals to research studies to Hispanics in the Phoenix area. We have 2 full-time bilingual/bicultural staff members who participate in the ADCC to recruit and assess Hispanic patients. We continue to partner with the Latino community

through a Promotore program and outreach activities. We continue to expand this program to include greater inclusion of local participants through our outreach efforts with various community groups, which has improved our Latino recruitment. This has considerably enhanced the AARC and ADCC efforts in reaching out to underserved communities in Phoenix.   The AzADCC, on the whole, currently has approximately 150 participants who have completed at least one epoch . Over one third of the BNI's ADCC participants are Hispanic, we have approximately 50 Hispanics currently enrolled, with some Hispanics enrolled for as long as 11 epochs. We are currently completing data analysis of the differences in retention and patient profiles of Hispanics who are recruited from BNI's community efforts, Mayo's efforts through their Cohort Study, and those patients who enroll from Neurology in order to discuss recruiting trends within our Consortium.

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
Shi, Jiong	MD, PhD	Neurologist
Wu, Jie	MD, PhD	Neuroscientist
Braden, Blair	PhD	Post-Doctoral Fellow
Yin, Junxiang	PhD	Post-Doctoral Fellow
Han, Pengcheng	PhD	Post-Doctoral Fellow
Mar, Lily	MS	Clinical Coordinator
Amaya, Vanessa	BS	Clinical Coordinator
Pipe, James	PhD	Director: Keller Center for Imaging Innovation
Debbins, Josef	PhD	Engineer: Keller Center for Imaging Innovation
Shi, Jiong	MD, PhD	Neurologist
Steinke, Kyle	MS	Research Assistant

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 and Arizona State University, 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. For our current cross sectional efforts, new tests have been added with the intent of developing a battery sensitive to subtle cognitive decline that precedes the symptomatic expression of mild cognitive impairment (MCI). To this end 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 compiled these specific tests into a "preclinical battery". We have administered this preclinical battery to a cohort of APOE e4 homozygotes (a group that has been shown to have biomarker evidence of preclinical Alzheimer's disease) between ages 50 and 69, and to a control group of APOE e4 noncarriers in the same age range. Unfortunately, none of these tests proved to distinguish the groups.
2. grouped our participants on the basis of subjective cognition using our own Multidimensional Assessment of Neurodegenerative Symptoms questionnaires. These are highly detailed paired self and informant based questionnaires that survey subjective impression of change in cognitive, behavioral, and movement categories. We found that while subjective cognitive change is associated with greater psychological distress, it is also associated with both reduced cognitive performance and with greater predictive value of future incident MCI. We further showed that self impressions of change precede informant impressions of change.
3. we have added several experimental neuropsychological measures that claim greater sensitivity than traditional clinical measures. These include the Iowa Gambling Task, the CogState (1-back test and others), the Parra Binding Task, as well as several behavioral measures including the Autism Quotient, Community and Social Ladders. We to be analyze our results with regard to our preclinical AD and e4 noncarrier test cohorts in late 2013.

The bulk of our efforts have been dedicated to longitudinal analyses, and we have shown the neuropsychologically defined onset of AD 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 AD, 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. 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 pre-MCI 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.   Study of public and research participant understanding, desires, and plans with regard to possible preclinical genetic and biomarker testing for AD risk and preclinical AD.

2.   continuing to establish immortalized cell lines and biobank plasma and serum from our cohort members, and sharing them with investigators for a variety of related purposes

3.   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

4.   compare the sensitivity of nontraditional neuropsychological tests with existing state-of-the-art measures in the detection of preclinical Alzheimer's disease

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

        This research proposal has been peer reviewed and approved by the Mayo Clinic Institutional Review Board.

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

MIDWESTERN UNIVERSITY
Institutional Abstract

Midwestern University provides a diverse group of scientific researchers and clinicians from a variety of disciplines to the efforts of the Arizona Alzheimer's Consortium. These contributions can be broadly characterized as efforts to understand modes and mechanisms for the early detection, tracking, and treatment of Alzheimer's disease and associated disorders. The goals of Midwestern University are to leverage this diversity of thought and establish a cadre of investigators with the common goal of contributing to our understanding of neurodegenerative disorders and aging, to inspire collaboration within Midwestern and with investigators at other institutions, and to complement and enhance the efforts of other Consortium institutions and investigators around the state.

Midwestern University has established the Midwestern Alzheimer's Advisory Committee (MAAC) to lead the efforts of the Alzheimer's Consortium at Midwestern. To enhance the diversity of thought while contributing productively to the Consortium, the MAAC holds an annual open intramural competition for the Consortium funding allocated to Midwestern. The MAAC currently consists of faculty from 7 different departments and 4 different colleges, and we expect these numbers will increase for FY2014-15. The MAAC consists of investigators who are funded by the Consortium as well as those who are not currently funded but remain active in the organization. Midwestern University is currently engaged in a major expansion of its research programs and capability, and the Consortium effort is well-placed to leverage this expansion as well as contribute significantly to its completion. Future goals for Midwestern University's Consortium efforts include broader roles in basic science understanding, patient evaluation and treatment mechanisms, education and outreach, and clinical recruitment.

Midwestern University investigators can capitalize on support mechanisms which enhance their ability to conduct Consortium-relevant research. For instance, faculty salaries are not dependent on extramural support, most of the research technicians are University-funded, the University provides generous funding for capital equipment, and several intramural support options are offered. This allows the MAAC to focus funds on enhancements, productivity, and new directions for research and to meaningfully fund a larger group of investigators than would otherwise be possible.

Thus, the overall Consortium-related research program at MWU has several specific aims:
1) Continue to develop and test functional assays for the early detection of Alzheimer's disease and other neurodegenerative diseases.
2) Continue to analyze the early effects of the APOE4 genotype and other emerging risk factors in young adult human carriers of the genes, as well as in transgenic animals, to deduce mechanisms and modes for the reduction of the risk each presents for neurological disorders.
3) Establish and enhance new neuroscientific techniques, such as CLARITY, and leverage these to increase our understanding of disease mechanisms and pathology.
4) Support the development and evaluation of new pharmacological treatments that could have a positive impact on Alzheimer's disease and other neurological conditions, and support research on the cellular and subcellular targeted delivery of relevant treatments.
5) Continue to evaluate the dysfunction within and contribution of various neurotransmitter systems in Alzheimer's disease and related disorders, such as Parkinson's disease, prominently including the nicotinic and muscarinic receptor systems of the brain.
6) Continue work to deduce the causes and effects of mitochondrial dysfunction in neurodegenerative disorders, including energetic dysfunction, fission, fusion, and trafficking of mitochondria, and mitophagy.

7) Support research in the involvement of inflammatory molecules in the pathophysiology of Alzheimer's disease, related disorders, and CNS injury.
8) Support ongoing efforts in the psychological evaluation of and intervention within the aging population.
9) Enhance the ability of the Midwestern Clinics to recruit, evaluate, and intervene in geriatric populations; assist in the efforts of diverse specialties to contribute to the treatment and care of patients suffering from neurodegenerative disorders and the well-being of their caregivers.

MIDWESTERN UNIVERSITY
Key Personnel

Name (last, first)	Degree	Role on project
Valla, Jon	PhD	Chair, Midwestern Alzheimer's Advisory Committee; Assistant Professor, Biochemistry
Jentarra, Garilyn	PhD	Assistant Professor, Biochemistry
Kaufman, Jason	PhD	Associate Professor, Anatomy
Olsen, Mark	PhD	Associate Professor, Pharmaceutical Science
Jones, Doug	PhD	Assistant Professor, Pharmacology
Vallejo, Johana	PhD	Associate Professor, Physiology
Jones, T.B.	PhD	Associate Professor, Anatomy
Bae, Nancy	PhD	Assistant Professor, Biochemistry
Hernandez, Jose	PhD	Associate Professor, Biochemistry
Buhlman, Lori	PhD	Assistant Professor, Biomedical Sciences
Gadagkar, Sudhindra	PhD	Assistant Professor, Biomedical Sciences
Jones, Carleton	PhD	Associate Professor, Biomedical Sciences
Amin, Kiran	PhD	Professor, Clinical Psychology
Flint, Melissa	PsyD	Acting Director, Clinical Training, Clinical Psychology
Kokjohn, Tyler	PhD	Professor, Microbiology & Immunology
Weissig, Volkmar	PhD	Chair, Pharmaceutical Science
Call, Gerald	PhD	Associate Professor, Pharmacology
Potter, Pam	PhD	Chair, Pharmacology
Carroll, Chad	PhD	Associate Professor, Physiology
Yevseyenkov, Vladimir	OD, PhD	Assistant Professor, Optometry

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, Diabetes, Cardiovascular, & Metabolic Diseases, Genetic Basis of Human Disease, Integrated Cancer Genomics, Neurogenomics, Pathogen Genomics, and Pharmaceutical 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.

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
Key Personnel

Name (last, first)	Degree	Role on project
Anderson, Brian	JD	Neurogenomics Project Manager
Courtright, Amanda	BS	Research Associate
Craig, David	PhD	Director, Neurogenomics
Dunckley, Travis	PhD	Co-Investigator, Molecular Profiling
Henderson-Smith, Adrienne	BS	Research Associate
Huentelman, Matthew	PhD	Principal Investigator
Lechuga, Cynthia	MBA,CRA	Grants Administrator
Liang, Winnie	PhD	Co-Investigator
Meechoovet, Bessie	BS	Research Associate
Reiman, Eric	MD	Consultant
Van Keuren-Jensen, Kendall	PhD	Co-Investigator, Neurobiology
Siniard, Ashley	BS	Research Associate
Richholt, Ryan	BS	Research Associate
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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.

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
Barnes, Carol	PhD	Investigator; Psychology, Neurology, Neuroscience & Physiological Sciences Programs, Evelyn F. McKnight Brain Institute
Beeson, Paige	PhD	Investigator; Speech and Hearing Sciences
Billheimer, Dean	PhD	Investigator; Biometry, Statistics Program
Furenlid, Lars	PhD	Investigator; Radiology
Glisky, Elizabeth	PhD	Investigator; Psychology, Evelyn F. McKnight Brain Institute
Hishaw, G. Alex	MD	Investigator; Neurology
Kaszniak, Alfred	PhD	Investigator; Psychology, Neurology, Psychiatry, Neuroscience Program, Evelyn F. McKnight Brain Institute
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
Scalf, Paige	PhD	Investigator; Psychology
Trouard, Theodore	PhD	Investigator; Biomedical Engineering, Evelyn F. McKnight Brain Institute
Wilson, Stephen	PhD	Investigator; Speech and Hearing Sciences
Witte, Russ	PhD	Investigator; Medical Imaging

Project Progress Reports

Project Progress Reports

Arizona State University

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

An Integrative Approach for the Discovery of Potential Therapeutic Targets for Alzheimer's Disease. Graciela Gonzalez, PhD, Matthew Huentelman, PhD, Richard Caselli, MD. Arizona State University, TGen, Mayo Clinic.

Project Description: Many methods have been proposed for facilitating the uncovering of genes that underlie the pathology of different diseases using data from targeted experiments that measure gene expression levels under specific conditions or analyze SNPs over the whole genome (GWAS). We address the specific problem faced by scientists when analyzing the results from high throughput experiments, trying to pinpoint key sets of genes among thousands for further, focused, empirical validation. Considering that empirical validation of even a single causative gene is a long and expensive process, trimming down the list of potential gene targets to a manageable size that includes the most significant prospects for further validation is clearly a critical problem.

The long-term goal of this work is to move beyond purely statistical and comparative methods for gene target selection, and advance towards a richer model of discovery based on the integration of multiple knowledge and data sources. The method will use selected data from microarray and GWAS assays along with topological analysis of protein interaction and gene ontology networks for the guided discovery of potential therapeutic targets that underlie the pathology of Alzheimer's Disease. The ranking methodology proposed has solid biological and mathematical basis and has been shown to be at least as accurate as the best ranking system currently available to researchers, but with capacity to allow novel hypothesis (gene targets) among the top rankings. We will add scoring that reflects the current support for a specific target gene that incorporates a measure of the likelihood that a currently unknown target could potentially be involved in Alzheimer's Disease pathology.

Aims and Objectives: Specifically, this project advances our prior work that resulted in an integrated knowledge base of the biological (genetic) basis of Alzheimer's Disease pathology, incorporating current knowledge from the literature, the AlzGene Database, and other sources, which can be dynamically updated as new information is published and directly via investigator suggestion. We completed in the past a simple command-line interface that allows researchers to access this data. The aims of the present work are to 1) enable the program to dynamically integrate data resulting from empirical assays, particularly microarray expression data and GWAS data, to the database, 2) add functional and other relationship annotations for each gene that might be relevant to the researcher (pathway, gene-disease, gene-function, and gene-drug), and 3) add a gene prioritization and scoring module, which would offer, for each of the suggested genes, a quantitative score that reflects the strength of the evidence for each gene's association with Alzheimer's Disease.

The outcomes of these aims will be validated with expert analysis (Huentelman and Caselli) of the resulting selection of targets. Further empirical validation (such as qrtPCR and immunohistochemistry) of any target of interest will be pursued with collaborators under separate funding, at their discretion.

Progress to Date: To date, we have used the organized knowledge from our knowledge base and completed its analysis cycle by hand as a proof of concept and functional validation of the data workflow that the interface seeks to duplicate. This resulted in a publication accepted for presentation at the AMIA Joint Summits in Translational and Clinical Informatics, with other publications in preparation. Data was integrated from the AlzGene database (available at http://www.alzgene.org), the Genetic Association Database, Drug Bank, PharmGKB, STRING, KEGG Pathway database, and the NCBI Gene db.

We have also completed the design of a graphical user interface for the gene prioritization system that takes as input a set of genes known to be relevant to Alzheimer's pathology, and expands it to include potentially relevant genes from those that interact with the known ones. Further analysis and experiments are ongoing to determine a small set of candidate genes for further validation. Implementation and testing of the system is ongoing.

ARIZONA ALZHEIMER'S CONSORTIUM
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Detection of oligomeric beta-amyloid and tau species as sensitive, selective biomarkers for Alzheimer's Disease. <u>Michael Sierks, PhD</u>. Arizona State University.

<u>**Project Description:**</u> The two major hallmarks of Alzheimer's disease (AD) are extracellular amyloid plaques containing fibrillar aggregates of the amyloid beta protein (Aß), and intra-neuronal neurofibrillary tangles (NFTs) containing aggregates of tau protein. While many studies have focused on the presence of fibrillar Aß and tau aggregates in AD, increasing evidence suggests that smaller aggregates that form earlier in the aggregation pathway are key species involved in the onset and progression of AD. Cortical levels of soluble Aß correlate well with the cognitive impairment and loss of synaptic function [1, 2]. Small, soluble aggregates of Aß are neurotoxic [3-5], inhibit long term potentiation (LTP) [4, 6, 7], disrupt neural connections [8] and cognitive function in transgenic animal models of AD [9-11]. In addition, elevated levels of oligomeric Aß are found in transgenic mouse models of AD [12] and in human AD brain [13] and CSF samples. Similarly, oligomeric tau also plays a critical role in AD as the pathological structures of tau most closely associated with AD progression are tau oligomers [14-16]. Therefore there is substantial evidence that oligomeric forms of both Aß and tau play critical roles in the onset of AD. 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 serum and CSF 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 a sensitive sandwich ELISA that can detect the presence of low concentrations of these biomarkers in serum and CSF. We generated highly selective antibody based reagents (nanobodies) that selectively recognize individual aggregate species of Aß and tau that have been implicated in AD [17-20]. Here we will utilize these nanobodies to detect the presence of these various aggregate species in post mortem and ante-mortem samples obtained from the consortium. Analysis of these samples will identify which aggregate species are the most promising biomarkers for early detection of AD and other neurodegenerative diseases.

<u>**Specific Aims:**</u> The specific aims of this project are:
1) Grow and purify nanobodies to oligomeric tau for use in a sandwich ELISA.
2) Assay postmortem tissue for the presence of oligomeric tau using novel sandwich ELISA

<u>**Progress to Date:**</u>
Aim 1). We are developing better methods to generate correctly folded nanobodies for use in the sandwich ELISA. The antibody fragments we use are prone to misfolding and aggregation, so care needs to be taken during purification and storage to promote proper folding and activity. We have varied purification protocols to determine which protocol produces reliable yields of active nanobody. We find that addition of sorbitol during the production process results in higher yields of correctly folded protein. We are testing different purification and storage protocols to also promote higher yields of correctly folded protein.

Aim 2) For the sandwich ELISA, we use the morphology specific nanobody from Aim 1 as a capture reagent, and a phage displayed version of second nanobody as a detection agent for detection of targets in CSF and serum samples. The phage displayed version of the nanobody is used to amplify the detection signal by several orders of magnitude. To increase sensitivity and to ensure that we are detecting tau variants in the ELISA protocol, we have generated a detection nanobody that binds all forms of tau

including monomeric tau. Use of the pan-specific tau nanobody as the detection nanobody ensures that we are detecting tau aggregates. We have identified two clones for use as a detection nanobody and are currently modifying the genetic sequences to enable their use in the assay.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Metabolic stabilization of multifunctional radical quenchers. Sidney M. Hecht, Ph.D. Center for BioEnergetics, Biodesign Institute, Department of Chemistry & Biochemistry, Arizona State University.

Specific Aims: We have developed several structural series of compounds which we call multifunctional radical quenchers (MRQs); they may be regarded as functional analogues of coenzyme Q in that they function in electron transport in the mitochondrial respiratory chain, and can augment ATP production in cells with mitochondrial defects (Khdour et al., 2013). Unlike coenzyme Q, they also suppress reactive oxygen species (ROS) and lipid peroxidation, preserve mitochondrial membrane potential and confer cytoprotection to cultured cells under induced oxidative stress. Some MRQs also mitigate the effects of $A\beta_{1-42}$ in differentiated SH-SY5Y cells. MRQs produce their "antioxidant effects" in lymphocytes from individuals with Friedreich's ataxia (FRDA), Alzheimer's and Parkinson's diseases, Leigh's syndrome and Leber's hereditary optic neuropathy (Goldschmidt et al., 2013). Four specific aims include 1) designing and synthesizing metabolically stable MRQs, 2) evaluating the ability of the analogues to function as MRQs in cultured cells 3) evaluating the stability of the new compounds in liver microsome preparations, and 4) evaluating the most promising compounds in mice for tolerability and pharmacokinetics following oral administration, especially as regards CNS penetration. Successful realization of these goals will afford a compound optimally suited for evaluation as a therapeutic agent in animal models of Alzheimer's disease and aging, as well as other mitochondrial disorders.

Background and Significance: It has been reported that there are aberrations in the electron transport chain (ETC) and mitochondrial function in Alzheimer's disease (AD) brain. The elevated amyloid beta (Aβ) levels in AD promote ROS production, the latter of which damage cellular macromolecules and diminish mitochondrial function. This in turn accelerates neurodegeneration. In this sense, AD is similar to other neurogenerative diseases; obviating the effects of ROS would likely blunt the progression of numerous neurodegenerative diseases. We have prepared and studied a number of types of MRQs, which can be regarded as analogues of coenzyme Q. The MRQs transport electrons between mitochondrial respiratory chain complexes. The MRQs have also been designed to traffick single electrons more readily than CoQ; they can accept electrons from superoxide, and thereby suppress ROS chemically. In their reduced forms, the MRQs suppress lipid radicals by donating H atoms. They also maintain mitochondrial membrane potential under induced oxidative stress, and augment ATP levels in cells having suboptimal ATP (Khdour et al., 2013). Identifying an optimized, metabolically stable MRQ derivative would enable the therapeutic potential of the MRQs to be evaluated in suitable animal models.

Preliminary Data: We have described the design/synthesis/cellular evaluation of our MRQs in a number of recent publications. The best MRQs are believed to work catalytically; they are effective in cells at low nanomolar concentrations (Arce et al., 2011). The MRQs can restore ATP levels in cells from mitochondrial disease patients. In collaboration with Dr. Paul Coleman (Banner Health) we have studied MRQ effects on the expression of genes under epigenetic control. Dr. Coleman has monitored a number of genes for epigenetic chromatin modifying enzymes; he has evidence of epigenomic disturbance in Alzheimer's disease patients compared to age matched controls. There are unequivocal similarities between human Alzheimer's brain tissue and a neuronal cell culture model (differentiated SH-SY5Y cells) treated with sub-lethal doses of oligomeric $A\beta_{1-42}$. Selected MRQs recovered the expression of >90% of the epigenetic genes analyzed. We posit that regulation of epigenetics at the level of chromatin structure enables the maintenance of gene product level sufficient to sustain normal cellular function; accordingly, we wish to study the effects of the MRQs on gene expression in an *in vivo* model of brain and cognitive

aging. Four MRQs have been administered to mice in a single oral dose (100 mg/kg) without ill effects. Repeated dosing of one MRQ in a mouse model of FRDA did not result in toxicity, but tissue analysis suggested that the MRQ underwent significant metabolism, presumably in the liver. For definitive evaluation in animal models, we need an optimized, metabolically stable MRQ.

Experimental Designs and Methods: We have prepared and evaluated more than 125 MRQs. In another application submitted to the Arizona Alzheimer's Consortium "Evaluation of multifunctional radical quenchers for cognitive and neuroprotective effects in rats", we propose to choose 12-15 of these based on their properties as MRQs and anticipated reasonable metabolic stability, and test them for stability in liver microsomes. The best three will be tested in young and aged rats by Dr. Carol Barnes (U. Arizona) for tolerability, and brain tissue accumulation. We hope to achieve improvements in memory, sensory and motor function. In contrast, this application seeks to prepare new MRQ derivatives designed to have essentially complete metabolic stability. This will be done by systematically replacing metabolically susceptible (CH_3O and CH_3N) functional groups in the best MRQs (as judged by cell culture assays) with metabolically inert CF_3O and CF_3N groups, respectively. The fluorinated analogues will be evaluated in cellular assays for their ability to suppress ROS and lipid peroxidation, augment ATP production and confer cytoprotection to cultured cells (as described in the references listed below). Metabolic stability will first be studied *in vitro* using liver microsomes, accessible commercially or by a published method (Omura and Sato, 1964). Each compound will be tested at 10 μM concentration and three times (0, 60, 120 min). Incubations will contain 2 mg of microsomal protein and 1 mM NADPH (plus a NADPH-regenerating system) in phosphate buffer. Positive (*S*-mephenytoin) and negative (no NADPH-regeneration) controls will be included. HPLC analysis will be used to identify/quantify the test compounds. To study bioavailability, we will use female mice (age 6-8 weeks; 20-30 g; three mice/compound). The compounds will be orally administered (by gavage) in olive oil suspension (100 mg/kg body weight) or by i.v. injection (1 mg/kg). Bioavailability in blood will be measured following a single dose; accumulation in tissue will be measured after dosing for 7 days. Blood and tissue samples will be collected at predetermined times. The compounds will be recovered by aqueous partition with n-butanol; assay will be by reversed phase HPLC.

Proposed One-Year and Long-Term Outcomes: The results of this study should result in the identification of at least one potent, metabolically stable MRQ suitable for more extensive animal testing to establish behavioral, cognitive, physiological, morphological, molecular and epigenetic effects of the compounds in animal models of Alzheimer's disease, and other mitochondrial diseases. The results should also enable funding of the work through R01 and U01 mechanisms at NIH, not to mention licensing of our optimized MRQs to a pharmaceutical partner for development.

Progress to Date: We have prepared and tested a number of compounds for stability in a mouse liver microsome assay. One MRQ prepared previously (and tested in a mouse model of Friedreich's ataxia) was found to be degraded in the microsomal preparation described above to the extent of about 40% within 30 minutes (i.e. 60% remained). This compound had shown no effect in the mouse model, and was not detectable in tissues from the treated animal. The compounds prepared and tested as part of the present study generally had better stability than the compound described at the beginning of this section. As a consequence of these efforts, we now have three MRQs whose recovery after 30 minutes of incubation with microsomes was between 70 and 80%, four compounds whose recovery was between 80 and 90%, and three compounds whose recovery was greater than 90%. One of the last group of compounds was completely stable after 30 minutes, and was found to take several hours to undergo significant metabolism in the microsomal assay.

The most stable analogue was tested in mice. Following administration of a single oral dose (100 mg/kg), we were able to detect the compound both in blood and in the mouse brain. After 24 hours, the compound was present at low micromolar concentrations in the mouse brain, which should certainly be sufficient to realize the therapeutic effect of the compound. Three other compounds having greater than 85% stability in the microsomal assay were tested in mice and could be detected in the blood and/or brain, but at levels lower than the compound exhibiting the best microsomal stability. We believe that compounds exhibiting no less than 95% recovery after 30 minutes of incubation with microsomes will have sufficient stability to be detectable in blood and brain at therapeutic useful concentrations following oral administration (although, some may not be bioavailable for other reasons).

Importantly, we have identified functional groups whose presence significantly reduces the rate of microsomal metabolism, and whose presence seems compatible with maintenance of MRQ functions. We are continuing our structural optimization work guided by the above-described results.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Latino/Hispanic Perspectives on Technological and Skill Building Interventions for AD Patients & Family Caregivers. David W. Coon, PhD, Winslow Burleson. Arizona State University.

Project Description: In 2012, approximately 5.2 million Americans were living with Alzheimer's disease (AD). Between 2010 and 2025, 1 the percentage of persons age 65 and older with AD is expected to increase 67% in Arizona. Compared with non-Hispanic Whites, Hispanics/Latinos are more likely to be living with AD; and, a recent review and meta-analysis of ethnic differences in dementia treatment, care, and research found consistent evidence that minority groups accessed dementia diagnostic services later than their non-Hispanic whites. Hispanics, in particular, reported longer duration of memory loss at time of referral to diagnostic dementia services. Moreover, the authors concluded that this was due to later presentation to services, rather than cultural bias of instruments or premorbid differences in educational attainment.

As noted in the National Plan to Address Alzheimer's Disease, identifying AD in the early stages creates advantages for early-stage patients/people (EPs) and their current or future care partners (CPs). (For example, EPs can still participate fully in legal, financial, and care decision-making; and, both informal and formal support can be mobilized for current and future concerns.) The period following a diagnosis of AD can be a challenging time for EPs and CPs. AD and its diagnosis can start a cascading stress process that unfolds over time leading to negative consequences related to their health and emotional well-being. [Care partner is often used in lieu of caregiver in the earlier stages of the disease.] These findings reinforce the CDC's recognition of family caregiving as "a public health priority of national concern."

While the emphasis on early detection and treatment is growing, there has not been a corresponding emphasis on early psychosocial skill building interventions that would address the CP's or EP's mental health and well-being at earlier stages of the disease, and any research to date has focused on well-educated, English-speaking, non-Hispanic whites. Similarly, the vast majority of cognitive assistive technologies for people with AD and their family caregivers have been developed and tested on non-Hispanic white younger people, excluding diverse groups of people with AD. The majority of AD family caregivers report that daily dressing struggles are the most common source of caregiving frustration related to activities of daily living (ADLs) for early to middle stage individuals with AD, yet supportive technological inventions are noticeably absent.

Our proposed project addresses key limitations of previous studies by using focus groups and focused interviews with Latino/Hispanic families, professionals and other stakeholders impacted by AD to identify effective recruitment strategies to engage Latinos/Hispanics earlier in the progression of AD, and receive input on the potential applicability, acceptability and usability of technological and skill-building interventions to assist persons with AD and their care partners or family caregivers. The project is an interdisciplinary collaboration of ASU professors as well as well- established community partners that serve the Latino/Hispanic community.

Aims and Objectives: Aim 1. Conduct a series of focus groups and focused interviews with Latino/Hispanic families, members of the promotora networks, and community representatives working with Latino/Hispanic families to:

(a) identify strategies to increase the recruitment and retention of Latinos/Hispanics into ADRD research efforts and interventions, with an emphasis on individuals in the earlier stages of ADRD (EPs) and their care partners (CPs); and,(b) obtain input on the applicability, acceptability, and usability of technological and skill building interventions for early- to moderate-stage individuals (EPs) and their (CPs).

Aim 2. Analyze the qualitative data from the focus groups using techniques based on grounded theory and content analysis to identify the predominant themes and issues reported by the respondents.

Aim 3. Use the findings from data collected in Aims 1a and 1b to enhance future grant applications and disseminate findings to interested Arizona Alzheimer's Consortium researchers as well as other stakeholders in the scientific and lay communities. A variety of NIH (particularly NIA and NINR) program announcements and recent RFAs are focused on the development, implementation and evaluations of interventions to improve quality of life for individuals with AD as well as their family caregivers.

Progress to Date: To date, six focus groups of 51 participants were held in the community in English and Spanish including three groups of professionals/staff serving the Latino community and three groups of family/informal caregivers. Focus groups were audiotaped and have been transcribed, translated into English, and verified. Data entry of telephone screens with basic sociademographic quantitative data has been completed. Data analysis is underway to uncover key themes and exemplars to achieve project goals.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Plasticity of odor coding in the mouse olfactory bulb. <u>Brian H Smith, PhD</u>. Arizona State University.

Project Description: Early olfactory processing in insects and mammals share many common features, including different forms of plasticity at synapses in neural networks that process olfactory information. Yet we understand very little about how these mechanisms contribute to changing the spartiotemproal codes for odors that are relayed to higher brain centers. The proposed research will evaluate hypoetheses about how plasticity changes the code in ways that are important for odor detection and discrimination. In future studies this work will lead to investigation of the causes of olfactory deficits in neurodegenerative disorders.

Specific Aims: Some of the earliest and predictive manifestations of age-related neurological disorders are manifested in declines in olfactory perception. These declines correlate to early manifestations of aberrant proteins, which are clinical hallmarks of these diseases, in the Olfactory Bulb. Yet we do not yet understand how these proteins disrupt OB neural networks to interfere with olfactory processing. This understanding will be important to help manage the inevitable decline in quality of life experienced by people who suffer from these diseases. The focus of this proposal is to transition the PIs laboratory into work with a mouse model such that the work can be applied to mouse models of neurological diseases (Alzheimer's and Parkinson's diseases). NIH-funded research in the PI's laboratory on the honey bee as a model for olfactory processing has led to the identification of how plasticity in early processing, identical to plasticity identified to date in the OB, may be critical to enhance detection and discrimination of odors. The broader hypothesis is that aberrant proteins in the OB disrupt the modulatory pathways in the OB that drive this plasticity, which leads to the decline in olfactory perception. Experiments combining behavioral conditioning protocols with electrophysiological recordings from the mouse OB will test these hypotheses derived from the honey bee work in the mouse.

Progress to Date: We have successfully set up two behavioral protocols for olfactory conditioning of mice. Furthermore, we have been successful in implanting multielectrode recording arrays into the mouse olfactory bulb. Using these implants we can record neural activity as the mouse makes choices between different odorants based on reward.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Bioidentical hormone therapy: effects on cognition as a function of transitional menopause progression. Heather Bimonte-Nelson, PhD. Arizona State University.

Project Description: The aim of this study is to determine how bio-identical estrogen therapy (E@) interacts with timing of hormone therapy initiation during menopause, systematically testing window of opportunity effects on cognition.

Overarching Rationale: By the year 2050 there will be an estimated 88.5 million people in the United States over the age of 65, and over half of these individuals will be postmenopausal women (U.S. Census Bureau, 2010). Menopause has been linked to many symptoms that affect quality of life, including hot flashes and memory decline (Curtis & Martins, 2006; Sherwin, 1988). Hormone therapy (HT) is given to attenuate menopause-induced symptoms. In 2010, a NIA-sponsored workshop was held to better understand effects 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 optimal window for interventions, including effects of HT in transitional menopause. This is important now more than ever given recent controversies driving many new hypotheses regarding an optimal critical window for interventions, personalized HT, and safety of HT. Such issues were discussed at the Window of Opportunity for Estrogen and Progestin Intervention During Aging and Alzheimer's Disease (AD) Conference this past summer (Fort Worth, TX), where I was honored to be an invited speaker, a symposium chair.

Modeling Menopause: In women, the menopause transition has been related to memory changes (Sullivan et al., 2001; Weber & Mapstone, 2009). Rodent studies have found that ovarian hormone loss induces cognitive decrements. Using young rats, we and others showed that ovariectomy (Ovx, surgical menopause) disrupts spatial working memory (Bimonte & Denenberg, 1999; Daniel et al., 1999). Despite the vast insight rodent models have yielded on the effects of surgical hormone loss on cognition, surgical menopause only models <13% of women (North American Menopause Society, 2012). The majority of women undergo menopause as a transitional hormone loss resulting from ovarian aging and follicular depletion, rather than a surgical hormone loss. In women, as aging ensues decreased ovarian follicular reserves result in declines in estrogen and progesterone, leading to the cessation of ovarian cyclicity. In contrast, the aging rat undergoes a persistent estrus state due to chronic anovulation, rendering intermediate estrogen levels, or a pseudopregnant/persistent distrust state characterized by high progesterone levels; in this species aging alters the response of the hypothalamus-pituitary axis to gonadal hormones. Thus, the primary mechanism of reproductive senescence in women is follicle depletion, while in the rat it is the hypothalamic-pituitary axis. About a decade ago, the transitional menopause rodent model, "VCD" (4-vinylcyclohexene diepoxide), was introduced. Our laboratory has been fortunate to work and publish with a creator of this model, Dr. Loretta Mayer, to study cognition. VCD produces follicular depletion in rodents, resulting in ovarian failure (Hirshfield, 1991; Mayer et al., 2002). Ovarian tissue then yields decreased progesterone, estrogen becomes deplete, androgens increase, cyclicity ceases, and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels become elevated, a profile resembling transitionally menopausal women.

Estrogens and the Window of Opportunity: 17β-estradiol (E2) is the most potent naturally-circulating estrogen, followed by estrone (E1) and estriol, in order of receptor affinity (Kuhl, 2005). While research suggests that E2 can exert positive effects on cognition in postmenopausal women with Alzheimer's disease (Asthana et al., 1999), and that two weeks of E2 treatment can enhance memory in non-demented elderly women (Wolf et al., 1999), the use of E2 as HT is just beginning to increase in the clinic. E2 is the primary estrogen used to test cognitive effects of HT in animal models. We, and others, have shown positive E2 effects on spatial working and reference memory mazes in young and middle-aged rodents (Bimonte-Nelson et al., 2010, for review). Recently, we evaluated CEE (trade name: Premarin), the most commonly prescribed estrogen HT, on rodent cognition. CEE contains the sulfates of at least ten estrogens, including E1 and estriol, which are found naturally in women; all others are unique to horses (Kuhl, 2005). Since CEE is over 50% E1-sulfate, and contains only trace amounts of E2, effects of E2 cannot be generalized to CEE (Bhavnani, 2003; Sitruk-Ware, 2002). Our recent results showed that CEE enhanced memory in the middle-aged Ovx rat when given cyclically via injection (Acosta et al., 2009, 2010) and also when given tonically, a dose-specific effect (Engler-Chiurazzi et al., 2011). We then tested whether the memory effects of CEE were impacted by type of menopause, surgical (Ovx) vs. transitional (VCD). We found that CEE benefited Ovx rats on working and reference memory, as well as memory at a very high working memory load. In contrast, for both memory domains, CEE impaired VCD-treated rats that had undergone transitional hormone loss (Fig 1; Acosta et al., 2010). Thus, in the same study, CEE was beneficial in surgically menopausal rats, but detrimental in transitionally menopausal rats. Of note, the CEE in the Acosta et al. (2010) study was given after follicular depletion in the VCD treated rats. We now question whether these effects will occur when the estrogen is the bioidentical E2, and if giving HT before, instead of after, the transition to menopause will still result in a negative cognitive impact. The timing of our Acosta et al. (2010) study potentially missed an earlier critical window of sensitivity since follicles were depleted when the estrogens were given. Clinical studies support the critical window hypothesis (Khoo et al., 2010; MacLennan et al., 2006; Maki, 2006; Maki & Sundermann, 2009; Resnick & Henderson, 2002; Zandi et al., 2002). In naturally menopausal women, HT initiated post-menopause was detrimental to cognitive performance, whereas HT initiated prior to menopause was beneficial (Greendale et al., 2009). Further, peri-menopausal HT use enhanced memory and hippocampal function (shown using fMRI) in women (Maki et al., 2011).

Progress to Date: At this time we have ordered and received the rats for the study, and have initiated the follicular depletion model via the VCD administration. Follicular depletion after VCD treatment takes 90 days. We have also initiated the hormone treatments concordantly for the appropriate groups. Follicular depletion was recently completed (theoretically, we will know for sure after animals have been sacrificed and we quantify and confirm ovary status), and behavioral testing has just begun.

Regarding publications associated with this award, I had my first journal editorship with three related papers in this special issue. I was a co-editor on a special issue in Brain Research, for the "Special Issue on Window of Opportunity for Hormone Therapy", and my painting of my view of endocrine neuroscience made the cover art. I have attached the papers to this progress report.

Project Progress Reports

Banner Alzheimer's Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Alzheimer's Prevention Initiative. Eric M. Reiman, MD, Pierre N. Tariot, MD, Jessica B. Langbaum, PhD, Adam S. Fleisher, MD, Kewei Chen, PhD, Napatkamon Ayutanont, PhD. Banner Alzheimer's Institute.

Project Description: 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 developed to rapidly evaluate promising presymptomatic Alzheimer's disease (AD) treatments in people who, based on their age and genetic background, are at highest imminent risk for developing symptoms. The API proposes two complementary presymptomatic 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) ε4 carriers 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.

Specific Aims:
Aim 1: To conduct a presymptomatic trial/surrogate marker development program in ADAD mutation carriers within 15 years of their estimated age at clinical onset.
Aim 2: To further refine trial designs for other presymptomatic treatment trial programs/surrogate marker development programs in cognitively normal individuals who are highest imminent risk for ADAD or LOAD.
Aim 3: To continue to develop registries to support future presymptomatic treatment trials.
Aim 4: To continue to conduct biomarker studies of ADAD mutation carriers to assist in designing future presypmtomatic treatment trial programs/surrogate marker development programs.

2013-2014 Progress: 1) API's first prevention treatment trial in cognitively unimpaired autosomal dominant AD mutation carriers met its stated goal of launching enrollment in 2013 (Clinicaltrials.gov Identifier: NCT01998841), along with establishing the required trial infrastructure in Colombia (including new cyclotron/radiochemistry, PET/CT, and 3T MRI systems, clinical trials capabilities, and regulatory approvals). 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. It has 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. It is 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) We were awarded a $33.2 million grant from the NIH in September 2013 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. Recently, the NIH director announced an NIH-industry

partnership called the Accelerated Medicines Partnership (AMP) to accelerate the evaluation of interventions to treat and prevention several major diseases. We are pleased to report that AMP will proved 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. We convened an expert advisory committee to help us vet the candidate amyloid-modifying treatment options from pharmaceutical companies who have some of the most promising anti-amyloid treatments and are on track to formally announce a partnership in the coming months. As with our first trial, we anticipate contributing $10-$15 million in philanthropic funding. **3)** Two manuscripts were accepted for publication (Ayutyanont et al., *J Clinical Psychiatry,* in press; Langbaum et al., *Alzheimer's & Dementia*, in press) describing our work using to empirically derive a composite cognitive test score that is sensitive to detecting and tracking the preclinical stages of AD, anticipate clinical onset, and can be used to evaluate preclinical AD treatments. The API composite cognitive test score continues to be refined and extended to other longitudinal cohorts, it will serve as the primary endpoint in the API's first preclinical AD trial, and it is now being considered by several other groups as they plan their own preclinical AD treatment trials. **4)** We continue to optimize the Alzheimer's Prevention Registry, a web-based registry focused on encouraging enrollment into North American-based prevention studies. The Registry, which aims to enroll 250,000 by end of 2015 and currently has over 27,000 enrollees, 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. Dr. Langbaum received an Arizona AD Center pilot study based on the Registry and a pilot apolipoprotein E (APOE) ε4 genotyping and disclosure program. **5)** We exceeded our ambitious goals for the Colombian API Registry, to date having enrolled 3,407 autosomal dominant kindred members, including 852 mutation carriers, into this Registry, which includes extensive information on memory and thinking tests, DNA and genetic test results.

6) We are nearly finished collecting 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.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Arizona Alzheimer's Research Registry. Jessica B. Langbaum, PhD., Pierre N. Tariot, MD, Eric M. Reiman, MD. Banner Alzheimer's Institute.

Project Description: The explosion of information about the genetics, pathology, and molecular pathology of Alzheimer's disease (AD) has led to the discovery of a wide portfolio of specific interventions to interrupt the pathobiology of Alzheimer's disease. The portfolio includes medications, immunotherapy, and possibly even lifestyle modification interventions. There is a critical need to accelerate the field's capacity to develop these compounds and interventions. This means applying state-of-the-art clinical trials methods, imaging techniques, and biological tests to the study of disease-modifying and prevention therapies, and doing so in a rapid and high-quality fashion. The Alzheimer's Research Registry (AAR) was established through the Arizona Alzheimer's Consortium as a clinical trials and clinical research study pre-enrollment program in Arizona in recognition of the fact that the success of current and future studies will depend on the number of people who would be willing to participate(1;2). In addition, the AAR was designed to serve as the prototype for a larger (at least 250,000 enrollees), national online registry focused on Alzheimer's prevention treatment trials as part of the Alzheimer's Prevention Initiative (API). During the past year, efforts focused on alerting and enrolling AAR registrants into the new online Alzheimer's Prevention Registry ("Registry"), promoting the Registry across the consortium and at consortium-led events, and assisting with recruitment into consortium-led prevention research. The goals of the current project proposal are to improve upon the Registry by creating new content focused on educating enrollees about Alzheimer's prevention research, new online surveys to keep designed keep participants involved and engaged in the Registry, continue to develop collaborations to increase Registry enrollment, and to demonstrate the Registry is successful at accelerating recruitment into AD prevention research studies.

Specific Aims:
Aim 1: To develop new content and surveys for the endALZnow.org website in order to increase enrollee engagement.
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 research studies, such as the Takeda/Zinfandel trial, the Alzheimer's Disease Cooperative Study (ADCS) A4 trial, and the API trial in apolipoprotein E (APOE) ε4 homozygotes.

2013-2014 Progress: 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. The Registry website (www.endALZnow.org) underwent an initial website redesign in July. In addition to redesigning the page, we made joining the Registry easier. Individuals are simply asked to provide their email address to start, and can provide additional demographic information at the time of enrollment or at a later time. Additional efforts are underway to optimize the website based on usability testing that occurred in January-February 2014. A/B testing will determine which changes are to be made. The Registry currently has over 27,000 enrollees, with a goal of reaching 250,000 by end of 2015. Planning is underway to promote the Registry through novel list-building mechanisms as well as incorporating SEO/SEM.

During the past year, a drip email campaign was developed that explains to Registry members what to expect after signing up. This campaign is currently being refined based on results of the usability testing. In addition, based on Registry member feedback, the Registry newsletter is now monthly instead of quarterly and has been redesigned. Within the next month, the website is being upgraded to include a searchable listing of available studies by geographic region.

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 Provoc, Banner Alzheimer's Foundation, GBGBAI and other stakeholders help promote the Prevention Registry through national and local communications as well as at invited speaking engagements. The Registry has been selected to be one of three programs promoted through the NIA/CDC/ACL "Recruiting Older Adults into Research" (ROAR) initiative. The list of Registry partners continues to grow, and now includes 22 organizations, with more expected to join in the coming months and years.

The importance of the online Registry has become even more apparent as the Alzheimer's Prevention Initiative (API), which is led by Banner Alzheimer's Institute, received $33.2 million grant from the NIH in September 2013 to its second prevention treatment trial in at least 650 cognitively unimpaired 60-75 year-old *APOE* ε4 homozygotes. Enrollment for this trial and other prevention studies conducted by other researchers across the country, such as the ADCS A4 Trial, will in-large part rely on referrals from the Registry.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

The development and application of advanced image analysis techniques for detection and tracking of Alzheimer's disease. <u>Kewei Chen, Ph.D. Napatkamon Ayutyanont, Ph.D., Hillary Protas, Ph.D, Adam Fleisher, MD, Jessica Langbaum, Ph.D. Eric M. Reiman, MD.</u> Banner Alzheimer's Institute, Arizona State University, and Arizona Alzheimer's Consortium.

<u>Project Description</u>: The Computational Image Analysis Laboratory at the Banner Alzheimer's Institute continues (1) to develop and test image analysis techniques to detect and track the brain changes associated with Alzheimer's disease (AD) and evaluate promising AD-modifying treatments in the most rapid and rigorous way, and (2) to rigorously conduct imaging pre-processing and statistical analyses on many research projects. Among the image analysis techniques for which we would like to further develop are (1) the fully automated "iterative principal component analysis (IPCA)" (Chen et al., 2004; Chen et al., 2007c), which characterizes rates of whole brain atrophy using sequential structural magnetic resonance images (MRIs) from the same person and has been used to demonstrate accelerated rates of whole brain atrophy in individuals with AD and (2) the voxel-based "hypometabolic convergence index (HCI) to characterize the AD-related magnitude and spatial extent of regional hypometabolism in a person's PET image(Chen et al., 2011). The objective of this project is to further refine new image analysis techniques and apply them to the acquired imaging data sets for detecting and tracking AD associated changes. We hypothesize that the improved imaging analysis techniques will results in higher sensitivity of capturing longitudinal change and cross-sectional group differences to support the use of imaging based biomarkers for symptomatic as well as pre-symptomatic clinical trials. We will make efforts to share our methodologies and to position our analytic team as a resource for our State wide consortium to fulfill its mission in the study of AD especially related to early detection and tracking, treatment and prevention of AD.

<u>Specific Aims:</u> 1) To further develop some of our new voxel-based image analysis techniques for early detection and tracking of AD including, but not limited to, integrating age-correction method and newly available SPM brain segmentation/brain mask definition to IPCA, extending the currently-cross-sectional HCI to longitudinal analysis, and extending FDG PET based HCI technique to characterize magnitude and pattern of amyloid deposition using amyloid PET images. 2) To apply these imaging analysis techniques to analyze imaging data such as FDG PET, structural MRI, and amyloid PET data from the National Institute on Aging (NIA)-sponsored AD Neuroimaging Initiative (ADNI) and from the Down syndrome project (PI: Marwan Sabbagh). 3) To make the analysis techniques implemented in a friendly to share within and without our consortium.

<u>2013-2014 Progress:</u> 1) We have couple more new publications with the collaborative researchers from Italy. The publications are all about new applications of our hypometabolism convergence index (HC) algorithm that was demonstrated its capacity for distinguishing AD from normal controls, slow AD progression from fast progression, and MCI patients who converted to AD from those who did not. Also, one of the findings was submitted to, and presented at, AAIC 2013. With the support from the State, we are further refining this index by examining various reference regions, better characterized normal database. We have some interesting findings and are collaborating with Prof. Yalin Wang from ASU to examine the FDG-PET based index with brain anatomical changes related to the conversion from MCI to AD. A manuscript is planned and is in the starting stage. We are also pleased to know that our collaborators in Italy actually started calculating HCI for their clinical patients. Related to another index we developed that is for the estimation of whole brain atrophy based on the iterative principal component

analysis (IPCA), we are glad to report that our IPCA findings about examining the differences among AD, MCI and NC, and estimated sample size for clinical trial has been published by the Journal of Neuroscience and Biomedical Engineering (NBE) after its acceptance earlier last year. 2) With the supports from the State and also from ADNI project, we finished our computation of HCI, regional HIC and also a new index generalized to florbetapir PET, called amyloid convergence index (ACI). We analyzed them statistically and also shared on the ADNI LONI website. Continuing our efforts, we are applying HCI, ACI and rHCI to a number of projects including our analysis of the possible conversion prediction for MCI patients to AD. We found that HCI is one of the most predictive. 3) Same as last year and every previous year, we continue to make available our statistical expertize, the computer software packages/procedures developed in house to researchers in our Arizona Alzheimer's Consortium. We have been constantly consulted for statistical questions in the AD related researches from researchers in the Consortium. A new neuroimaging display format implemented by our group (originally developed by Dr. Paul Thompson UCLA) has been used in a number of publications by ourselves and by collaborators inside and outside Arizona. In a recently publication in collaboration with researchers from Brown University, we reported the APOE4 effects on the brain structures in infants. The findings used analysis results from our group and the image display together with our non-trivial efforts to generate infant brain high resolution template. We continued our collaboration in the Down syndrome project with the PI, Dr. Marwan Sabbagh, we have new findings from multiple modal imaging data and the manuscript is finisehd it's drafting and on its way to submit. 5) With the state funding, we are able also to investigate a number of other techniques. The developed multivariate ROC technique with increased power for detecting abnormalities (disease status) was accepted for publication and was applied to analyze MCI converter FDG-PET and structural MRI data. Starting last year (2013) and continuing our efforts into 2014 (on-going), we are examining the causes of the high within-subject variability of the longitudinally measured amyloid accumulation using florbetapir PET. We developed a white matter reference techniques and corresponding procedure to QA and process florbetapir data. Compared to the amyloid quantitative index using cerebellum as the reference region, the index with the new white matter as the reference region is with much reduced within-subject variability, high statistical power and also correlated with the decline of psychological measures. Finally, we note our accomplishments in further refining and contributing to the launch of API's first presymptomatic treatment trial by computing the composite score and used to depict the age trajectory difference in cognitively normal APOE4 non-carriers, heterozygotes and homozygotes and the generalized use of ICA (independent component analysis) procedure from analyzing functional MRI data time series to analyze cross-sectional FDG-PET and florbetapir-PET data from ADNI (our continued efforts to define single imaging based biomarker).

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Native American Outreach Program. Nicole Lomay,Jan Dougherty, MS, RN , Richard Caselli, MD, Marwan Sabbagh, MD, Eric Reiman, MD, Pierre N. Tariot, MD, Anna Burk, MD. Banner Alzheimer's Institute, Mayo Clinic Scottsdale, Banner Sun Health Research Institute, University of Arizona, and Arizona Alzheimer's Consortium.

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

Background and Significance: Native Americans facing the problem of Alzheimer's disease (AD) constitute the most underserved and understudied population in the United States. Since 2006, we have established an outreach program to help address the educational and clinical needs of patients, families and health care professionals; developed culturally sensitive educational and service programs; and demonstrated to the Native American communities our strong interest in serving these needs whether or not they participate in research studies. We have continued to attract a number of interested participants from the Urban Native American community to participate in the Arizona Alzheimer's Disease Core Center (ADCC) Clinical Core. Eleven (11) of the participants have been in the Clinical Core for greater than 5 years while another 30 are either deceased or lost to follow up.

Preliminary Data and Plan: To date, 45 Native Americans have been followed through the ADCC and whose clinical findings are reported in a national database. Over 3000 Native Americans have participated in education and outreach efforts. We continue working relationships with numerous Arizona tribes and have had participation in the outreach efforts from tribes outside of Arizona including New Mexico, Colorado, California and Oklahoma. We will host the 10th Annual conference on AD in Native Americans in October in Parker, AZ and anticipate drawing 250 community participants. We will hold at least six public events to promote awareness in Urban and reservation communities. We will host the 5th annual pre-conference intensive for health care professionals prior to the annual conference and will offer the 4th annual memory screening for conference/community participants. Our outstanding Native American personnel and our other colleagues will continue to establish close working relationships with stakeholders from different tribes and nations.

Proposed One-Year and Long-Term Outcomes:
1. Continue outreach efforts to general Native American communities and education of health care providers for American Indians that will decrease the disparity related to diagnosis and treatment of AD in both reservation and urban dwelling Natives.
2. Retain the 22 Native American cohorts in the ADCC trial in the next 12-months recruit with a goal of 8 new participants.
3. Initiate study of a new cognitive assessment tool that is reliable/valid and sensitive to early cognitive changes in Native Americans.

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

Year End Progress/Summary:
1. A variety of education/outreach programs reached 916 community participants and another 272 professional staff. These efforts also include completion of the 10th annual conference on AD in Natives.
2. A total of 20 assessments have been completed: 18 returns and 2 new visits. One participant died and 4 participants have been withdrawn after repeated attempts to call without response back. The goal is to recruit/enroll another 4-5 participants in the coming year.

We have revised and continue to test a new cognitive screening tool, Southwest Indigenous Cognitive Assessment (SWICA) in two separate memory screenings and will continue to revise to create a more sensitive tool for detection of early changes. In addition, we are actively working with 3 separate work groups to formulate a Native Brain Health program for children, community at large and professionals. Once completed both memory screening and brain health materials will be widely replicated in Native American communities.

Project Progress Reports

Banner Sun Health Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Distribution of tau in peripheral tissues of Alzheimer's disease <u>Brittany Dugger, PhD, Thomas Beach MD, PhD, Alex Roher MD, Charisse Whiteside, Travis Dunckley, PhD</u>. Banner Sun Health Research Institute, Translational Genomics Research Institute.

<u>Specific Aims</u>: **Purpose:** Assessing the feasibility of a peripheral biopsy in Alzheimer's disease (AD) by determining the presence of pathological tau in areas outside of the central nervous system. **Aim 1. Utilizing immunohistochemical methods on autopsy tissue, we will survey the distribution of pathological tau deposits in biopsy accessible peripheral sites of subjects with AD as well as clinically normal elderly individuals.**

<u>Background and Significance</u>: Determining if peripheral pathologies are found in AD will indicate the feasibility of peripheral biopsy sites for improving the clinical diagnostic accuracy of AD, as well as providing new insights into the extent of histopathological disease spread. At present, the clinical diagnostic accuracy for AD is a major roadblock to finding new therapeutic agents.[1, 2] Although amyloid imaging will improve diagnostic accuracy, it cannot indicate disease stage as it is does not detect neurofibrillary tangles. As with cancer treatment, it is likely that drug response may depend on stage of disease. Some have investigated peripheral amenable areas for amyloid-β deposits, the other pathologic protein found in AD, but results have not been conclusive.[3] Peripheral tau pathology could reflect the central nervous system pathological stage of disease, known as Braak neurofibrillary tangle staging.[4]

Table 1. Frequency of p-tau immunoreactive neural elements in the cervical, thoracic, lumbar, and sacral portions of the spinal cord of non-demented controls (ND) and Alzheimer's disease (AD) cases. (Table taken from ref. 9).

spinal cord region	total Ns (ND, AD)	ND	AD	P values
Cervical:	37,45	43.2%	95.6%	<0.001
ventral		40.5%	71.1%	0.01
dorsal		2.7%	24.4%	0.01
intermediolateral		35.1%	28.9%	0.71
Thoracic:	30,45	36.7%	68.9%	0.01
ventral		33.3%	62.2%	0.03
dorsal		6.7%	6.7%	1.0
intermediolateral		3.3%	11.1%	0.39
Lumbar:	30,46	26.7%	65.2%	0.002
ventral		23.3%	50.0%	0.04
dorsal		6.7%	10.9%	0.70
intermediolateral		6.7%	15.2%	0.47
Sacral:	31,43	12.9%	53.5%	<0.001
Overall positivity (all regions)	23,46	51.4 %	95.7%	<0.001

<u>Preliminary Data and Plan:</u> A limited number of prior studies have examined peripheral tau deposition.[3, 5-7] Only one small study, with 10 normal controls and 21 AD subjects, that examined tau deposits in multiple organs other than brain,[8] found pathologic tau deposits in areas such as the aorta, liver, spleen and stomach.[8] We recently conducted a comprehensive examination of the distribution of tau deposits in the spinal cord of non-demented (ND) and AD cases.[9] Over 95% of AD subjects and over 50% of ND subjects had spinal cord tau deposition (Table 1). Furthermore, the density and distribution correlated with Braak neurofibrillary tangle staging, the pathological progression of AD. As the spinal cord innervates all peripheral organs through autonomic and somatosensory nerve fibers, and previous studies have demonstrated tau deposits in organs other than brain; we hypothesize tau deposits are likely to exist in amenable peripheral biopsy site. Additionally, work by Lee, Trojanowski and others indicate that such spread is probable with pathological protein deposits.[4, 10] In this study, we propose to extend our spinal cord findings and identify different phosphorylated tau species as well as the native form in peripheral areas that are amenable for biopsy. Immunohistochemistry, western blots, and enzyme linked immuno-absorbent assays will be used. We have expertise in these and similar methods, as demonstrated

through our publications.[9, 11-16] Since a brain biopsy is very risky and costly, using non-neuronal tissues that are more readily accessible and typically screened and probed in a health care setting could provide aid in AD diagnosis and treatment. If our hypothesis holds true, it will provide grounds for a peripheral biopsy site in AD, as well as further insight into the pathophysiology of AD.

Proposed One-Year and Long-Term Outcomes: Overall Significance: We anticipate by the end of this one year study to generate a conclusion on the feasibility of a peripheral biopsy site in AD. We anticipate at least one publication from these investigations. This pilot study will provide preliminary data for submission of a larger NIH or Alzheimer's Association grant for further analyses of peripheral involvement in AD and possibly a clinical trial of peripheral biopsy.

Milestone 1. Year 1, month 1-9
We will complete immunohistochemistry and western blot analyses.

Milestone 2. Year 1, month 7-10
We will begin formatting data for submission to an Alzheimer's based journal, as well as formatting data for a competitive grant application.

Milestone 3. Year 1, month 10-11 Future directions for competitive grant application
Results will be submitted to an Alzheimer's based journal by May 2014. We will begin formatting these data for a competitive NIH (R21) or Alzheimer's Association grant application to be submitted by June 16th 2014, which will focus on extensively examining all tau positive areas. This would entail expanding our groups to include other dementias and extending sampling parameters to include more of each positive area as well as perform needle biopsy (if feasible based on location of the positive tissues). We have done similar techniques with our study on a biopsy site for Parkinson's disease.[17]

Year End Progress Summary:
Preliminary western blots revealed that total tau is detectable in all peripheral areas analyzed but only a fraction of that compared to that found within the brain. To increase sampling and provide a better means quantitation we completed total tau enzyme linked immune-absorbent assays (ELISAs) on all areas for 18 Alzheimer's disease and 2 normal control cases. Of the peripheral tissues examined, we revealed that the submandibular gland (average±stdev: 120±25.9ng/mg) had the highest levels of total tau followed by the abdominal skin (21±16.1ng/mg), sigmoid colon (22±8.96ng/mg), scalp (14±5.68ng/mg), and liver (13±4.61ng/mg). The superior frontal gyrus contained 7889±2742ng/mg of total tau. Furthermore, immunohistochemistry staining of 5µm paraffin

Figure 1. Phosphorylated tau-immunoreactive nerve fiber in a submandibular gland from autopsied Alzheimer's disease patient. Photo taken at 40x magnification.

sections with a phosphorylated tau antibody (T231) on the same cases revealed positive nerve elements within the submandibular gland tissue (Figure 1).

We have submitted these results in abstract form to the American Association of Neuropathologist's Annual meeting and a manuscript is currently in draft form to be submitted this summer. We are currently conducting subsequent analysis of the submandibular gland, including more normal controls to understand how these tau levels may change based on pathological disease progression and are in preparation for submission of an R21 grant.

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ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Establish ApoE genotype-specific iPSC lines from peripheral mononuclear blood cells of living Subjects. Lih-Fen Lue, PhD; Douglas Walker, PhD; Thomas Beach, MD. PhD; Marwan Sabbagh, MD, Matt Huentelman PhD. Banner Sun Health Research Institute, Translational Genomics Research Institute.

Specific Aims: **Aim 1:** Bank fibroblast cells from skin tissues of autopsied cases of Whole Body Donation Program of BSHRI. **Aim 2:** Establish iPSC (induced pluripotent stem cells) lines from one ApoE4/4 and one ApoE3/3 subjects using fibroblasts that we have stored from Aim 1.

Background and Significance: Takahashi and Yamanada (2006) successfully reprogrammed adult somatic cells through introduction of exogenously transcription factors OCT4, SOX2, KLF4, and MYC to generate pluripotent stem cells (iPSC) [13]. Their seminal work has since then quickly made iPSC new sources for pluripotent cells for disease modeling, drug discovery, and cell therapy. The usefulness of iPSC has been supported by their successful differentiations into a long list of somatic cells with specific phenotypes and functions (examples in [1,8,10]). The iPSC also 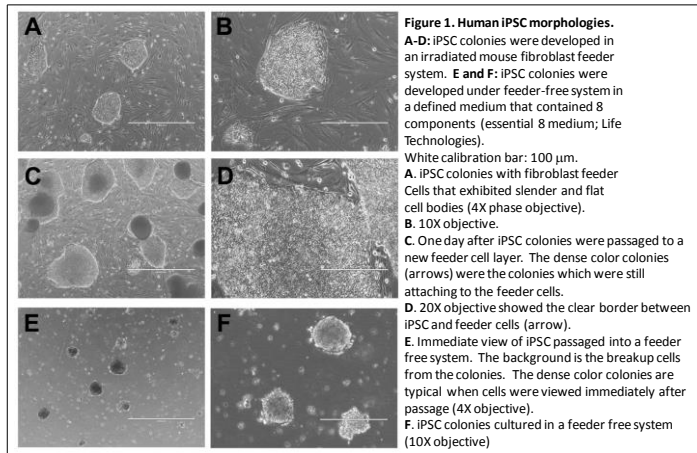have potentials to generate patient-specific "tissues" for future personalized regenerative medicine applications [2,11]. Currently, researchers are still searching for better disease model for Alzheimer's disease (AD). iPSC and derived cells are emerging as potential new models [6]. ApoE 4 genotype is the most powerful risk factor for sporadic AD and their roles in AD are still under scrutiny. This application is to start banking the fibroblast cells derived from autopsy skin samples. We will do this through the collaboration with Dr. Beach who is the Neuropathologist and the Head of the BSHRI Brain and Whole Body Autopsy Program. We propose to make fibroblasts derived IPSC from neuropathologically characterized autopsy cases; these will be of great resources with great potentials for modeling Alzheimer's disease and drug discovery [3,4]. We will bank fibroblasts from a total of 25 autopsy cases, and select one ApoE4/4 and one ApoE3/3 cases for reprogramming and differentiation. There have been findings of several ApoE4 disease mechanisms (examples in [5,7,12,14]). In our initial characterization of the differentiated neural cells, we will determine whether there are ApoE isoform-dependent inductions of lipid efflux [9]. This feature in iPSC-derived neurons and astrocytes can be used for assessing the feasibility of using these cells to model molecular mechanisms of ApoE in AD. ***Our long-term goal is to model the ApoE4 molecular mechanisms in Alzheimer's disease in iPSC differentiated neural and vascular cells and to facilitate genotype specific cell-based drug discovery. We hope to use the data from this project as disease study topic for R21 submission or a NIH-sponsored biospecimen banking program.***

Preliminary Data: Although the stem cell research is a new field for the PI, based on the experiences in cell biology and glial and brain vascular cell cultures from human autopsy cases in past 15 years, the fundamental techniques have already been well adopted by the PI. Some of the work using iPSC derived from H9 embryonic stem cell line is shown here. **Figure 1** demonstrated typical appearance of the human iPSC grown in feeder (A-D), and feeder-free (E-F) systems. **Figure 2** showed the results of flow cytometric characterization of the iPSC after reprogramming. Using flow cytometer to quantify the cell numbers expressing SSEA (Stage-specific embryonic antigen)-4 protein, the evidence of developing stemness (or de-differentiation state), the iPSC colonies consisted of 99.97% SSEA-4 positive cells, an indication of good stemness. The procedure included trypsinization of iPSC colonies and resuspending as single cell suspension. Then, cells were immunocytochemically labeled with an antibody for SSEA-4 conjugated with fluorescence dye. Cells were then filtered to remove clumps before subjected to flow cytometric analysis. In **Figure 3**, the characterization of the stem-ness of the iPSC was done by the immunocytochemistry using embryonic stem cell markers, tumor recognition antigen (TRA)-1-81 (at cell

surface) and OCT-4 (in nucleus). TRA-1-81 expression is in red fluorescence and OCT-4 immunoreactivity in green. The results shown here are examples of the characterization necessary during induction, colony formation, developing pluripotency, cloning, and expansion of the iPSC lines. Additional approaches and types of characterization will be included in work flow.
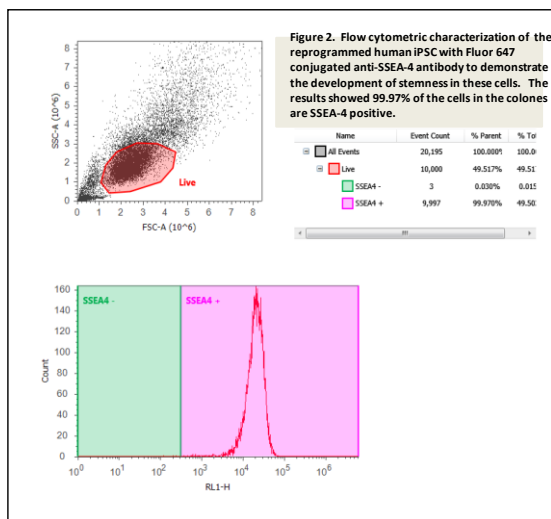

Figure 1. Human iPSC morphologies.
A-D: iPSC colonies were developed in an irradiated mouse fibroblast feeder system. E and F: iPSC colonies were developed under feeder-free system in a defined medium that contained 8 components (essential 8 medium; Life Technologies).
White calibration bar: 100 µm.
A. iPSC colonies with fibroblast feeder Cells that exhibited slender and flat cell bodies (4X phase objective).
B. 10X objective.
C. One day after iPSC colonies were passaged to a new feeder cell layer. The dense color colonies (arrows) were the colonies which were still attaching to the feeder cells.
D. 20X objective showed the clear border between iPSC and feeder cells (arrow).
E. Immediate view of iPSC passaged into a feeder free system. The background is the breakup cells from the colonies. The dense color colonies are typical when cells were viewed immediately after passage (4X objective).
F. iPSC colonies cultured in a feeder free system (10X objective)

Proposed One-Year and Long-Term Outcomes: We will bank the source cells of iPSC from a total of 25 autopsy cases and established iPSC from one ApoE4/4 and one ApoE3/3 cases. We plan to submit a R21 application to model molecular mechanisms of

Figure 2. Flow cytometric characterization of the reprogrammed human iPSC with Fluor 647 conjugated anti-SSEA-4 antibody to demonstrate the development of stemness in these cells. The results showed 99.97% of the cells in the colones are SSEA-4 positive.

ApoE in AD; the strategy from this study.

Milestones
Timeline
Banking fibroblasts from autopsy cases (25 cases)
July 1, 2013 to May 1, 2014
iPSC production, and characterization (2 cases)
December of 2013 to June of 2014
Stem cell differentiation procedure initiated (2 cases)
April of 2014 to June of 2014
Submission of one manuscript   July 1, 2014
Submission for NIH R21 grant application   October 16, 2014

Year End Progress Summary:
Autopsy cases that we have processed during this granting period: We have processed scalp skin samples from 6 autopsy cases in 2013 and 13 autopsy cases in 2014. A summary of the features of the cells that we have obtained and the clinical diagnosis is shown in the following table. The neuropathological diagnosis is currently unavailable. Thus far we have completed the banking of scalp fibroblasts from 4 normal control (NC) cases, 5 AD cases, 5 probable AD cases, 2 Dementia with Lewy Body (DLB), 3 Parkinson's disease (PD), 1 PD with dementia (PDD). Currently we are still expanding a subset of the cases which arrived at autopsy recently.

Protocol developed during this granting period: To create a bank of fibroblast cells, scalp samples were collected from autopsy donors of the Brain and Body Donation Program at BSHRI. These skin tissues were processed by washing and trimming off the hair and fatty tissue, then finely chopped into small pieces for plating. Cells were grown from these skin pieces by feeding every two to three days with medium containing serum and antibiotic. The cells were passaged three times then cryoprotected and stored in liquid nitrogen, ultimately collecting 15-20 tubes of cells per autopsy case. At the time of freezing, a cell pellet of 100,000 cells was collected for each case to use for ApoE genotyping. For skin cell characterization, one tube of frozen cells was thawed to passage once then plated onto coverslips. These plated cells underwent standard immunocytochemical procedures to detect proteins found in fibroblasts—vimentin and fibroblast surface protein. A database of the autopsy cases was recorded that

included demographical, clinical and pathological information, as well as cell processing and maintenance notes.

<u>Summary of the findings</u>: We have collected 20 cases thus far, which consists of 15 males and 5 females with a mean age of 83.2 ± 1.6 years (± standard error). Out of the 20 total cases, 15 of them have been genotyped for ApoE that found 6 carriers (3/4 or 4/4) and 9 non-carriers (2/3 or 3/3). All of the ApoE4 carriers were with the diagnosis of probably AD or AD except one with diagnosis of DLB. The rate of ApoE4 (-/4 and 4/4) carrier in the genotyped AD cases is 50% whereas in the total genotyped cases is 40%. There is 1 AD which has ApoE4/4. There are 7 cases with ApoE 3/3, including 1 AD, 1 DLB, 3 PD, and 2 NC cases. We have proposed to perform reprograming in one 4/4 and 1 3/3 cases. Currently, the reprogramming process is conducted in ApoE 3/3 case because we have more 3/3 cases than 4/4 case. We are going to continue banking from more cases especially from AD cases in order to obtain higher number of ApoE 4/4 cases.

All of the cases that have been stored for banking purposes have also been characterized for protein detection of vimentin and fibroblast surface proteins using immunofluorescence. Examples of the immunoreactivity are shown in the adjacent figures (green fluorescence: right: vimentin; left: Fibroblast surface protein; Blue fluorescence: nuclei).
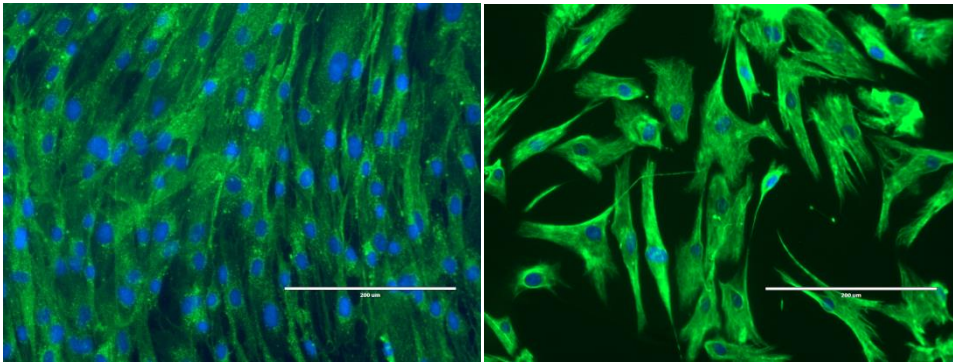
Case ID	Disease (clinDx)	Age	Gender	PMI (hrs)	Processing Delay (hrs)	ApoE Genotype	Characterization	
							FSP	Vimentin
13-63	AD	85	Female	3.27		3/4	+	+
13-65	PD	73	Male	4.10		3/3	+	+
13-73	pAD	86	Male	3.17		2/3	+	+
13-81	AD	76	Male	3.05		4/4	+	+
13-82	DLB	62	Female	3.48		3/3	+	+
13-83	pAD	85	Male	3.58		3/4	+	+
13-84	NC	91	Male	2.42		2/3	+	+
14-01	AD	89	Female	3.00		3/3	+	+
14-02	NC	86	Female	2.33	14	3/3	+	+
14-03	PD	90	Male	3.28	7	3/3		
14-04	PD	78	Male	3.70	0	3/3	+	+
14-05	NC	92	Male	2.87	1	3/3	+	+
14-06	AD	85	Male	3.50	1	3/4		
14-08	DLB	82	Male	5.5	1	3/4		
14-09	NC	89	Male	3.02	0			
14-10	AD	80	Male	4.23	13	3/4		
14-11	pAD	82	Male	3.98	45			
14-12	PDD	82	Male	4.25	4			
14-14	pAD	78	Male	4.13	50.5			
14-15	pAD	92	Female	4.87	16			

Processing delay is from the time of brain retrieval (does not include PMI); clinDx=Clinical Diagnosis; PMI=Post-mortem interval; AD=Alzheimer's disease; PD=Parkinson's disease; pAD=probable or possible Alzheimer's disease; DLB=Dementia with Lewy bodies; NC=Normal control; PDD=Parkinson's disease with dementia

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ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

The Role of Blood-Brain Barrier Dysfunction In Neurodegeneration. MiMi P. Macias, PhD, Alex E. Roher, MD, PhD, Marwan N. Sabbagh, MD, Raymond Migrino, MD. Banner Sun Health Research Institute, Carl T. Hayden VA Medical Center.

<u>Specific Aims</u>: Sporadic late-onset Alzheimer's Disease (LOAD), the most common form of dementia in elderly populations, is increasing in incidence worldwide. Accumulating evidence points toward reduced integrity of the blood-brain barrier (BBB) as an important early event contributing to development of Alzheimer's disease (AD). Aging-related alterations in the metabolic functions of the BBB such as decreased brain glucose influx, increased cerebrovascular ischemia, and accumulation of brain and vascular Aβ are postulated to contribute to the progressive opening of the BBB and consequent AD neurodegeneration (1, 19, 22). We propose to test the **hypothesis that molecular changes associated with BBB tight junction dysfunction are present and quantifiable in the postmortem brain tissues of patients diagnosed with AD compared to gender- and age-similar cohorts of non-demented controls (NDC) and non-AD dementia progressive supranuclear palsy (PSP) controls** by addressing the following specific aims:

Specific Aim 1. Quantify the expression levels of a panel of archetypal BBB tight junction (TJ) proteins (occludin, claudin-3, claudin-5, JAM-1, ZO-1, and cingulin) in the leptomeningeal vessels (≤ 500 μm diameter) of AD (n=20), NDC (n=20), and PSP (n=20) by Western blots and/or ELISA. Characterize the distribution and localization of the selected TJ proteins by immunohistochemistry (IHC).

Specific Aim 2. Quantify cerebrovascular changes in the RNA expression levels of the BBB TJ genes-of-interest listed above by real-time quantitative RT-PCR (qRT-PCR).

Innovation. BBB integrity is essential for optimal functioning of the brain, and critical TJ stability relies on expression of multiple proteins which interact to form the BBB junctional complexes. Thus far the relation between synchronous changes in BBB TJ proteins and AD pathology has not been determined. This current study will assess altered expression of BBB TJs as a coordinately regulated complex of multiple protein targets. The invaluable Institutional resource of postmortem brain tissues with medical histories supports our development of a human BBB tissue-based approach to determine an AD-associated expression profile for representative BBB TJ components in disease.

Significance. The etiology of AD, while known to involve genetic and environmental risk factors, is still not well understood. To identify molecular changes at BBB TJs associated with brain dysfunction and AD, this study will concurrently investigate, the expression changes in a panel of 6 primary TJ proteins of the human BBB, which is one of the key component in the neurovascular unit (NVU). Consideration of the significance of the BBB and understanding its role in AD pathogenesis are vital for future deployment of immunotherapeutic interventions and treatment strategies (29) to modify the progressive decline of this devastating dementia.

<u>Background:</u> Hallmark pathologies of AD include brain amyloid plaques and amyloid angiopathy, intracellular neurofibrillary tangles, and neuroinflammation resulting in progressive neuronal dysfunction and cognitive decline. Also, oxidative stress and inflammation (e.g., IL-1 and TNFα (12, 16)) conditions common to both AD and aging, disrupt TJs of the BBB (3, 8, 11) and exacerbate barrier leakiness and dysfunction (10, 14). The BBB formed by the endothelium of the cerebral blood microvasculature, is a dynamic interface that normally protects and maintains homeostatic conditions of the central nervous system (CNS), selectively restricting influx of nutrients, ions, small molecules, proteins and cells from blood to the brain parenchyma and efflux of metabolic waste products from the brain to the periphery (30). Increasing evidence supports cerebral microangiopathy and dysfunction of the BBB as contributors

to downstream neurodegenerative processes (1, 9, 15, 34). Major, and increasingly common, vascular risk factors favoring vulnerability and diagnosis of cerebral small vessel disease are age and hypertension (18, 27). The integrity of the BBB paracellular diffusion barrier notably depends on the intercellular TJ proteins that associate with their counterparts across adjacent endothelial cells. Transmembrane TJ proteins include occludin, claudins, and junctional adhesion molecules (JAM-1, -2, and -3). The TJ proteins interact with intracellular plaque proteins such as zonula occludens proteins (ZO-1, -2, and -3), cingulin, and afadin/*AF6* that associate with actin of the cytoskeleton and other cytoplasmic adaptor proteins (e.g., protein kinase C, tyrosine kinase) (21). Age-, injury-, and disease-related changes in BBB TJ permeability have been shown in human, animal, and *in vitro* systems (7, 13, 20, 28). AD brains have demonstrated altered expression of occludin and claudins in discrete structural compartments of the NVU (32, 33). For this study we will focus specifically on the TJ protein complexes of human capillary endothelial cells to identify a set of AD-associated changes in BBB TJ expression.

Study Samples: Age-related histological changes in the brain vasculature exhibit species and regional specificities (6). Therefore, this study will examine human postmortem leptomeningeal arteries for TJ expression profiles. Frozen brain tissue from AD (n=20), NDC (n=20), and PSP (n=20) age and gender similar individuals will be requested from the Sun Health Research Institute Brain and Body Donation Program (7). Because expression of the genes of interest is not restricted to brain endothelial cells, leptomeningeal vessels (≤500 micron diameter) will be isolated to enrich for microvessel compartments and simultaneously minimize brain parenchyma carryover in brain homogenate preparations. The non-AD dementia samples permit distinction of AD-specific from dementia-associated BBB changes.

The following six primary BBB barrier TJ proteins will be examined. **Occludin** (65 kDa) is a tetraspan, transmembrane TJ protein that provides intercellular connection across adjacent cell membranes (17). Brain endothelial cells (BEC) primarily express **claudin-3** and **claudin-5** (20-27 kDa) which have four transmembrane protein domains (16, 29, 30). **JAM-1** (32-40 kDa) is a single-pass, TJ membrane protein of the immunoglobulin superfamily. Intracellular **ZO-1** (225 kDa) is a cytoplasmic adaptor protein at BEC TJ complexes shown to respond to cerebral embolism and hypoxia *in vitro* (3). **Cingulin** (140 kDa) is a cytoplasmic plaque protein that complexes at TJs with ZO-1 and -2, JAM-1, and actin.

Proposed One-Year and Long-Term Outcomes: With availability of validated reagents and the experience of the collaborating investigators, we anticipate successful completion of the proposed specific aims and expect to submit an original manuscript for publication during the
final 2 months of funding. This pilot study will identify integral BBB TJ protein(s) as BBB markers that are altered in relation to AD. Data generated from this project is crucial for developing and pursuing additional NIH grant support to: **1.)** Compare and correlate BBB TJ changes identified in the current proposal, to indicators of AD brain "injury" status in cerebromicrovessels: brain Aβ and vascular amyloid accumulation as measure of progressive AD histopathology; TNFα to evaluate neuroinflammation; reactive oxygen species as measure of hypoxia/ischemia in AD compared to control brains. **2.)** Investigate, in vitro, the molecular mechanisms regulating the specific BBB responsive genes using short term cultures of primary cerebral endothelial cells, or using the human cerebral microvessel endothelial cell (hCMEC/D3) cell line (37). Identify critical transcription and/or post-transcriptional regulatory mechanisms responsible for AD-associated, modulated TJ gene expression. **3.)** Establish short-term human organotypic hippocampal slice cultures for functional assays. Organotypic cultures retain dynamic 3-dimensional tissue organization (4, 23, 25, 36) and can be treated with various exogenous stimulatory cues to link molecular mechanisms modulating TJ changes in disease to the distinct cell populations of the NVU. With preliminary data from this project, we expect to submit an NIH R21 Grant proposal by October 2013 and ADCC Grant application by early 2014. Better understanding of mechanisms regulating BBB TJ complexes in disease will provide opportunities to not only develop novel approaches to

repair/restore barrier integrity, but also modulate barrier permeability to permit selective entry of potential therapeutic agents into the CNS.

Year End Progress Summary: From the onset, the priority of this pilot project has been to take the most biomedically relevant approach to studying molecular changes in the blood brain barrier (BBB) associated with Alzheimer's Disease. A timely, critical comment made by a Grant Application Reviewer: "…It is important to investigate BBB gene expression in cerebromicrovessels (20-120 μm in diameter) rather than leptomeningeal vessels. This reviewer would suggest that the investigators should isolate cerebromicrovesels from the brains for the proposed study…" led to our re-review of the published literature and resulted in our commitment to perform our BBB Pilot Study in enriched parenchymal microvessel fractions prepared from frozen, postmortem human brains. We agreed with the Reviewer that the value of this study required us to undertake the technically challenging approach of developing a rapid, small-scale microvessel enrichment procedure that would support our downstream quantitative molecular studies of the BBB tight junction proteins and RNAs. We report at this time that the brain microvessel enrichment methodology has been successfully established (Figure 1), and the molecular biology investigations of the panel of BBB tight junction genes are proceeding essentially as described in the original Research Plan:

Figure 1. Microvessel-enriched fraction from frozen human postmortem brain (wet mount, 100X magnification). A representative phase contrast micrograph of brain microvessels extracted from parenchymal tissue using our newly developed rapid, small-scale methodology (i.e., homogenization, dextran centrifugation, and glass bead column filtration), demonstrates minimal contamination from neuropil, free nuclei, and parenchymal debris.

Specific Aim 1. Quantify the expression levels of a panel of archetypal BBB tight junction (TJ) proteins, (occludin, claudin-3, claudin-5, JAM-1, ZO-1, and cingulin) in the **cerebral microvessels** by Western blots and/or ELISA. Characterize the distribution and localization of the selected TJ proteins by **immunocytochemistry**.

Specific Aim 2. Quantify cerebrovascular changes in the RNA expression levels of the BBB TJ genes-of-interest listed above by real-time quantitative RT-PCR (qRT-PCR).

All 60 of the study's frozen, frontal lobe, brain specimens from Alzheimer's Disease, Non-Demented, and Progressive Supranuclear Palsy cases (n= 20 each) have been received from the Banner Sun Health Research Institute Brain and Body Donation Program. Processing and quantitation of microvessel BBB proteins and RNAs are underway as described in the Specific Aims 1 and 2.

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ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Comparison of Alzheimer's disease and Down syndrome post-mortem brain markers. Marwan Sabbagh, MD, Boris Decourt, PhD, Lynn Nadel, PhD, William Mobley, PhD. Banner Sun Health Research Institute, University of Arizona, University of California, San Diego.

Specific Aims:
Aim 1: To compare BACE1 levels and β-secretase activity, as well as a few AD amyloid pathology markers in post-mortem brain samples (performed by Sabbagh/Decourt Lab).
Aim 2: To establish whether or not endosomal pathology is linked to amyloid pathology in AD, DSAD and DSND post-mortem brain samples (performed by Mobley Lab).

Background: Down syndrome (DS) conveys a high risk for the early development of Alzheimer's disease (AD), with a gradual increase in the rate of AD from age 40 to 60. Virtually all individuals with DS have the plaques and tangles characteristic of AD by the age of 40[1]. Therefore, there is neurological change prior to the onset of dementia that could predict decline years down the road. In order to treat individuals with DS as early as possible and broaden our understanding of the early signs of AD pathology, a better understanding is needed of how neuronal and glial cellular pathology develops in Down syndrome with AD (DSAD), and how similar or different this pathology is between DSAD and idiopathic AD. Biologically, the fact that individuals with DS exhibit brain Aβ deposition is not mysterious: the *APP* gene that codes for Aβ is located on the distal arm of chromosome 21, precisely the region setting out DS. What is mysterious is why, with such heavy Aβ burdens by age 40, it often takes another 20+ years for people with DS to display AD symptoms, and, most of all, why some people with DS escape the dementia. Recently, a starting point for unraveling these questions has become available. In 1996, Lemere et al. found that brain Aβ deposition starts as early as age 12 but Aβ40 deposits were not detected until age 30, when degenerating neurites around plaques were observed[2]. She also found that Aβ42 immmunoreactivity was always higher than Aβ40 at any given age. Combined with other findings, this underscores that amyloid deposition is an early and seminal event in the pathogenesis of the dementia in the setting of DS. However, much is still unknown regarding the cerebral changes occuring in the DSAD brain. **Here, we hypothesize that Aβ metabolism and endosomal pathology have not only striking similarities but also important differences in DS compared to non-DS brains, at each stage in the progression of clinical and neuropathological AD.**

Proposed One-Year and Long-Term Outcomes: Before the end of June, we plan to complete all experiments for this project. In June 2014, we will conduct a thorough statistical analysis by comparing data for all group for each molecule studied, as well as identifying eventual correlations between variations in the different measured outcomes. The data will be used to prepare a manuscript during the summer of 2014. If the project is successful, we will seek additional sources of DSAD and DSND brain tissues to apply for an NIH grant by the end of 2014 to continue the project. In addition, the data collected here will be used to apply for additional grants (Alzheimer's association, Down Syndrome Research and Treatment Foundation) to test the whether an immunomodulatory drug can slow down the cognitive decline observed in a mutant mouse model od Down syndrome, aiming to test the drug in clinical trials in the future.

Preliminary Data and Year End Progress Summary: As of early April 2014, we have gathered all samples we could to complete the project. Table 1 provides the details about these samples. Frozen tissues have been split and are currently being processed by both BSHRI and UCSD investigators for biochemical analyses. Fixed tissues from Down syndrome subjects are undergoing the same sectioning as cognitively

normal and Alzheimer's brain tissues for accurate comparison following histological and immunhistochemical stainings (Dr. Mobley's lab).

<u>Table 1</u>: Samples gathered for the project.

Disease Status	Fixed Tissues		Frozen Tissues		Origin
	Planned	Collected	Planned	Collected	
Cognitively normal	8	8	8	8	BSHRI
Alzheimer's disease	8	8	8	8	BSHRI
Down Non Demented	8	2	8	2	UCI
Down Demented	8	9	8	8	1 BSRHI + 8 UCI

UCI = University of California Irvine

In the coming weeks, all frozen samples will be subjected to BACE1 mRNA and protein quantification, as well as Aβ levels assessment (Drs. Sabbagh and Decourt).

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ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Is Interleukin-34 a key regulator of microglia function in Alzheimer's disease? <u>Douglas G. Walker, PhD, Matt Huentelman, PhD, Andis Klegeris, PhD.</u> Banner Sun Health Research Institute, Translational Genomics Research Institute, University of British Columbia Okanagan.

<u>**Specific Aims:**</u> **Aim 1.** To correlate changes in IL-34 expression with progression of microglial activation and Alzheimer's disease pathology. **Aim 2.** To determine the effects of IL-34 induced signaling on properties of human microglia.

<u>**Hypothesis:**</u> There are reduced levels of IL-34 in AD brains, which will promote a damaging microglia inflammatory phenotype.

<u>**Background and Significance**</u>: This collaborative project will examine the cytokine **interleukin-34** (IL-34) in human brains and its effects on human microglia phenotypes and function from different aspects. IL-34 is a recently discovered cytokine with a significant role in neuroinflammation, but has not been studied in relation to Alzheimer's disease (AD). There is now evidence that IL-34 could be a key soluble regulator of neuroinflammation, with a relatively unique feature of being primarily produced in brain by neurons (1;2), and features shared only with fractalkine (3;4). IL-34 binds to the colony stimulating factor 1 receptor (CSFR-1), which is mainly expressed by microglia and shared with colony stimulating factor-1(CSF-1), but these cytokines show differences in signaling (5-7). Recent findings on IL-34 from animal models suggest human focused studies are now needed. IL-34 treatment of microglia reduced neurotoxicity induced by their activation with oligomeric Abeta (Aβ) through induction of heme oxygenase-1 and the Aβ degrading insulin-degrading enzyme (8). Another study demonstrated that IL-34 was required for maintenance of microglia in the adult brain (1); a finding confirmed in that adult IL-34 gene deficient mice had significantly fewer microglia than wild-type mice (2). In addition, IL-34 was shown to be neuroprotective when administered to kainic acid-lesioned animals (9). To support this, it was shown that IL-34 induced an immunosuppressive phenotype in cultured macrophages (10). Recent data have suggested that damaged neurons released enhanced levels of IL-34 (4). Based on these published reports and our preliminary studies, we are exploring the idea that reduced levels of IL-34 signaling might permit the development of a more classically activated inflammatory phenotype. This can be assessed *in vivo* using correlative measures of IL-34 expression in brains in relation to degrees of AD pathology, with mechanisms involved examined in *vitro* using IL-34 treated-human microglia. Due to the time and resources available, the extent of these pilot studies are restricted, but these data should indicate whether enhancing IL-34 signaling has therapeutic potential, and extended studies justified.

<u>**Preliminary Data**</u>:
   a)   The key feature of data were provided to support this application was the demonstration that IL-34 was a potent mitogen for human microglia. This was demonstrated in cultures in comparison with macrophage colony stimulating factor.
   b) We demonstrated that there was a deficit of IL-34 in human brain samples as shown by western blots and RNA expression (see Figures below).


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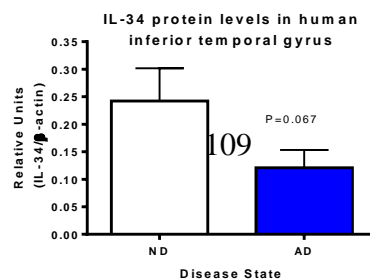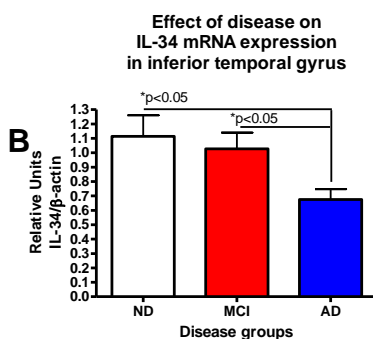
Proposed One-Year and Long-Term Outcomes: By the end of one year of funding, we will know if changes in IL-34 expression, and by implication IL-34 mediated CSF-1R signaling in human AD brains correlates with tissue damage. By defining the differentiation state induced by IL-34 compared to that induced CSF-1 could indicate which signaling pathways need to be stimulated. As these studies are highly innovative due their focus on IL-34 and potentially significant due to the focus on AD, the data generated will form the basis of publications and request for federal funding to address many of the potential therapeutic aspects of IL-34.

Milestones for Project: Assuming that the data is acquired in the expected manner, a publication on Aim 1 should be submitted by March 1st, 2014 at the latest; a publication primarily based on Aim 2 should be ready by the end of the funding period June 30th 2014.

Year End Progress Summary: This project has progressed on several fronts.
a). Collection of microglia samples for RNA sequencing. The major feature of this application has been the preparation of RNA from different microglia cases that have been stimulated with interleukin-34. For comparison, we also prepared samples that had been stimulated with macrophage colony stimulating factor (MCSF-1). We have suitable RNA materials from 5 separate cases. These have been quality controlled for RNA integrity and yield. These are to be sent to TGEN (Neurogenomics Division) for deep RNA sequencing. The aim is to obtain a profile of genes induced by IL-34. This will be the foundation to determine whether treatment with IL-34 or its receptor agonist will be useful for modulating AD related inflammation.
b) Studies on IL-34 on microglia inflammation and Aβ metabolism. Key targets were identified to study in relation to IL-34 and inflammation, namely CD33, transforming growth factor beta and amyloid beta metabolism. What is significant from the studies below is that we showed that transforming growth factor beta-1 (TGFβ-1) is not affected by IL-34. This is in direct contrast of the published data by Ma [14] using rodent microglia that TGFβ-1 was a key factor. It illustrates the value of human microglia studies for target validation. The findings on Aβ metabolism are preliminary and did not reach statistical significance but illustrates that IL-34 could promote Aβ uptake and breakdown. This was a component part of this application, but is dependent on receiving additional microglia samples for the study.
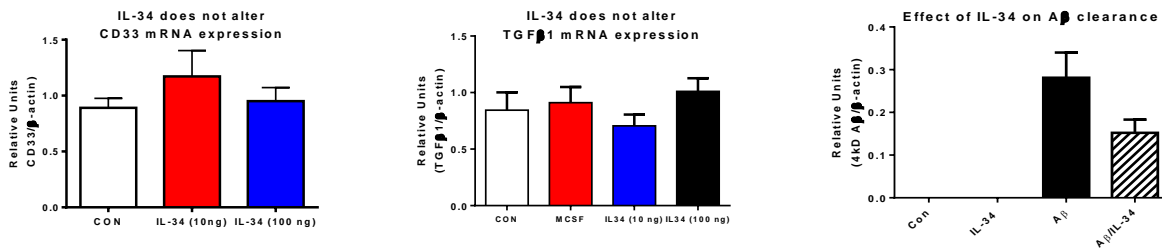
IL-

c) **IL-34 is also involved in Parkinson's disease inflammation**. The potential neuroprotective feature of IL-34 was indirectly demonstrated using tissue samples from PD cases.   In PD, similar to AD, inflammation is a prominent pathological feature. Protein measures of tyrosine hydroxylase and IL-34 in human substantia nigra samples indicated a significant correlation between TH levels and IL-34 levels.
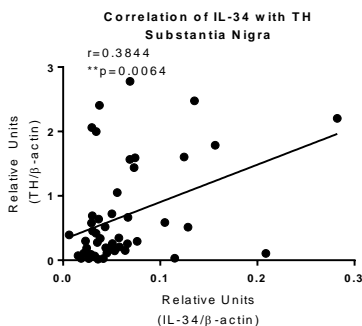
This indicated indirectly that higher levels of IL-34 were found in samples with higher levels of TH. We have shown that TH levels negatively correlate with markers of activated microglia and inflammation.   This supports the hypothesis that IL-34 is neuroprotective by preventing inflammation.
d) IL-34 expression in neurons. It has been an initial hypothesis that the primary source of brain IL-34 was neurons. We have investigated

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this further; we have shown significant levels of expression in in vitro human neurons. The expression was only affected by IL-34 protein, not other cytokines. We have also detected microglia and endothelial cell expression of IL-34, which are new findings. These are being investigated further.

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Publications and Grants: This work is not ready for publication yet, further data are needed. Once the RNA sequencing data is available, this work will be publishable. In the meantime, we have produced a grant application to the Arizona Biomedical Research Commission on this work as part of their recent competion. This grant is still under review.

Project Progress Reports

Barrow Neurological Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Studies in Cerebral Metabolism. <u>Jiong Shi, MD, PhD, Pengcheng Han, PhD, Junxiang Yin, PhD, Thomas Beach, MD, PhD, Eric Reiman, MD, Winnie Liang, PhD, Richard Caselli, MD.</u> Barrow Neurological Institute, Banner Sun Health Research Institute, Banner Alzheimer's Institute, Mayo Clinic Arizona

<u>**Cellular Metabolism Studies:**</u> The focus of this laboratory is to study the role of energy metabolism and, more specifically, mitochondrial function, in brain aging and age-related neurological disorders, primarily Alzheimer's disease. Normal cerebral metabolism requires large quantities of energy and mitochondria, the main source of cellular energy, are particularly affected in older brains. PET imaging studies have revealed regional specific metabolic deficits in AD. Impaired mitochondria generate less energy while emitting toxic byproducts that further harm the brain. Within this context, we have discovered that ketones, a group of physiological compounds produced by the liver following fasting or consumption of the low-carbohydrate, high-fat ketogenic diet, protect neurons in various models of neurological disease by enhancing mitochondrial function.

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.

Our previous studies have shown that soluble Aβ42 aggregates are toxic to neurons by inhibiting neuronal excitability and long-term potentiation, increasing levels of reactive oxygen species and oxidized proteins, and decreasing mitochondrial respiration driven by complex I. We now find that exposure to extracellular Aβ42 aggregates is associated with an increase in intracellular Aβ aggregates. The consequences of intracellular Aβ accumulation remain unclear however. We have demonstrated that ketones enhance mitochondrial respiration driven by complex I and prevent Aβ42 toxicity. Our recent results show however that ketones further reduce intracellular levels of Aβ aggregates in cells exposed to extracellular Aβ42 aggregates.

To gain further insight into the consequences of Aβ internalization and into the neuroprotective effects of ketones, we have designed a series of experiments that systematically characterize intracellular Aβ in neurons, astrocytes and microglia and that attempt to identify the underlying pathways using unbiased proteomic approaches. Our ultimate goal is to identify novel pathways that regulate Aβ metabolism and that might be amenable to pharmacological intervention. We are studying neurons and glia separately as mechanisms that regulate Aβ metabolism might differ depending on cell type.

<u>**2013-2014 Progress:**</u> Our ongoing experiments are aimed at demonstrating the neuroprotective effects of ketones in Alzheimer mice that chronically overproduce Aβ42. We studied the effects of ketones on mitochondrial activity and on long-term potentiation (LTP) in hippocampal slices from triple transgenic Alzheimer (3xTgAD) mice and age-matched controls at various ages. Older 3xTg AD mice exhibited various synaptic abnormalities that were associated with decreased complex I activity and increased complex II activity relative to age-matched controls. Treatment with ketones reversed all the abnormalities. We further investigated the protective effect and mechanism of ketone bodies on learning

and memory in APP (PDGFB-APPSwInd) mice. After 2 months of ketone treatment, APP mice showed significantly improvement of learning and memory. During the four-day learning period in Morris water maze, the escape latency in APP mice without treatment was significantly longer than that in B6 controls (67.38±5.26s vs. 48.33±5.13s, p<0.01 on day 4). In comparison with untreated APP mice, ketone treated APP mice had reduced latency (49.01±5.45s, p<0.05) on day 4, a longer time on the target platform (15.02 ± 2.64 s vs. 10.53±2.30s, p<0.05) at the probe test, and a higher discrimination index in the novel object recognition test (26.29±5.22s vs. 12.48±3.97s, p<0.05), and no significant behavioral differences on the rotarod test. These studies have shown that ketone bodies improve the learning, memory and mitochondrial activity in a mouse model of AD. These findings provide a foundation for the use of ketones and ketogenic interventions in the treatment and prevention of AD.

In addition to investigating the molecular mechanisms underlying the effects of Aβ42 and ketones, we discovered that Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) is a potential biomarker for AD. PACAP has neurotrophic and neuroprotective properties. It is one of three genes down-regulated in three mouse models of AD. We found that PACAP expression was reduced by as much as 62% in human AD brains. This reduction was correlated with Braak stage (tau protein) and beta-amyloid (Aβ) neuritic plaque burden. We have recently published this result in Neurology. We also observed similar PACAP reduction in 3T×AD transgenic mice. Treatment with PACAP effectively protected cultured neurons against Aβ-induced toxicity by 128 %. PACAP modulates AMPK which in turns stimulates mitochondrial SIRT3 production. Similar to PACAP, SIRT3 was reduced in AD patient and 3T×AD transgenic mice. Treatment with PACAP increased mitochondrial SIRT3 expression. Knocking down SIRT3 compromised the neuroprotective effect of PACAP, and this was reversed by over-expressing SIRT3. Collectively, these results suggest that PACAP-SIRT3 pathway may represent a novel therapeutic strategy for AD.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Using multimodal MRI and cognitive testing to investigate early brain changes in presymptomatic APOE ε4 Carriers. <u>Leslie Baxter, PhD, Richard Caselli, MD, Kewei Chen PhD, Josef Debbins, PhD, Yalin Wang, PhD, Jieping Ye, PhD, Corriane Rogalsky, PhD, Vishar Barisha, PhD.</u> Barrow Neurological Institute, Mayo Clinic Arizona, Banner Alzheimer's Institute, Arizona State University.

<u>**Project Description**</u>: This is a multi-institution, multi-disciplinary collaboration between Barrow Neurological Institute (BNI), Mayo Clinic-Arizona (MCA), Banner Alzheimer's Institute (BAI), and Arizona State University (ASU). By harnessing the strengths of all of the institutions, we are examining early brain changes in preclinical individuals to discover the mechanisms of brain change associated with increased genetic risk of Alzheimer's Disease (AD) and develop new ways to gauge therapeutic change. This project was designed to investigate at-risk participants in order to examine very early changes that can occur before the typical age of onset of AD. We also have partnered with ASU and BAI collaborators to investigate imaging methodology that will capture subtle changes in brain integrity. We are specifically interested in the relationship between aging and potential early changes of AD as observed in a wide age-range of APOE e4 carriers compared to noncarriers. We expect regional brain changes in the APOE carriers in the regions critical for memory functioning, including mesial temporal and posterior cingulate while normal aging changes may occur in frontal regions, following a more anterior to posterior gradient. On a group level, APOE carriers are expected to show decreased brain integrity compared to noncarriers that differ from the normal aging pattern, signaling an underlying increased risk of Alzheimer's Disease in the APOE carrier group. We also aim to examine the relationship between cognitive measures and regional brain changes, in carriers and non-carriers.

2013-2014 Progress: We currently have baseline MRI data from 94 well-characterized, cognitively normal participants, and 51 of these participants at a second time point. At our baseline scan, we have found interesting evidence that even within when still cognitively intact, APOE e4 carriers show changes in several aspects of brain integrity. Our initial baseline data found differences in entorhinal cortex thickness in APOE ε4 carriers in 30-50 year olds, but not in older individuals. In order to better address whether the findings that the older APOE e4 carriers do not show the expected structural differences in entorhinal or mesial temporal regions, we are currently scanning approximately 16 additional individuals, half carriers, who are over the age of 70 and still cognitively normal. These individuals may represent genetically at risk individuals who are maintaining good cognitive functioning. We are currently examining the relationship between longitudinal brain changes and cognitive functioning in the APOE cohort, and longitudinal changes in the smaller sample. We are also collaborating with Dr. Yalin Wang and Dr. Jieping Ye in the Computer Sciences Department at ASU on several projects aimed at utilizing new methodology in brain imaging research. For example, with Dr. Wang's tensor-based morphometry methodology, we are correlating cognitive functioning with morphometry to see if we can better distinguish subtle temporal lobe changes that may not be apparent with currently used methodologies. Dr. Ye is using a moving window, sparse coding approach on data from an fMRI encoding task to determine dynamic changes in regional activity during encoding. Our preliminary analyses indicate that patients with MCI engage more fronto-frontal connections in addition to fronto-temporal connections to perform this task compared to age-matched controls. We also have new collaborations with ASU Speech and Hearing colleagues Drs. Rogalsky and Berisha to investigate memory and language changing in aging using machine learning algorhythms; we will be submitting for additional funding this summer.

Project Progress Reports

Mayo Clinic Arizona

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Normal and Pathological Aging (Preclinical Alzheimer's Disease). <u>Richard J. Caselli, MD</u>. Mayo Clinic Arizona, Arizona Alzheimer's Consortium.

<u>**Project Description:**</u> 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 consortium including brain imaging studies at BAI (Reiman) and BNI (Baxter), genetic studies at TGen (Huentleman), epigenetic studies at BSHRI (Coleman), and our NIA-Alzheimer's Disease Core Center (incorporating the UDS into this cohort).

<u>**Specific Aims:**</u>
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

<u>**Background and Significance:**</u> 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. Our work to date has helped to differentiate normal from pathological aging, thus facilitating a new era of preclinical research with intervention trials scheduled to begin in 2014. This in turn has led to two new themes that will guide future research:
1. The extension of preclinical testing into the clinical domain and how genetic predisposition and biomarker evidence of presymptomatic stage disease should be managed with regard to disclosure and intervention
2. The expansion of precision medicine and its application to Alzheimer's disease beyond single gene-defined risk that includes whole exome/genome, epigenetics, and the microbiome.

<u>**Preliminary Data:**</u> 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 706 individuals including 409 APOE e4 noncarriers, 215 e4 heterozygotes,

and 82 e4 homozygotes. Of these, 566 have completed two or more epochs of testing, providing data for longitudinal studies. Through December 2013, 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 (on the AVLT memory test) aging trajectories for each of 3 APOE genotypes (Caselli RJ et al. New Engl J Med 2009), and subsequently on all remaining cognitive domains (multiple tests) (Caselli RJ et al, Alz Dem 2013) 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 (Caselli RJ et al. Neurology. 2011) and preclinical amyloid deposition (Caselli RJ et al, Neurology 2011) 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 (Caselli et al, Alz Dem 2012).   In addition to continuing our ongoing 2012-2013 goals described in last year's progress report, we have completed or are nearing the completion of all of our 2013-2014 goals including:

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 (data presented and manuscript under review)

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 submitted for the Alzheimer Association International Conference)

3. do traditional neuropsychological tests or newer computerized cognitive assessment tools correlate better with neuroimaging-derived AD biomarkers? (abstract submitted for the Alzheimer Association International Conference)

4. Complete our 2012 goal of 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.

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, DNA, and frozen viable lymphocytes.   Immortalized cell lines are established for those undergoing brain imaging (collaborative study with Dr. Eric Reiman). Neuropsychological (and related) testing is performed every 2 years under age 80 and annually over age 80. Individuals developing MCI or AD are trolled 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. Extending our survey of public attitudes regarding preclinical genetic and biomarker testing for Alzheimer's disease to members of our Arizona cohort and to identify personal traits that correlate with attitudes and envisioned reactions (e.g., consideration of suicide)

2. Complete our study comparing 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. (This will have implications regarding the relative stage of disease clinical MCI patients are assumed to have as they are included in experimental trials as "early stage" when in fact they may be at a later stage than previously realized)

3. Complete our analysis of computerized cognitive assessment tools to determine whether they correlate better with neuroimaging-derived AD biomarkers than traditional neuropsychological tests, or whether reaction times might be earlier indicators of decline than actual scores?

4. Complete our goal of whole genome and epigenetic analyses of unexpectedly young onset AD patients (and controls)

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Predicting Cognitive Decline in Cognitively Normal Individuals. <u>Cynthia M. Stonnnington, MD</u>. Mayo Clinic Arizona, Arizona Alzheimer's Consortium.

<u>**Project Description**</u>: 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.

<u>**Specific Aims**</u>:
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.

<u>**Background and Significance**</u>: 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.

<u>**Preliminary Data**</u>.
1. From a total of 139 ADNI participants who were diagnosed as MCI and had baseline FDG PET and MRI imagning 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 database 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.

   From our longitudinal APOE database 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.

3. From our longitudinal APOE database, 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 Aβ burden in comparison to nondecliners (see: Stonnington CM, Chen K, Lee W, Locke DE, Dueck AC, Liu X, Roontiva A, Fleisher AS, Caselli RJ, Reiman EM. Fibrillar amyloid correlates of preclinical cognitive decline. Alzheimers Dement. 2013 Apr 11. [Epub ahead of print] PMID:23583233. DOI:10.1016/j.jalz.2013.01.009.)
   .

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 Aβ 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.

Progress report:
1. Completed AIMS 1-3 and part a of AIM 4. Will be completing part b of AIM 4 by May, 2014 in collaboration with Jieping Ye (expertise with machine learning methods) and Yalin Wang (expertise in advanced imaging processing methods) at ASU.
2. Platform presentation at AAIC, July 2013:
   Chen K, Stonnington CM, Ayutyanont N, Reschke C, Thiyyagura P, Protas H, Liu X, Roontiva A, Parks SA, Bauer R, Lee W, Fleisher AS, Reiman EM. Baseline FDG PET and volumetric MRI predicts Alzheimer's disease conversion from mild cognitive impairment: An ADNI study. Alzheimer's Association International Conference, Boston, MA. 2013 Jul 17.

3. Poster presentation at the 9th Congress of the International Neuropsychiatric Association meeting, September 25-27, 2013:
Stonnington CM, Chen K, Ayutyanont N, Reschke C, Thiyyagura P, Protas H, Liu X, Roontiva A, Parks SA, Bauer R, Lee W, Fleisher AS, Reiman EM. Combined Baseline Neuroimaging and Cognitive Tests in Patientswith Mild Cognitive Impairment Predict Conversion to Alzheimer's Disease: An ADNI Study.
4. Enrolled 27 subjects (and 5 more scheduled) in study, entitled The Cognitive Effects of Lorazepam in Healthy Older Individuals with TOMM40 Variable-length Polymorphisms.

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APOE Genotypes, Brain-Derived Neurotropic Factor (BDNF), and Cognitive Function Among Hispanics in Phoenix, Arizona. <u>Yonas E. Geda, MD, MSc</u>. Mayo Clinic Arizona, Arizona Alzheimer's Consortium.

Project Description: The Center for Individualized Medicine of the Mayo Clinic has funded Dr. Lawrence J. Mandarino and colleagues in order to establish a health registry of self-identified Hispanics. This registry builds upon the well-established rapport and working relationships that Dr. Mandarino has established with the Latino community in Phoenix, AZ. The recruitment of study participants will start as of June 1, 2013. The plan is to recruit 500 Hispanics per year. In 4 years' time, ~2,000 study participants will be recruited. Dr. Yonas E. Geda and colleagues will establish an ancillary study in which they will investigate APOE, brain-derived neurotropic factor (BDNF), and cognitive function among Hispanics in Phoenix, AZ.

The overarching goal of the project is to recruit 500 cognitively normal, self-identified Hispanic subjects aged 40-90 years. We will conduct a one-time blood draw for APOE genotyping and BDNF. Participants will undergo cognitive assessment by using the CogState. The CogState is a computerized cognitive evaluation that is not dependent on culture and language. CogState is brief (15-20 minutes); requires minimal administrative oversight; has a web-based platform; has high face validity; and is easy to understand, even for non-English speakers and people with little computer experience. CogState has essentially no practice effects after initial familiarization.

Specific Aims:
1) To conduct APOE genotyping in order to characterize the relative risk of developing Alzheimer's disease among Hispanics.
2) To determine serum BDNF and conduct BDNF genotyping among Hispanics.
3) To measure executive function, learning, and recall by using CogState.
4) To determine the frequency and distribution of demographic variables, i.e., age, sex, socioeconomic status.

Background and Significance: Arizona investigators have made substantial contributions to the field of aging by identifying subjects that are at increased risk of developing Alzheimer's disease by virtue of their APOE status (Caselli RJ et al., New Engl J Med 2009). The Arizona team is also one of the first to report the neuroimaging changes (brain PET scan changes) in phenotypically normal persons with either 3/4 or 4/4 genotype (Reiman et al., New Engl J Med 1996). This work was primarily based on a Caucasian sample. In the proposed study, we will expand our contribution to the field by enrolling 500 Hispanics into the study of aging and pre-mild cognitive impairment state. Furthermore, we will also build on our expertise in lifestyle factors and aging (Geda et al., Arch Neurol 2010) in order to investigate potential biological molecules that are implicated in neurotropic activity in the brain.

Preliminary Data:
1) Between 2009 and 2011, two co-investigators on this application (Dr. Mandarino and Dr. Gabriel Shaibi) collaborated with stakeholders in the Latino community of Phoenix, AZ. Their goal was 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. Following an extensive effort, they were able to recruit 700 study participants aged 7-85 years. As part of their study, they administered a survey on physical exercise. At the same time, they also biobanked plasma, DNA, RNA, and immortalized lymphoblastoid cell lines. To date, we have completed the assay of the serum BDNF on biospecimens collected from the 357 Hispanic study participants. We also completed the SNP genotyping of the BDNF gene. Sequencing of the BDNF gene is pending.

2) Sanger sequencing of BDNF gene from the Latino cohort.

   a. A summer research student (Sara Dawit, a medical student from the University of Kansas School of Medicine) led the project on Sanger sequencing of the BDNF gene. The resultant abstract from her work is accepted for presentation at the 2014 annual meeting of the American Academy of Neurology. Additionally, Sara has won a prestigious award given to 10 medical students by the American Academy of Neurology. The details of the project are as follows:

   We obtained blood samples from 357 Latinos (234 females). The mean (SD) age was 41.7 (8.3) and 41.5 (9.4) years for men and women, respectively. Participants included self-identified Latino persons recruited between 2009 and 2011 for a cardiometabolic disease study. Informed consent for future DNA research was obtained. Participants underwent extensive medical evaluation, including a self-administered survey on physical activity. The mean (SD) BMI for those who reported physical exercise was 29.5 (4.9), and for those who did not report exercise was 31.9 (7.5). In order to determine whether previously identified polymorphisms associated with disease were also carried in the genomes of our population, we conducted Sanger sequencing of three targeted exon regions of the BDNF gene. Custom python scripts were developed to convert raw sequencing reads and quality metrics to trimmed reads which were then aligned to the BDNF reference sequence using the (BWA) package. Polymorphisms were identified and characterized using IGV.

   A known SNP (rs2353512) associated with addiction and neuropsychiatric morbidity was found in our sample. Although our sample was overweight or obese, we did not find a well-known polymorphism associated with obesity (Val66Met [G->A/C->T rs6265]). No variations between sequence and reference were observed in region 2 (aln 136-582) or region 3 (aln 25-223).

Table 1
Hispanic Study Participants: Descriptive Statistics by Sex

Variable	Male (N = 123)	Female (N = 234)	*P* Value
Age (Years)	41.9 ± 9.2	41.7 ± 8.7	0.9
BMI (kg/m²)	29.4 ± 6.2	31.1 ± 6.2	0.02
Self-Reported Regular Exercise (Yes/No)	81/42	118/116	0.006
Data presented as mean ± SD.			

Experimental Designs and Methods: We will assemble a cohort of 500 adult Hispanics. We will collect blood specimens in order to conduct APOE genotyping. We will store the blood samples in order to create a resource. We will bank the blood including serum, plasma, and DNA and then send DNA to the lab of Dr. Rosa Rodemaker in order to determine APOE genotyping. We will determine serum BDNF level.

Proposed One-Year and Long-Term Outcomes:
1) To get IRB approval in order to conduct APOE genotyping of Hispanics.

2) To investigate the association between APOE genotypes (3/4 or4/4 versus others) and cognitive function.

3) To analyze the serum BDNF assay and examine its correlation with physical exercise data among Hispanics in Phoenix, AZ.

4) To characterize the BDNF genotype and explore whether the BDNF gene mediates the association between serum BDNF and physical activity.

5) val66met SNP polymorphism is the most widely investigated SNP. We will conduct SNP genotyping of the BDNF gene.

6) To conduct sequencing of the BDNF gene.

7) To investigate the association between APOE genotype and neuropsychological function as measured by CogState.

8) To investigate the association between BDNF and neuropsychological function as measured by CogState.

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Arizona Alzheimer's Disease Center Biorepository for Plasma and Serum. <u>Richard Caselli, MD, Geoffrey Ahern, MD, PhD, Leslie Baxter, PhD, Steven Rapcsak, MD, Marwan Sabbagh, MD, Roy Yaari, MD</u>. Mayo Clinic Arizona, University Medical Center, Barrow Neurological Institute, Banner Sun Health Research Institute, Banner Alzheimer Institute, Arizona Alzheimer's Consortium.

Project Description: In response to the recommendations of our external scientific advisory committee members, we are establishing a longitudinal biorepository of plasma and serum samples that will serve as a core resource for investigators supporting biomarker discovery and related research.

Specific Aims:
A. To create a biobank of serum and plasma of this cohort.
B. To function as a core resource collaboratively supporting other investigators

Background and Significance: The Clinical Core of the Arizona Alzheimer's Disease Center (ADC) is a consortium of five recruitment sites that function as a standardized unit under a single Clinical Core Director. The Clinical Core maintains a target of 500 participants at all stages of the aging-dementia spectrum including 200 normal controls, 100 patients with mild cognitive impairment (MCI), and 200 with Alzheimer's disease (AD) and other forms of degenerative dementia. Embedded within these diagnostic categories are defined Latino and Native American cohorts. In addressing goal 5 of our strategic aims (articulated in our original grant proposal), "to procure and maintain biospecimens for clinical and translational research including but not limited to DNA, brain and related tissues," we now seek to create a shared biorepository resource, housed at Mayo Clinic Arizona (MCA) where there exists such a facility currently serving such a function for MCA researchers to provide a new service to our research participants that is the storage of plasma and serum.

Progress to date: This project began collecting its first samples in May 2013 and is intended to continue longitudinally. For the brief funding period 119 unique patients contributed 938 plasma and serum samples. The biorepository has already been utilized by an ADC investigator, Dr. Jiong Shi to who samples were sent on 93 patients for his Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) biomarker study.

Experimental Designs and Methods: New participants (and existing participants for whom this will be a new procedure) will be drawn for a total of 20 mls. Tubes will be one lavender EDTA (10 mls), one Red top (10 mls) will be drawn/collected at the respective sites, shipped to MCA and prepped for Plasma/Serum storage at the MCA Biorepository. MCA will incur the costs for this service that will be charged back to the MCA portion of the ADC budget. Requests for biospecimen utilization and sharing will be managed by the MCA biorepository as an ongoing service. Participants will be consented at their respective sites by the local investigators. Samples will be collected only once at this time with the possibility of increasing sample frequency to annual visits pending future funding arrangements. Requests for sample use will be adjudicated by the Clinical Core site PI's who meet on alternate weeks at the Diagnostic Consensus Conference, the forum in which scientific decisions of this nature (typically requests for clinical/cognitive data or DNA until this point) are handled.

Proposed One-Year and Long-Term Outcomes: Our proposed one year goal is to collect serum and plasma samples on all existing members of the cohort as they return for their scheduled annual evaluations.

ARIZONA ALZHEIMER'S CONSORTIUM
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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.

Project Progress Reports

Midwestern University

ARIZONA ALZHEIMER'S CONSORTIUM
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Modes and mechanisms for the early detection, tracking, and treatment of Alzheimer's disease and associated disorders. J. Valla PhD; G. Jentarra PhD; J. Kaufman PhD; M. Olsen PhD; D. Jones PhD; P. Potter PhD; J. Vallejo PhD. Midwestern University, Arizona Alzheimer's Consortium.

<u>Funded Project Descriptions</u>:
1) Functional Assays for the Early Diagnosis of Neurodegenerative Disease (Valla)
 <u>Specific Aims</u>: To finalize and clinically test a promising early diagnostic blood test for AD.
 <u>Background and Significance</u>: The ongoing research in our laboratory and others has indicated that mitochondrial functional declines specific to AD brain can be detected in peripheral cells, including and especially platelets. Our work has also indicated that these same changes can be detected in platelets from subjects who have been diagnosed with MCI.
 <u>Preliminary Data and Plan</u>: In the last year, we have approx tripled the velocity of our reaction, which is key to the detection of the expected functional deficit. We have also founded a company for the development and commercialization of this patent-pending assay, using a grant from the Arizona Commerce Authority and ASU SkySong, a technology incubator. We will initiate a pilot clinical trial (N=10 AD, N=10 aged control) utilizing ADCC subjects to demonstrate proof-of-concept.
 <u>Proposed One-Year and Long-Term Outcomes</u>: Complete pilot clinical trial this year, investigate SBIR/STTR mechanism for potential submission, initiate larger (N=~300) clinical trial across multiple subject classes for sensitivity and specificity data.
 <u>Year End Progress Summary</u>: Preliminary clinical trial is ongoing; no results as yet.

2) Mechanisms of AD Risk in Young-Adult APOE4 Carriers (Valla, Jentarra, Vallejo)
 <u>Specific Aims</u>: Multi-investigator collaboration to determine the foundation of the AD risk associated with the APOE4 genotype, utilizing postmortem human tissue and mouse models.
 <u>Background and Significance</u>: Previous published work in the Consortium has demonstrated that young-adult APOE4 carriers show dysfunction in energy metabolism in AD-vulnerable areas of the cortex. The underlying mechanism is unknown but would be a promising target.
 <u>Preliminary Data and Plan</u>: Previous work has shown that young-adult APOE4 carriers demonstrate significant reductions in energy metabolism in posterior cingulate cortex. This decrease was most prominent in the outermost lamina (Layers I-III) of the cortex, a pattern similar to that seen in AD. Protein expression, gene expression, and various subcellular and membrane structures will be assessed, particularly in regard to energy metabolism.
 <u>Proposed One-Year and Long-Term Outcomes</u>: We anticipate completing most data collection this summer and early fall and preparing a larger NIH grant proposal (R01 or R15) for follow-on work in these mechanisms for the October or February deadlines.
 <u>Year End Progress Summary</u>: Preliminary data generated showing considerable disruption of brain energy metabolism in young adult APOE4 carriers; data supported a new R01 proposal submitted to NIA February 2014. Two manuscripts are in the planning stages.

3) A combined CLARITY/MRI investigation in the mouse (Kaufman, Jentarra)
 <u>Specific Aims</u>: Establish the CLARITY protocol for mouse brain, ensure that chemical optimization of tissue for MRI will not interfere with CLARITY and subsequent IHC, and localize known markers using CLARITY-based IHC and register these data with MRI.

Background and Significance: CLARITY is a pioneering advance in obtaining high-resolution histological data while maintaining large-scale anatomical topography. Since CLARITY has not been applied to AD tissue, there is a significant opportunity to validate this new method in AD.

Preliminary Data and Plan: This new method for clearing and staining intact, whole brains was only recently introduced, but work here is already underway. A CLARITY system will be custom-built and tested. Both a gadolinium-treated brain as well as an untreated brain will undergo the CLARITY protocol. IHC will be performed on both brains.

Proposed One-Year and Long-Term Outcomes: Our priority is to jump-start a CLARITY-based research program, taking advantage of existing resources at MWU. Subsequently, we will validate the CLARITY procedure in AD models and tissue. This key step will provide critical preliminary data that is both immediately publishable and necessary for obtaining funding for a systematic analysis via a R15 grant mechanism.

Year End Progress Summary: Working with both mice and rats, we have been able to harvest brain tissue, embed the brain in hydrogel, and clear it of lipids to produce a near-transparent tissue-hydrogel matrix. PI also attended a CLARITY workshop held at Stanford University.

4) Synthesis and Evaluation of Novel FTO Inhibitors for the Treatment of Alzheimer's Disease (Olsen)

Specific Aims: To evaluate existing FTO inhibitors in an AD cell assay and to synthesize and evaluate new FTO inhibitors with tailored anti-AD activities.

Background and Significance: FTO is a highly expressed 2-oxoglutarate-utilizing enzyme in the brain involved in the demethylation of RNA N6-methyladenosine (m6A) residues, which are associated with microRNA binding sites. These agents are safe, brain-penetrating, and neuroprotective.

Preliminary Data and Plan: Tetronimide FTO inhibitors have already been synthesized and evaluated for FTO inhibition. One has also been demonstrated to modulate microRNAs. These compounds are the subject of a provisional patent filed (US #61/704,014). A neuroblastoma cell line will be incubated in the presence of amyloid to induce oxidative stress. Cells will be treated with FTO inhibitors, and cellular viability will be monitored. FTO inhibitors that enhance neuroblastoma cell survival will be identified, and potentially advanced to an animal model of AD held by Dr. Shi at Barrow Neurological Institute.

Proposed One-Year and Long-Term Outcomes: We plan a publication describing FTO inhibitors in this AD model in the next year and will propose an NIH R01 to be submitted on Blood Brain Barrier Penetrating Epigenetic Modulators for the Treatment of CNS Disease, targeting epilepsy, stroke and AD.

Year End Progress Summary: R01 submitted with collaborators in Rhode Island (MWU TC $514,625). Two patents were filed in September 2013 regarding the compounds under study and their applications.

5) Muscarinic Receptor Dysfunction in a Human Neuroblastoma Cell Line (Jones, Potter)

Specific Aims: To characterize dysfunction and uncoupling of muscarinic receptor-mediated cell signaling in a human neuroblastoma cell line.

Background and Significance: Although cholinesterase inhibitors alleviate some of the cognitive deficits in AD their effectiveness is limited by two factors: continuing degeneration of cholinergic neurons and uncoupling of muscarinic receptors from G-proteins and cell signaling. New therapeutic strategies can directly target post-synaptic muscarinic receptors.

Preliminary Data and Plan: Previous work has demonstrated that muscarinic receptor dysfunction is positively correlated to the extent of plaque formation and cognitive deficits in AD. Uncoupling of receptors will be assessed by examining displacement curves of an antagonist (3H pirenzepine) by an agonist (oxotremorine-M) in the presence and absence of GppNHp, along with Western blotting and ELISA.

Proposed One-Year and Long-Term Outcomes: We will examine the relationship between muscarinic receptor uncoupling and β-amyloid aggregation, including assessing and treating an AD animal model to decrease uncoupling, signaling dysfunction and cognitive deficits; this will be the focus of a planned R15.

Year End Progress Summary: Findings were subject of a podium presentation at the 2014 Experimental Biology meeting; preliminary data generated was used to support Arizona ADCC Pilot Grant (February 2014): "Characterization of M1 receptor uncoupling in Alzheimer's disease".

Project Progress Reports

Translational Genomics Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Novel biomarker and genetic risk factor identification in Alzheimer's disease. Matthew Huentelman, PhD. Translational Genomics Research Institute, Arizona Alzheimer's Consortium.

Project Description:

Aim 1 – Identify the genetic basis for the clinically rare phenotypes/diseases through exome sequencing. We will receive DNA for each of the described clinical subjects from our collaborators and sequence their exome using NGS technology.

A. DNA isolation and exome sequencing. We will isolate DNA from each collected sample. The biospecimen source of the DNA will vary based on the individual donor. For those living donors it will likely be either saliva or blood-derived. For expired donors it will likely be brain tissue derived. Note that for some of the mentioned donors we have already collected, purified, and assessed DNA samples.

B. Exome sequencing and analysis. We will sequence the exome using the Illumina TruSeq exome capture kit. This kit targets approximately 62Mb of the known human exome. Samples will be sequenced at target coverage of approximately 100X per targeted basepair. Analysis will be performed using available NGS analysis tools. We will prioritize genomic variants based on the frequency of their observation in at least 500 exomes from "control" (non-neurological disease) exome samples in-house at TGen as well versus ~7,000 publicly available "population" control samples. The data from these samples is already in existence and is freely and openly available. We will prioritize variants that are rare and therefore have not been deposited in any public database of common variation (like dbSNP). Finally, variants will be prioritized based on the known biology of each gene variant including impact on protein structure and function.

In this project, we propose to leverage the clinical expertise and experiences of four different clinician scientists from within the Arizona Alzheimer's Institute to identify patients who represent in their clinical experiences rare and potentially uniquely informative individuals for study. These include: (**1**) individuals who are homozygous for the APOE E4 risk factor but who are still cognitively normal over the age of 80 (n=4, the median age at onset for dementia in E4 homozygotes is 70), (**2**) one individual who has a protective APOE genotype of E2/E3 but is currently displaying signs of dementia at age 77 ("gene-mates" of this individual are typically dementia free until age 90), (**3**) one individual with symptoms consistent with frontotemporal dementia that was diagnosed and confirmed postmortem with amyotrophic lateral sclerosis as well, (**4**) four individuals from a family with follows a pattern of inherited late onset Alzheimer's disease (typically early onset Alzheimer's disease follows a familial inheritance), and finally (**5**) six individuals who lived to at least 80 years of age were cognitively normal and upon autopsy exhibited no amyloid plaque deposition in the brain. We will attempt to identify the genetic association with each of these unique phenotypes/diseases in the exome of the sequenced individuals. We will also explore the sequencing of other rare or "exceptional" phenotypes and diseases as they present themselves to the clinical core physicians within the Consortium.

Progress Report: We have completed the exome sequencing of the proposed groups and have actually extended the numbers within each targeted group as follows:

1. **E4 homozygotes over the age of 80 and cognitively normal, n=8 completed exome sequencing.** Analysis has identified potential candidates that are protective and during the next year we plan to explore their effects further.
2. **E2/E3 individuals demonstrating dementia symptoms under the age of 80, n=4 completed exome sequencing.** We also have some compelling candidates in this group and plan to expand the cohort and explore the effects of the candidates during the coming year.
3. **Individuals over 80 years of age who were cognitively normal and demonstrated no amyloid plaques at autopsy, n=12 completed exome sequencing who did not carry an E4 allele and n=2 completed exome sequencing who did carry one E4 allele.** As above we will explore the biology of the top candidates from this project.
4. Within the Colombian family segregating very late onset Alzheimer's disease we have identified a likely causal variant within the superoxide dismutase gene. We are currently modeling the effect of this variant in vitro.
5. The causal variant for the FTD-ALS patient is still elusive. It is important to note that this patient is negative for all known genetic associations for ALS and FTD including the recent c9orf polymorphism. We have also identified another FTD-ALS patient that is negative for all known mutations/variants. This represents a unique opportunity to explore this disease combination.
6. Lastly we have also been recruiting individuals with early onset AD without family history of canonical AD gene mutations. In collaboration with the Mayo Clinic we have identified a patient with a mutation in PSEN1 in this collection. Interestingly the other 4 patients we have analyzed are negative for all mutations in the known genes.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Characterization of Altered DNA methylation in Alzheimer's Disease. <u>Travis Dunckley, PhD</u>. Translational Genomics Research Institute, Arizona Alzheimer's Consortium.

Project Description:
Aim: Determine potential functional consequences of altered DNA methylation in Alzheimer's disease. We have identified regions in the genome of Alzheimer's disease patients with differential DNA methylation profiles compared to matched control individuals and to individuals with Parkinson's disease (PD). DNA methylation is known to regulate the transcription of affected genes. We will assess potential functional significance of the methylation differences that we previously identified by sequencing the RNA from patients diagnosed as either AD, PD, or neurologically normal controls. These patients are the same as those for which DNA methylation analyses were performed. We will apply appropriate statistical comparisons to determine if any methylation changes are associated with differential expression of specific genes or pathways. Statistical correlations of significant methylation differences with specific gene expression differences could provide functional context around altered DNA methylation in AD.

Progress Report: All samples have been sequenced and the quality of the data validated. Statistical analyses are ongoing to identify sites of differential methylation associated with differential gene expression.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

RNA sequencing and validation of expression changes in healthy posterior cingulate astrocytes in Alzheimer's disease. Winnie S. Liang, PhD, Shobana Sekar, Jackie McDonald, Jonathan Adkins, Lori Cuyugan, Jessica Aldrich, Ahmet Kurdoglu, David W. Craig, PhD, Thomas G. Beach, MD, Geidy Serrano, PhD, Eric Reiman, MD. Translational Genomics Research Institute, Banner Sun Health Research Institute, Banner Alzheimer's Institute, Arizona Alzheimer's Consortium.

Background: For our ADCC pilot project, we used laser capture microdissection to isolate healthy ALDH1L1+ astrocytes from the posterior cingulate (PC) of Alzheimer's disease (AD) patients and healthy elderly controls. The premise of this study is to understand the role of posterior cingulate astrocytes in AD pathogenesis given the role of astrocytes in glucose uptake and energy metabolism and the well-described metabolic deficits that characterize specific regions of the AD brain, particularly in the PC and precuneus.

Preliminary Data and Plan: We generated whole transcriptome libraries from each sample and performed paired end RNA sequencing on the Illumina platform. Overall, we collected data from 6 Alzheimer's patients and 8 controls and generated over 2.7 billion reads and 226.9G of Q30 data. Preliminary analysis of data using DEseq indicated that non-coding RNAs and immunity-related genes demonstrated altered expression in AD ($P<0.05$). To improve statistical significance, we plan to increase our group sizes to n=10 per sample group, and thus plan to perform RNA sequencing on an additional 4 AD PC astrocyte samples and 2 control PC astrocyte samples. We plan to re-analyze the entire dataset following the addition of new samples and will subsequently perform validation on significantly altered transcripts ($P<0.05$). Identification and validation of dysregulated transcripts in AD PC astrocytes will lend insight into the potential role of these cells in disease.

Year End Progress Summary: We have completed LCM collection of astrocytes from the additional 6 subjects (4 AD subjects and 2 control subjects), RNAseq library construction, and next generation sequencing of these samples. We have also completed differential expression analysis and are finalizing qPCR validation of selected differentially expressed genes. Overall, we generated over 5.22 billion reads and 295.10G of Q30 sequencing data. Using DESeq2, we identified 226 differentially expressed genes (corrected $P<0.05$). Pathway analysis indicated that the most impacted molecular pathway is immune system response processes. We additionally performed a comparison of APOE4 carriers versus non-carriers and identified 618 differentially expressed genes (corrected $P<0.05$). Pathway analysis indicated that the most impacted pathway is DNA damage processes. We additionally identified dysregulated expression of mitochondrial genes in the APOE analysis to suggest that energy metabolism pathways may be altered in PC astrocytes in APOE4 carriers. We are currently finalizing validations and are working on a manuscript with a targeted submission date of June 2014. We are also exploring the identification of circular RNAs in our data set and are currently working on evaluating approaches to identify these transcripts.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Identify miRNA species that are associated with AD neurodegeneration. Kendall Van Keuren-Jensen, PhD, Kasandra Burgos, PhD, Layla Ghaffari, Ivana Malenica, Amanda Courtright, Ben Rakela, Thomas Beach, MD, PhD. Translational Genomics Research Institute, Banner Sun Health Research Institute, Arizona Alzheimer's Consortium.

Project Description: We will utilize small RNA sequencing [focused on miRNAs] to identify those miRNAs that are differentially expressed between AD, Parkinson's disease, and matched control patients. The inclusion of the PD sample set will allow us to determine the existence of miRNAs that are specific for AD-related neurodegeneration. We will profile both blood and cisternal CSF from postmortem donors using next generation sequencing. Statistical analysis of the data will identify those miRNAs that are associated with AD and highlight those that might be most useful as biomarkers and also potentially indicate which biochemical processes could be examined for AD relevance in targeted drug agent development. We assessed both CSF and serum, as we do not know which biofluid gives the better signal to noise ratio.

Progress: We have completed the sequencing and analysis of miRNA data generated from 69 Alzheimer's patients, 67 Parkinson's patients, and 78 neurologically normal controls. We sequenced one CSF and one serum sample from each subject. The manuscript was recently accepted to PlosOne and will be published soon. The sequencing data will also be available on dbGaP – accession phs000727.v1.p1.

We were able to correlate features of pathology such as tangles, plaques, and Lewy Bodies, along with disease status. CSF had more miRNAs detectable that were significantly different, however serum also had significant miRNAs indicative of disease status. One of the more interesting findings was an increase in serum levels of miR-34c-5p between Parkinson's patients and Parkinson's patients with dementia. This same miRNA was significantly increased in patients with Alzheimer's disease when compared with controls. miR-34c was previously found by Zovoilis et al. to be significantly increased in hippocampus and cortex of patients with Alzheimer's disease. They went on to show that elevation of this miRNA impairs memory consolidation, and when it is knocked down, memory is restored. We received additional funding from the Michael J Fox Foundation to follow this up.

In order to get a better understanding of where and what cell-type the miRNAs are coming from and appearing in CSF and serum, we received cortical tissue from Dr. Beach. We have cut the tissue and have begun using Locked Nucleic Acid hybridization probes to our target miRNAs. We are interested in whether or not we can obtain cell specific information, providing us with greater insight into how miRNA deregulation alters disease course – or if disease alters miRNA expression.

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Project Progress Reports

University of Arizona

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Patient Recruitment and Outreach for Alzheimer's Disease and Related-Disorders. <u>Geoffrey Ahern, MD, PhD, Steve Rapcsak, MD</u>. University of Arizona, Arizona Alzheimer's Consortium.

<u>**Specific Aims**</u>: 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 <u>primary specific aims</u>:

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 areas community with educational information on AD and related disorders and the opportunity to participate in related research, including clinical trials.

<u>**Background and Significance**</u>: 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), 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). 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.

<u>**Experimental Designs and Methods**</u>: Participants for the Arizona ADC will be identified and enrolled in the Clinical Core if they meet standardized criteria for enrollment that includes presentation at a diagnostic consensus conference. New subjects will be included with AD dementia, MCI, and healthy controls. Additionally, patients with early onset AD and frontotemporal lobar dementia spectrum disorders will be enrolled to increase the breadth of patient groups engaged in research as part of the Arizona ADC

Clinical Core. All subjects receive an extensive standardized assessment of cognitive and behavioral functions with the battery of clinical ratings and neuropsychological tests used at all participating clinical core data collections sites. All clinical ratings and neuropsychological test results obtained for enrollees will be entered into a standardized HIPPA compliant Arizona ADC database that will be combined with test results from all participating data collection sites across the Arizona Alzheimer's disease consortium. In addition, clinical data collected from participating subjects will be submitted to the National Alzheimer's Center Consortium (NACC) database to be combined with results of tests from all other NIA ADCs across the United States. As part of our Alzheimer's Disease Center, Drs. Ahern and Rapsak have continued to lead complementary efforts at the UA for the recruitment and longitudinal follow up of patients with MCI, AD, and various other forms of dementia to develop the necessary patient base and infrastructure for conducting therapeutic trials aimed at disease modification and prevention. All southern Arizona study-related activities have continued to be based at the University of Arizona and enrollment of new study participants from the University Medical Center and from satellite clinics in Green Valley, AZ and Northwest Tucson continues to be underway in order to further expand our patient base.

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 will provide a presentation on new directions in the treatment and prevention of AD at the upcoming Annual Conference on Successful Aging (ACoSA), a conference developed and organized by collaborating Arizona ADC 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 year's ACoSA meeting is Successful Aging: Reducing your Risk for Alzheimer's disease.

Progress Report: During the period from 4/1/2013 through 3/30/2014, 40 patients have been (re)evaluated at the UA ADCC. Three patients passed away during this period and their brains were acquired for pathological examination.

Through our continued recruitment efforts, we have increased the number of participants in the Clinical Core. In particular, we have recruited several patients with early onset AD and subjects at risk for AD due to positive family history. We are continuing to work on increasing our recruitment of subjects with FTLD and now have a working relationship with our neuromuscular specialist colleagues who follow FTLD/ALS patients in their clinics. With respect to outreach and education, Dr. Rapcsak has given several community lectures for the Alzheimer's Association and has appeared on Arizona Illustrated on Channel 6 TV in a segment on Alzheimer's Disease. He is also involved in organizing a multi-disciplinary memory disorders clinical program at the Southern Arizona VA Health Care System.

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ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Risk Factors for Brain Aging & Preclinical Alzheimer's Disease. <u>Gene Alexander, PhD, Elizabeth Glisky, PhD, G. Alex Hishaw, MD, Matthew Huentelman, PhD, David Raichlen, PhD, Lee Ryan, PhD, Ted Trouard, PhD</u>. 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 and physical activity. This integrative approach will support efforts to investigate health-related factors, including hypertension and cerebrovascular risk, exercise and physical activity, 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 <u>hypothesis</u> is that the common health risk factors of hypertension and mild TBI, as well as the beneficial effects of exercise/physical activity 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 the brain-based effects of these health factors will be affected by normal genetic variation related to the preclinical risk for AD.

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

<u>Secondary Aims</u>: This study will provide substantial added value by 1) acquiring a battery of neuroimaging scans to advance new multi-modal image analysis methods to detect the earliest effects of preclinical AD, 2) exploring how differences in normal genetic variation related to risk for AD and cognitive decline influence brain aging and cognitive performance in the elderly, 3) <u>developing and submitting new external collaborative grant proposals on brain aging and preclinical AD</u>, 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 [1] 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 [2-4]. 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 [5-6] 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 can often be affected in mild TBI, including disturbances in processing

speed, executive functions, and memory [7-10]. 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 effective 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 long-term aerobic exercise can improve cognition during aging, especially executive function and memory, and can reduce the risk of developing dementia and AD [11]. In older individuals, high levels of physical activity are correlated with increased brain volume, as well as increased functional connectivity needed for efficient cognitive processing [11]. Studies investigating brain structure, function and connectivity in older adults are critically needed to help determine the potential for exercise as an intervention to support healthy brain aging.

Preliminary Data: We previously reported patterns of MRI gray matter volume

associated with healthy aging [12-14] using a multivariate model of regional covariance, the scaled subprofile model (SSM) [15]. We recently found a pattern of gray matter related to APOE □4 in young to early middle aged adults (p<0.0005), suggesting longstanding brain morphological differences related to this genetic risk for AD [16] (Fig. 1). We observed dissociations between cerebral metabolic networks related to APOE □4 and brain aging in a cohort of □4 homozygotes and non-carriers with

Fig. 2. Resting fcMRI in Aging

Fig. 1. SSM VBM of APOE

positron emission tomography [17]. Preliminary results from fcMRI in healthy aging showed greater functional connectivity in frontal brain regions in young-old (ages 50-74) relative to older (ages 75-91) elderly participants (Fig. 2). Using SSM network analysis, we found a pattern of gray matter volume associated with age (p<1e-26), with greater effects of brain aging related to poorer cognitive performance and the presence of hypertension. These findings support the use of MRI to evaluate the effects of health and genetic risk factors for preclinical AD.

Design and Methods: We plan to enroll 30 medically-screened, community-dwelling adults, 65 to 84 years of age, including those with and without well-treated essential hypertension. Elderly subjects will be recruited from Dr. Alexander's Lab and SAHAR. All subjects will be evaluated by Dr. Hishaw to exclude neurological and psychiatric illness or injury and will be assessed for adequacy of blood pressure control over three clinic visits. The subjects will receive neuropsychological tests to evaluate memory, language, executive function, visuospatial abilities, motor skills, and processing speed, as well as a set of computerized tests, developed and implemented by Drs. Ryan, Glisky, and Alexander, to assess specific components of executive function [7,18]. MRI scans will be acquired on a Siemens 3T Skyra system and MRI sequences will be implemented working with Dr. Trouard to evaluate volumes and thickness of gray matter (3D T1), white matter tract integrity (DTI), cerebral micro-hemorrhages (SWI), white matter hyperintensities (FLAIR), cerebral perfusion (ASL), and resting state functional connectivity (fcMRI). Measures of exercise/physical activity will be obtained and supervised by Dr. Raichlen to test their relation to brain imaging and cognitive measures in our sample. In addition, the subjects enrolled in the proposed study will have had DNA stored and genotypes determined by Dr. Huentelman at TGen for common candidate genes known to affect aging and preclinical AD (i.e., APOE [19], FTO [20], BDNF[21], COMT[21], HTR2A[22], KIBRA [23]). Subjects and data from this work will also be leveraged to provide a control sample for a complementary study underway (PI: Hishaw) comparing elderly adults with mild TBI to demographically matched controls using the same cognitive and MRI battery, reflecting a new collaboration with the UMC Trauma Surgery Center.

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 project investigating 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 and other external funding sources. Specifically, this project will provide key data and methodological developments to support pending and planned grant applications by the project investigators, including an NIH application to evaluate the interactive effects of aging and TBI, an NIH R01 proposal to investigate the effects of differences in exercise/physical activity on brain aging and cognitive function, and an NIH R01 application 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 to support the Arizona ADC.

Strengths of this proposal include its focus on: clinically-applied research questions with potential for important benefits for the elderly population in Arizona and nationally; "state-of-the-art" methods in cognition, neuroimaging, and genetics; an innovative, multimodal hypothesis-driven approach; potential outcomes that may help to identify interventions to slow or prevent cognitive decline; and multi-disciplinary AAC collaborations supporting new external grant proposals on the clinical neuroscience of brain aging and preclinical AD.

Year End Progress Summary: During this year, we have continued to implement a number of important methodological developments to support our translational research efforts in studying risk factors for brain aging and cognitive health, including the application of novel multimodal neuroimage analysis methods. In addition, our team of UA ADC investigators for this individual project have been actively involved in the submission of 9 new grant proposals in the past year and have been collectively included as co-authors on 13 manuscripts published, in press, or submitted with methodological developments and research findings in support of this multi-disciplinary effort. Drs. Alexander, Ryan, and Glisky have continued to collect data with their new computerized test battery of executive function for use in our studies of age-related cognitive decline and to evaluate the effects of the aging related health factors such as hypertension. Pilot datasets with this novel cognitive battery have been collected to evaluate the potential of these tests for identifying cognitive profile differences related to healthy aging and risk factors for cognitive decline and a manuscript on this new set of executive function tasks is in preparation.

Using cognitive and neuroimaging methods, we have made great progress in our human aging studies with our continued data collection in progress. A manuscript is in preparation on our findings showing greater functional connectivity in frontal cortex in young elderly compared to older elderly adults (Fitzhugh et al., in preparation; Fig. 2). Preliminary data from associated studies of human hypertension assessed with ambulatory blood pressure monitoring in Dr. Alexander's lab have shown lower levels of cognitive performance related to diminished differences in diural/noctural variation in blood pressure and a manuscript on these findings has been submitted (Haws et al., in revision). A follow up study was performed as part of a successfully defended Master thesis by Kari Haws, a graduate student in Dr. Alexander's lab, to evaluate the brain imaging effects of diurnal/nocturnal blood pressure differences and was presented at the Society for Neuroscience meeting in San Diego, CA. A manuscript of these findings is in preparation. These findings also supported the submission of a new grant proposal to the Arizona

Biomedical Research Commission (ABRC) evaluating the effects of sleep and diurnal blood pressure variation on brain aging and age-related, cognitive decline (PI: Alexander; Co-I: Ryan, Glisky, Raichlen, Hishaw, Bootzin). Dr. Alexander also further developed his ongoing collaboration with colleagues at the University of Miami and Columbia University by applying a novel analytic method to evaluate the link between blood pressure control and microvascular disease-associated regional cerebral atrophy with complementary data from the Northern Manhattan Study (NOMAS). A manuscript from this work is in preparation (Kern et al., in preparation). In addition, in the past year and with encouragement from the NIA, we re-submitted a subproject from our original Program Project Grant application (PI: Alexander; co-PIs: Barnes, Billheimer, Coleman, Huentelman, Ryan, Trouard), as a separate re-formatted R01 application (MPIs: Coleman, Barnes, Alexander). This new R01 submission focuses on the use of epigenetics, neuroimaging, and state of the art behavioral assessment in a novel transgenic rat model of hypertension and is currently pending consideration for funding by the NIA. In addition, Dr. Hishaw (PI) together with Dr. Alexander continues work on the UA Faculty Seed Grant to obtain pilot data to support our plans for an R01 grant submission on TBI and aging. In addition, a NIH R21 grant (PI: Alexander) was submitted to investigate the use of novel imaging and cognitive markers of mild TBI effects in older adults.

To further studies of the effects of exercise as a health factor influencing brain aging, pilot data were collected by Dr. Alexander collaborating with Dr. David Raichlen in Biological Anthropology at the UA to evaluate the effects of endurance training on brain structure, function, and connectivity, as well as on cognition using our new battery of cognitive tests. Analyses for this work are underway and a UA Faculty Seed Grant (PI: Raichlen, co-PI: Alexander) was funded to support plans for submission of an external grant proposal to evaluate aging and exercise fitness. During this time, Drs. Alexander and Raichlen were commissioned this year by the journal *Trends in Neuroscience* to submit an article outlining a novel hypothesis developed from their collaboration on the relation between exercise, the APOE genotype, and the evolution of the human lifespan and this manuscript is now in press (Raichlen and Alexander, in press). Further, this work will support a new NIH R01 grant submission planned for the summer by Drs. Alexander and Raichlen to further investigate the potential of exercise as an intervention for reducing the effects of cognitive aging and the risk for AD. Extending this work to focus on how sleep differences in combination with physical activity impact brain aging and the preclinical risk for AD, Dr. Alexander has developed a collaborative NIH R01 application for submission (PI: Alexander; Co-Is: Raichlen, Ryan, Glisky, Hishaw, Bootzin). In addition, Dr. Alexander was invited to participate as a field center PI for a large collaborative NIA R01 application submitted this year in collaboration with the University of Florida (prime site), University of Miami, and Florida State University to conduct a multi-center clinical trial in response to a NIA RFA for a novel cognitive training paradigm in aging (PI UA Subcontract: Alexander; Co-Is: Trouard, Allen, Kaszniak, Hishaw; MPIs: Cohen, Marsiske) and pilot data from the current project helped to support this multi-center submission.

Members of our ADC research group, including Drs. Alexander, Ryan, Glisky, Raichlen, and Hishaw have also participated in UA efforts for community outreach in the Tucson metro-area and Green Valley to meet with and provide lectures for the general public, as well as for primary care providers, geriatricians, and local neurologists to increase awareness of issues on aging, age-related cognitive changes, Alzheimer's disease, and the ADC research programs. In addition, Drs. Alexander and Ryan continued to spearhead 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. We had our second annual daylong conference in February, 2014 with the topic of "Reducing your risk for Alzheimer's disease". The conference for this year exceeded all expectations including approximately 300 participants with presentations by UA and ASU ADC investigators, including Drs. Alexander, Ryan, Glisky, Hishaw, Ahern, and Coon. Plans for our next year's conference are currently underway.

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ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Cognitive and neural consequences of gradual induction of hypertension in middle age: Potential interaction with body weight loss. Carol A. Barnes, PhD, Gene E. Alexander, PhD, Ted P. Trouard, PhD. University of Arizona, Arizona Alzheimer's Consortium.

Specific Aims: In the previous year, pilot experiments were conducted using a transgenic model of hypertension in the rat, the data from which were included in the submission of one project in a four-project Program Project Grant (Alexander, P.I.). While the entire PPG was not funded, the rat hypertension project received a perfect score, and is currently being considered by the NIA for funding following disaggregation of the full Program Project Grant. If the funds are not forthcoming via this means, then we will submit the project as an R01. In depth analysis of the MRI data obtained from the transgenic hypertension rat model (Alexander) suggests that the body weight loss observed during the 6 week course of induction of hypertension could be a confounding variable for the observed MRI differences noted in the treated versus non-treated transgenic rats. The purpose of the study in the past funding period was to conduct an experiment in which MRI scans (7T scanner, Trouard) and cognitive tests (Barnes) are given before treatment and after treatment (exactly as in the transgenic rat experiment), but the treatment group in this case will be body weight loss over 6 weeks, matched to the weight loss levels experienced by the rats with induced hypertension. Blood pressure will also be monitored over this time period, to duplicate the procedures used in the hypertension induction experiments, in this 'weight loss only' control group.

Background and Significance: Human hypertension typically begins to develop in middle age, and is observed in nearly three quarters of adults by the age of 70 years in the United States. Because of the high prevalence of hypertension in elderly populations, it is important to understand the impact that this precursor to cardiovascular disease has on the brain and cognition. Most models of this condition to date have used young animals, require surgical or pharmacological induction, and the hypertension induced is rapid in onset. Spontaneously hypertense rats have also been studied, but the condition is present at young ages that do not mimic the onset of the most common forms of hypertension in humans. One promising model for hypertension is the inbred transgenic rat (F-344 background) that has the cytochrome P450 promoter (Cyp1a1) inserted to drive the expression of the mouse renin (Ren2) gene. The promoter is activated by dietary addition of the aryl hydrocarbon indole-3-carbinaol (I3C). The ability to regulate gene expression in the Cyp1a1-Ren2 transgenic rat allows dose-controlled rate of development and duration of hypertension (Mitchell et al., J Renin-Angiotension-Aldosterone Systems, 2006). Thus we have used these rats at ages equivalent to mid-50s in human years, to elevate blood pressure over a 6 week period (longest interval tested) in the past funding period, and we have added the control weight loss experiment in the present funding period. This animal model has the potential to help us understand the impact of the interacting effects of age and hypertension on brain, body and cognitive outcomes.

Preliminary Data and Plan: In addition to the blood pressure and end organ damage observed in the I3C-treated rats, the hypertense animals were slower to learn the spatial location of an escape platform on the Morris swim task (a task that is sensitive to medial temporal lobe function) but not on cued versions of the task (dependent on higher order visual cortices) compared to control animals without gene induction (i.e., no I3C). This suggests that direct manipulation of cardiovascular integrity can result in significant impairments in cognition in the middle-aged rat (Hoang et al., SfN Abstract, 2011). Furthermore, analysis of MRI scans revealed a regional brain network pattern of gray matter loss following the gradual induction of hypertension in these transgenic rats (Fitzhugh et al., SfN Abstract, 2012). Because body weight was

not controlled in those experiments, the study in the present funding period was developed to answer whether body weight change alone, over the same time period, can produce the changes in behavior or biological measures that we obtained in the transgenic rats.

Proposed One-Year and Long-Term Outcomes: The data obtained will allow us to publish the data collected in the transgenic rats, and to know that this model is still viable should we receive funding for this project from the NIA.

Year-End Progress Summary: Over the past year we conducted a control experiment designed to answer the question of whether weight loss, by itself, has any effect on grey matter volume or on blood pressure. F344 rats (the same strain as the Cyp1a1-Ren2 transgenic rats) were slowly food deprived to attempt to mimic the weight loss that occurred when the transgenic rats in our hypertension experiment were exposed to dietary addition of aryl hydrocarbon indole-3-carbinaol (I3C) to drive the expression of the mouse renin (Ren-2) gene, which slowly rendered these animals hypertense. Blood pressure was significantly elevated with this dietary treatment, and the diet may have been less palatable than normal chow. While we are not able to specify why the animals lost weight, we clearly observed that they did slowly show weight loss over the course of the 6 week treatment period.

The Barnes lab took blood pressures and monitored weight following food restriction in the nontransgenic F344 over the same 6 week period as the transgenic rats were exposed to the I3C diet. MRIs were taken before initiation of food restriction and after the end of this treatment period, exactly as had been done for the transgenic rats. The Barnes lab transferred the rats for MRIs to the Trouard lab (twice per rat), and all scans were successfully completed in the 7T scanner. The results in terms of weight loss were comparable between the hypertension and control weight loss groups (~100gm loss over the 6 weeks), but blood pressure was stable for food restricted rats at ~180 mmHg throughout that time. The MRI data are available for analysis by the Alexander lab. Once that is complete, we can put all components of the experiment together to add to the manuscript that will be published on both the transgenic and control data.

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The influence of hypertension on the compensation response in older adults. <u>Lee Ryan, PhD, Ted Trouard, PhD, Gene Alexander, PhD</u>. University of Arizona, Arizona Alzheimer's Consortium.

<u>Specific Aims:</u> Studies with functional magnetic resonance imaging (fMRI) have shown that some older adults compensate for cognitive difficulties by recruiting prefrontal cortical regions, a finding referred to as the compensation response (CR). The present study will investigate the influence of hypertension on the CR in older adults (ages 60 to 75), using an object-in-context source monitoring task with three levels of difficulty. Source monitoring judgments rely heavily on frontal executive functions (Glisky & Kong; 2008). In this study we propose to examine the following three aims:

Aim 1) To examine how the CR, as measured by fMRI, relates to individual differences in performance as task difficulty increases parametrically.
Aim 2) To examine how three components of executive function ability – updating, switching, and inhibiting – affect the expression of the CR.
Aim 3) To determine how hypertension and executive function abilities independently affect the expression of the CR.

In addition to fMRI, measures of perfusion and vascular responsivity will be obtained to better understand the influence of hypertension on the BOLD signal separate from task-related activation.

<u>Background and Significance</u>: Recent MRI studies have shown that some, but not all, older adults compensate for cognitive difficulties by recruiting brain regions, most notably prefrontal cortex, that may mitigate age-related changes in brain structure and function (Park and Reuter-Lorenz, 2009). Little is known, however, about the factors that determine who can or cannot engage such compensatory mechanisms. This study will consider two important sources of individual differences in older adults, hypertension and executive function abilities.

Essential hypertension is a common condition associated with multiple changes in the vascular system that affects over 55% of Americans. There is considerable evidence that vascular pathology has a significant effect on age-related cognitive functions, particularly executive functioning, and is associated with greater age-related brain volume declines (De Leeuw et al., 2001; Raz et al., 2003; den Heijer et al., 2005). While treatment for hypertension reduces cognitive effects it does not remove them altogether (Raz et al., 2005).

Executive functions are often impaired in older adults relative to young adults, including processes such as updating and monitoring information, switching between tasks, and inhibiting prepotent responses (reviewed in Reuter-Lorenz et al., 2005). Working memory tasks are particularly reliant on all of these abilities (Vaughan & Giovanelli, 2010). Park and Reuter-Lorenz (2009) have suggested that the executive functioning capacity of an individual predicts the degree to which they are capable of engaging in compensation as they experience age-related changes in brain structure and function. However, this hypothesis has yet to be tested empirically.

Jennings et al. (2008) compared hypertensive and normotensive older adults, ages 59 to 68, on a working memory task with two levels of difficulty while undergoing PET scanning. While normotensive subjects showed the typical CR increases in frontal activation during the more difficult condition, hypertensive individuals showed *decreased* activation in dorsolateral prefrontal areas as a function of increasing task

difficulty, with *increases* in parietal and hippocampal regions. Jennings et al. (2008) suggest that hypertension undermines the ability of individuals to engage frontal lobe regions. However, it is equally plausible that hypertension influences the CR primarily because of its negative impact on executive functions. One possibility is that individual differences in executive function abilities may determine expression of the CR, regardless of hypertension status. Alternatively, hypertensive individuals may express a pattern of CR that is qualitatively different than the CR that is expressed by normotensive individuals, even those with poor executive function abilities.

The present study will investigate the degree to which executive functions determine engagement of frontal lobe regions in hypertensive and normotensive individuals. During fMRI scanning, participants will be given a working memory task that requires source monitoring for objects in contexts. Because both working memory and source judgments rely heavily on updating and monitoring for optimal performance, we expect that this specific ability will be most predictive of who can engage in compensation in this particular task, regardless of hypertension status.

Experimental Design and Methods:

Participants. 45 adults, ages 60-75, will complete medical history questionnaires and blood pressure measurements. Exclusion criteria will include neurological conditions, current psychiatric conditions, cognitive impairments suggestive of dementia, and incompatibility with MRI (e.g., metal implants, claustrophobia). Approximately half the participants included in the study will be hypertensive. These participants will be matched on age, education, and gender to normotensive participants. An individual is considered hypertensive if they have a prior history of hypertension and are currently taking anti-hypertension medication. Participants with blood pressure measurements outside the normal range (BP > 140/90) who are not currently medicated or who may be hypotensive (diastolic < 70) will be excluded.

Methods. Participants will undergo neuropsychological testing to assess areas of cognitive functioning, including updating, switching, and inhibitory executive functions. Based on prior research in our laboratory (Ryan et al., 2011), we anticipate that a range of executive functions will be observed within both the hypertensive and normotensive groups. During fMRI, participants will be tested on a working memory task that requires source judgments. Participants see a series of everyday objects in typical contexts (e.g., a vase on a table). Afterwards, the same objects are presented in two different contexts, side-by-side, and the subject must decide where the object was seen originally. The task includes three levels of difficulty created by varying the item set size on each study-test trial from 2 to 4, to 6, in order to observe increases in activation in response to increasing task difficulty. Structural volumetric MRI, 3D ASL perfusion, diffusion tensor, and hypercapnia challenge (breath-hold) BOLD imaging (Thomason et al., 2007; Handwerker, 2007) will also be obtained, in order to assist in interpreting task-related BOLD signal differences related to hypertension.

Dr. Ryan will be responsible for recruitment and neuropsychological testing of the participants, and will oversee acquisition of MRI scans. She will also be responsible for the analysis of the fMRI and diffusion data, and will conduct analyses that test the combined impact of hypertension and executive functioning on expression of the CR. Dr. Trouard will assist with the implementation, acquisition and analysis of the ASL perfusion and hypercapnia challenge data, as well as provide quality assurance for all MR imaging. Dr. Alexander will provide expertise in multi-modal image analysis. All three investigators will participate in the preparation of manuscripts, presentations, and grants.

Year and Long-Term Outcomes: Based on experience from the PI's prior research projects, we anticipate that data collection will be completed well within the one-year project timeline. The study,

combined with prior publications from Drs. Ryan's and Alexander's laboratories on this topic, will provide a strong basis for an RO1 grant. The PI intends to submit a grant on this topic during the year following completion of the study.

Year End Progress Summary: We are on track to complete acquisition of fMRI data from 40 participants by June 30th. Because the cost of scans increased after writing this proposal, funding is available for 40 participants rather than the 45 scans previously proposed. To date, we have obtained full neuropsychological testing and fMRI data from approximately half the participants. Preliminary fMRI data were presented at the Cognitive Aging Conference in Atlanta (April, 2014).

In addition to fMRI data, we are collecting vascular responsivity measures using breath-hold BOLD imaging. This imaging protocol was piloted in the fall on three older adults. Breath-hold data will be shared with Dr. Stephen Wilson in the department of Speech Language and Hearing Sciences in order to expand the dataset that he is collecting as part of his AAC pilot project on vascular responsivity in older adults.

In addition to the fMRI data, we have obtained behavioral data from an additional 41 older adults on the six executive function tasks that assess updating, switching, and inhibiting, bringing the total participant count between three laboratories (Drs. Alexander, Glisky, and Ryan) to over 150. This summer, we plan to analyze the collective data set which will be published as normative data for the six tests. The tests will be available on the UA Psychology website for use by other research sites.

After completion of project data collection in June, data will be analyzed in July and August. We will begin working on publications during the summer months as well, as well as an RO1 submission on hypertension and cognitive functioning.

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2013-2014 Scientific Progress Report

Age-related changes in PRC and BA38 influence perceptual processing. <u>Paige E. Scalf, Mary A. Peterson.</u> University of Arizona, Arizona Alzheimer's Consortium

Specific Aims: The ability to differentially represent familiar and novel objects is critical to an animal's survival. "Represent" in this context refers not only to the ability to maintain information about previously encountered exemplars of an object, but also to the ability to use that information to appropriately modulate the perceptual processing of an object currently in view. Aging appears to compromise this capacity; older rats, monkeys and humans have difficulty both remembering and discriminating familiar from novel complex objects that share many features but differ in how those features are arranged. Both lesion and neuroimaging studies indicate that the perirhinal cortex (PRC) of the medial temporal lobe (MTL) plays a critical role in this type of familiarity/novelty judgment. The PRC may be structurally and functionally compromised by normal aging; its deterioration, however, may be only partially responsible for age-related decrements in familiarity/novelty discrimination. Using a paradigm we recently developed, we observed that the temporal pole (BA38) as well as the PRC plays a role in familiarity/novelty judgments in young observers. In particular we found that the PRC is recruited in such tasks when stimuli are presented in the right visual field (RVF) whereas BA38 is recruited when the stimuli are presented in the left visual field (LVF). Furthermore, our pilot research with this paradigm suggests that both the PRC and BA38 modulate lower-level extrastriate activation to familiar features according to whether the configuration in which they appear is familiar or novel. Thus, outputs from the PRC and BA38 appear to modulate regions of the brain specialized for perceptual processing, consistent with the hypothesis that these MTL areas play a role in perception. Here we propose to use RVF and LVF presentations of novel and familiar stimuli to separately probe responses of the PRC and BA38 while young and older adults discriminate between familiar and novel stimuli. The results will elucidate the extent to which age-related declines in BA38 and the PRC contribute to age-related decrements in complex object discrimination. BA38 is widely identified as being structurally compromised in both healthy aging and Alzheimer's disease. Yet until now the functional consequences of BA38 deterioration for object perception have received little attention. The proposed experiment will also investigate the consequences of aging to familiarity-related modulation of lower-level perceptual processing by both BA38 and the PRC. By examining the coupling between activation in these MTL areas and activation in extrastriate cortex the proposed experiment will provide valuable insight into how aging compromises the ability to discriminate familiar versus novel objects.

This experiment has the following specific aims.

Specific Aim #1. Investigate whether age-related changes in PRC function alter its ability to mediate familiarity-related modulations of extrastriate perceptual processes.

Specific Aim #2. Investigate whether age-related changes in temporal pole function alter its ability to mediate familiarity-related modulations of extrastriate perceptual processes.

B. Significance, Innovation, Approach

Significance: Normal aging appears to compromise the ability to use and maintain information about familiar objects. This is particularly true when the configuration of an object's features is critical to its identification. Relative to their younger counterparts, older rats, monkeys and humans have difficulty learning or comparing objects that have a large number of overlapping features, and so must be distinguished on the basis of those features' configurations rather than on their simple presence or absence (Ryan et al., 2012; Presty et al., 1987; Insel et al., 2008; Raz et al., 1998; Bachevalier, 1993; Moss et al.,

1988; de Lima et al., 2005; Burke et al., 2010; Burke et al., 2011). For example, monkeys asked to learn which of two LEGO-constructions is associated with a food reward show age-related deficits in leaning only when the constructions' features overlap by 86% or more (Burke et al., 2011). Furthermore, older animals require more trials to learn which of two highly similar objects will be rewarded, presumably because they have difficulty perceiving their subtle differences. Once these differences have been learned, however, older animals have no difficulty remembering those objects (Burke et al., 2012). Becoming familiar with the perceptual aspects of an object changes the animals' perception of it, making it easier to discriminate from a highly similar object. The dissociation between learning the difference between the object pairs and maintaining that information once learned suggests that there is a critical interaction between the knowledge we maintain about an object and our ability to perceive that object when it is present. Work with older humans demonstrates that they too have difficulty discriminating between unfamiliar objects with a large number of overlapping features (Ryan et al., 2012). Aging appears to impair the process of representing the perceptual information that will render two highly similar objects discriminable.

Maintaining and supporting representations of both previously encountered and currently present complex visual is known to be critically dependent the perirhinal cortex (PRC) (see Ranganath & Ritchey, 2012). Lesions to the monkey and rat PRC impair performance on the delayed non-match to sample task that requires that monkeys recognize a novel object as such in order to receive a food reward (e.g., Mishkin & Delacour, 1975). More recent data suggests that damage to the human PRC impairs the ability to discriminate between two physically present items if that comparison requires feature configurations (rather than simple features) to be processed (Barense et al., 2005; 2007).
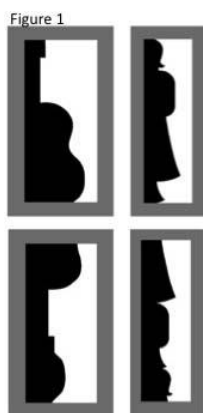
Previous experience with objects informs not only our ability to identify familiar and novel objects as such; it also informs processes that segregate visual scenes into separate objects. Participants asked to report whether they perceive a border as the contour of an object lying on its left or right side are more likely to perceive an object on a given side when a portion of a familiar configuration is depicted there (e.g., a guitar, a woman; see top row in Fig. 1) compared to when the same parts are rearranged to form a novel configuration (see bottom row in Fig. 1; Peterson, et al., 1991; Peterson & Gibson, 1991; 1994a & b). (For sample data see Fig. 2, Controls) Note that these effects of *configural familiarity* occur implicitly (Peterson et al., 1991; 2000). Thus, familiarity with objects influences even fundamental processes of visual perception.

Patients with MTL damage that extended into the PRC showed substantially and significantly smaller effects of configural familiarity on scene segregation than control observers without brain damage or with damage to the hippocampus (HC) only (compare patients MTL2 and MTL 3 in Fig. 2 to Controls and HC cases). This pattern of results was obtained because MTL patients were more likely than control observers to perceive objects on the side of a border where familiar parts were arranged in novel configurations; and they were slightly less likely than control observers to perceive objects on the side of a border where a familiar configuration lay. Thus, damage to the PRC of the MTL allows effects of part familiarity to be observed, whereas when the PRC is intact, effects of configural familiarity but not part familiarity are evident. To account for these results, Barense et al. (2012) proposed that when the PRC is intact, it modulates low-level part familiarity responses as a function of the familiarity or novelty of the configuration they comprise.

Figure 3
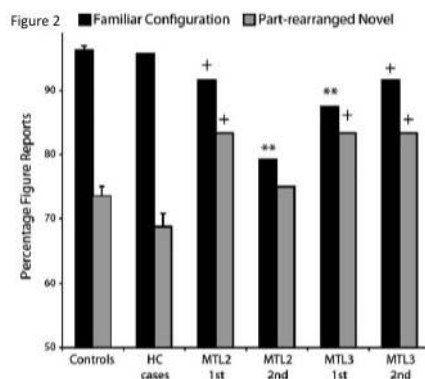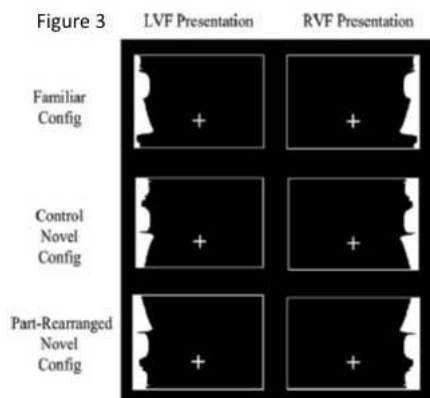
Peterson, et al. (2012) reported functional neuroimaging data confirming Barense et al.'s proposal, at least for stimuli presented in the RVF. Their participants viewed stimuli in the RVF, 4° from fixation, and judged whether they depicted real world or novel objects (Fig. 3, right column). Peterson et al. observed concomitant changes in bilateral PRC and left hemisphere (LH) V2 activation as a function of whether an ensemble of familiar parts formed a familiar or a novel configuration (first and third rows of Fig. 3). We note that the individual parts were the correct size to fall within the receptive fields of V2 cells (2° at 4° eccentricity), whereas the configurations were too large (6°) to do so. Hence, changes in V2 responsiveness must be modulated by a brain region with cells sensitive to the entire configuration. PRC may plausibly play this role because its activation covaries with that of LH V2. We note that the PRC did not respond differently stimuli in the different conditions when they were presented in the LVF, although BA38 did (see below).

One question explored in the proposed experiment is, "How does normal aging affect PRC structure and function, including its modulation of low-level visual responses?" Both rats (Rapp et al., 2002) and humans (Insausti et al., 1998A; Insausti et al., 1998B); seem to show preserved PRC structure throughout the lifespan, but PRC function seems to decline with age. For example, cellular function appears to be compromised in the older rat PRC cortex (Liu et al., 2009; Rushaidhi et al., 2012). Relative to younger adults, older human adults are impaired at visually discriminating objects when they are composed of highly similar features, whereas their ability to discriminate objects composed of different features remains intact (Ryan et al., 2012). Furthermore, PRC activation, which in young adults is greater for the former than the latter condition fails to show equivalent increases in older adults (Ryan et al., 2012).

It is not known whether aging impairs the PRC's ability to modulate low-level part familiarity responses as a function of the familiarity or novelty of the configuration they comprise. We initially assessed this by a post hoc examination of the performance of older and younger participants across a number of experiments with somewhat different conditions: Both older and younger subjects were much more likely to perceive the central border as the contour of an object *on the right* when that region portrayed a familiar configuration rather than a novel configuration made of spatially rearranged familiar parts (Fig. 4). Thus, the object location reports of older subjects *for regions on the right of a central border* are not like those of PRC-damaged patients, suggesting that aging may not impair the PRC's role in this perceptual task. In the current experiment, we will use functional neuroimaging as a more sensitive measure of whether aging alters the ability of PRC to modulate extrastriate function.
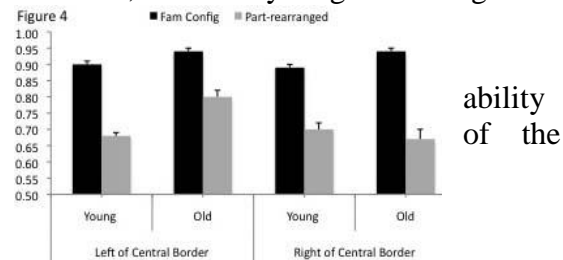
Another question explored in the proposed experiment is, "How does normal aging affect BA38 structure and function, including its modulation of low-level visual responses?" This question arises from the study by Peterson et al. (2012): When they asked participants to make a real-world/novelty judgments regarding stimuli presented to the LVF (see left column of Fig. 3) they found that activation in bilateral BA38 varied with the familiarity/novelty of the ensemble of familiar parts, whereas activation in the PRC was unaffected by the familiarity of the ensemble of familiar parts. Moreover, BA38 activation co-varied with activation in right hemisphere (RH) V2. We note that BA38 is silent with respect to the familiarity of part ensembles that are presented to the RVF (Peterson et al., 2012).

We are not the first to observe BA38 involvement in object perception and memory (see Ranganath & Ritchey, 2012). Neurons in BA38 respond selectively to complex visual stimuli (Nakamura et al., 1994) and are active during the delay period of visual working memory tasks (Nakamura et al., 1995). Cooling of BA38 prevents monkeys from learning to discriminate among new visual objects, but does not prevent them discriminating previously learned visual objects (Horel et al., 1984). In humans,

BA38 is selectively activated by the requirement to discriminate familiar and unfamiliar faces and scenes (Nakamura et al., 2000). Damage to BA38 typically results in semantic dementia, a syndrome usually associated with a loss of abstract categorical knowledge about real world items (for a review, see Hodges & Patterson, 2007). Semantic dementia is not typically thought of as affecting perception; our data, however, suggests that the temporal pole may play a role in encoding or maintaining information about objects and modulating processing in lower-level visual regions (Peterson et al., 2012; cf., Barense, et al, 2010).

It is well established that aging reduces the structural integrity of BA38 (Insausti et al., 1998; Allen et al., 2005; Fjell, et al., 2009; Taki et al., 2012) and its resting metabolic rate (Eberling et al., 1995). Furthermore, perfusion rates of the temporal pole regions predict visuospatial processing deficits in healthy older adults, adults with mild cognitive impairment, and adults with Alzheimer's disease (Alegret et al., 2010). Our pilot analysis shown in Figure 4 suggests that aging may reduce the influence of configural familiarity on the perceptual processing of information presented *to the left of a central border* Older participants were more likely to perceive novel configurations comprising familiar parts as objects when they lay on the left rather than the right side of the central border. As a consequence, the effect of configural familiarity was reduced on the left side of the border compared to the right side of the border. For younger participants effects of configural familiarity were equal on the two side of the border. These data may indicate that when perceptual information is presented to the LVF, and thus likely to recruit BA38 that in turn modulates perceptual processing, older adults show deficits. As such, these results would be consistent with the hypothesis that the contributions of BA38 to visual perception are compromised in normal aging. The proposed experiment uses fMRI to directly address this hypothesis.

Innovation: The available data suggest that both the function of PRC and the structure and function of the temporal pole may be compromised by normal aging. In the experiment proposed below, we will independently investigate how normal aging influences each of these structures' ability to modulate low-level perceptual processing carried out by V2. Our paradigm uses lateralized stimulus presentation to separately investigate the influence of the PRC and BA38 on the perceptual processing of familiar and novel configurations (Peterson et al., 2012). RVF presentation activates LH V2 and bilateral PRC; these regions' activation covaries as a function of the configural familiarity of the presented familiar parts. In contrast, LVF presentation activates RH V2 and bilateral BA38; these regions' activation also covaries as a function of the configural familiarity of the familiar parts presented. This paradigm is the only one of which we are aware that allows the PRC and BA38 to be independently recruited during the processing of visual stimuli.

Approach: The methods used will be similar to those described in Peterson et al. (2012). Briefly, we will examine BOLD signal in both PRC and V2, a visual area whose small receptive fields (approximately 2° at 4° eccentricity in the upper visual field; Kastner et al., 2001; Bles et al., 2006; Scalf & Beck, 2010) are likely to encompass the constituent parts, but not the configural wholes, of our lateralized stimuli (see Figure 3). Employing lateralized visual stimuli allows us to accurately locate their representations within V2, which can be separately analyzed. Our previous results with young adults suggest that when stimuli are presented to the RVF, we should observe differential activation in LH V2 and in bilateral PRC for Familiar Configurations and familiar parts in Part-Rearranged Novel Configurations. When stimuli are presented to the LVF, we should observe differential activation in RH V2 and bilateral BA38 to Familiar Configurations and Part-Rearranged Novel Configurations. For older adults, however, we might expect a somewhat different pattern of results; specifically, we will look for evidence that PRC and the temporal pole are less able to modulate the V2 response to the familiar parts in the appropriate hemisphere as a function of the familiarity/novelty of the configuration. We will also acquire high-resolution anatomical data that will support voxel-based morphometry (VBM) analysis (see Erickson et al., 2007 for methodology) of age-related changes in the structural integrity of the PRC and BA38. We anticipate that

reductions in the structural integrity of these regions will correlate with the sensitivity of V2 to the familiarity of configurations of familiar parts.

Subjects: Data from 12 younger adults (ages 18-30) and 12 older adults (ages 60-75) who are right handed and have normal or corrected-to-normal vision will be analyzed in the proposed studies. Equal numbers of females and males will be studied. We note that the data reported in Peterson et al., (2012) were collected on a different MRI (3T Signa, GE) using different acquisition parameters (spiral in-out) than will be used for this experiment (3T Skyra, Siemens, EPI acquisition); that data from young adults, therefore, cannot be compared to the older adult data we will collect in this experiment. We must therefore reacquire young adult data for the current experiment. University of Arizona student participants will be recruited via an experiment management system website. We will also ask University permission to recruit participants through flyers posted on the University of Arizona campus or use email advertisements sent to various listservs. Older adult member of the community will be recruited through flyers posted on the campus, in local newspapers, at local YMCA community centers or through email announcements sent to local listservs and posted on Craig's List. Older participants' cognitive health will be assessed using the Modified Mini-Mental State Exam (3MS; McDowell, et al., 1977); participants with scores lower than 51 will not be admitted to the study (e.g. Scalf et al., 2007). Exclusionary criteria also include any prior history of neurological disorder, traumatic brain injury associated with an alteration of consciousness, serious medical illness that could result in cognitive impairments, and drug or alcohol abuse. Prior to fMRI scanning, participants will undergo eye-movement training in which they will be trained to maintain fixation throughout the task described below (See Peterson et al., 2012; Scalf & Beck, 2010).

fMRI Data Acquisition: We will acquire data using a Skyra 3 Tesla Scanner equipped for parallel echo planar imaging (EPI; Munich, Germany). Data will be collected using a 32-channel head coil. Stimuli will be presented using back projection. We will collect echo planer images (EPI) from the entire brain using a gradient echo sequence (TR=3 s; TE = 25 ms; flip angle = 90º; field of view = 190 mm X 190 mm; voxel size 3mm X 3mm X 3mm, 1mm gap) in 48 ascending coronal slices. Standard phasic retinotopy data collection and analysis will also be performed on each participant (e.g. Sereno et al., 1995). We will include a block-design localizer run that allows us to identify the region within LH and RH V2 in each participant that responds to the stimulated regions in the RVF and LVF. In addition, a high resolution anatomical scan (MPRAGE; 1mm isotropic) will be acquired to both assist in registering images to standard space and to submit to the VBM analysis described above.

Stimuli: The stimuli will be the same as those used by Peterson et al.,(2012; See Fig. 3). We used stimuli of three configuration types (24 stimuli per type). The *Familiar Configuration* silhouettes (Fig. 3, top row) portray portions of objects whose configurations and parts were likely to be familiar to participants (i.e. a standing woman, a guitar). The *Part-Rearranged Novel Configuration* silhouettes (Fig. 3, bottom row) are created by dividing the *Familiar Configurations* into parts at minima of curvature and spatially rearranging the parts to form a novel configuration. The *Control Novel Configuration* silhouettes (Fig. 3, middle row) are created by inverting the *Part-Rearranged Novel Configuration* silhouettes. Each stimulus will be presented twice, once in the RVF and once in the LVF.

Experimental Design and Equipment: Because our number of stimuli is small, we will employ a slow-event related design. Each trial will begin with a 10-second fixation period; one second before stimulus onset, the fixation cross will brighten from grey to white to alert the participant to the upcoming stimulus. Participants will maintain fixation on this white cross during a 2-second presentation of the stimulus. The phrase, "Real World?" will then appear at fixation for 2 seconds, prompting the participant to indicate via a button press whether the silhouette depicted a real world or novel object. Participants will perform six runs of 24 trials each. In each run, half of the images will appear in the RVF and half will appear in the

LVF. Images from each of the three configuration types will appear 8 times in each run. Images will appear once and only once in each visual field throughout the experiment.

Data Analysis: Data will be submitted to multivariate analysis using FEAT 5.98. Our model will include configuration type and visual field of presentation as regressors of interest (6 total regressors). Trials with incorrect real World vs. Novel responses will be included in the model as events of no interest.

Visual Cortex: We will use activation identified in the localizer run to identify RH and LH V2. We will use Featquery (Smith et al., 2004) to extract and compare the mean parameter estimates for the *Familiar Configuration* and the *Part-Rearranged Novel Configuration* conditions from the ROI's in V2. We will also examine the data collected from older adults to determine whether the structural integrity of the PRC predicts the sensitivity of LH V2 to configural familiarity, and the structural integrity of BA38 predicts the sensitivity of RH V2 to configural familiarity.

Temporal Lobe Structure: We will examine BOLD signal in BA38 and BA35 (the PRC) from the Talairach-to- MNI-conversion digital atlas (Lancaster et al., 2000) to identify regions of interest (ROIs) in the MTL. We will use easythresh (within FEAT 5.98) to identity clusters of voxels ($Z > 2.3$) that show sensitivity to configural familiarity whose extent is greater than would be predicted by random variation in activation ($p < .05$).

Timeline: We anticipate that subject recruitment and data collection will require eight months to complete. Data analysis should require an additional 3 months to complete. This data should provide a strong background from which to prepare an application to the National Institute on Aging for R01 funding. This application will focus on how-age related changes in structure and function of the anterior and middle temporal lobe regions affect the perceptual processing of older adults. We will be particularly interested in determining the consequence of age-related changes in the ventral temporal system to the ability of extrastriate system to support active perceptual processing. Our anticipated submission date is 6/5/2014. We anticipate submitting a publication reporting these data immediately after this date.

Progress Summary: The Siemens 3T Skrya MRI and Eye-Link 1000 eye-tracker at the University of Arizona Biomedical Research lab were installed and operational in August of 2013. In the fall of 2013, we implemented our experiment on the software at the new center, and collected pilot data that allowed us to optimize our parameters for our new imaging and eye-tracking systems. We began collecting data from young adult participants. We also established contact with the older adult population in Tucson. In January of 2014, we began collecting data from older adult participants. We currently have collected data from 16 young adult participants (4 pilot) and 5 older adults participants, have scheduled data collection for 3 more older adults and are actively recruiting our final participants. Data analysis is ongoing and is speeded by the acquisition of a new analysis machine funded by the grant from the AAAC. We anticipate data collection and analysis to be completed by June 30th of 2014.

ARIZONA ALZHEIMER'S CONSORTIUM
2013-2014 Scientific Progress Report

Enhanced Delivery of Neurotherapeutics via FUS, MRI and SPECT. Ted Trouard, PhD, Lars Furenlid, PhD, Terry Matsunaga, PhD, Russ Witte, PhD, Marek Romanowski, PhD. University of Arizona, Arizona Alzheimer's Consortium.

Summary: The overall goal of this project is to develop minimally invasive techniques for efficiently delivering drugs to the brain using magnetic resonance guided focused ultrasound (MRgFUS). Foundational proof of principle experiments have been carried out over the last decade that demonstrate the ability of MRgFUS to safely and temporarily open the blood brain barrier (BBB) and allow delivery of pharmaceuticals that do not normally cross the BBB.

Specific Aim 1: Optimize the MRgFUS technique for opening the blood brain barrier in laboratory mice. Mr. Mike Valdez, a PhD candidate in the Biomedical Engineering GIDP, will interface a new, MRI-compatible FUS instrument to the current 7T small animal imaging instrument.

Specific Aim 2: Manufacture novel microbubble (μB) liposome drug delivery agents. Novel μB-liposome complexes will be developed based on recently described methods. Liposomes loaded with Gd-DTPA and fluorescent labels will be generated and conjugated to μBs. In vitro tests will be carried out to demonstrate the release of liposome contents with the application of FUS. In vivo tests will be carried out in mice that demonstrate the effectiveness of this novel nanoparticle for specific delivery of the contents of the liposome to the brain.

Specific Aim 3: Image the distribution of drugs delivered by the methods developed in Aims 1 and 2. Small animal SPECT experiments will be carried out in conjunction with MRgFUS BBB opening and delivery of pertechnetate to assess BBB opening. Small regions of BBB will be opened in the midbrain of mice using the techniques developed in Aims 1 and 2. Opening will be verified with contrast-enhanced MRI. pertechnetate will then be injected and the brains of mice will be imaged with FaCT (FastSPECT II and CT) imager in the Center for Gamma Ray Imaging.

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) [1]. Unless significant advancements are made to safely deliver drugs to the brain, drug development for neurological disease will remain limited [2]. This is true for increasingly prevalent neurological disorders such as Alzheimer's disease and Parkinson's disease [3]. While there have been several techniques proposed to circumvent this problem, there has been limited success. Intraventricular infusion is a poor method of delivering drugs to the brain not only because it requires skull penetration, but also because drugs are rapidly cleared by the CSF and diffusion of drugs into tissue is slow [4]. Chemical disruption of the BBB can cause chronic neuropathologic sequelae [5] and vascular damage [6].

Relatively recently, MRgFUS methods have been demonstrated that use ultrasound energy in the presence of microbubble (μB) contrast agent to temporarily open the BBB [7,8]. The ultrasound causes intravascular μBs to cavitate, creating a mechanical force that temporarily disrupts the tight junctions of the endothelial cells that make up the BBB, making it permeable to larger molecules. MRgFUS techniques have been pioneered by a handful of research groups who have carried out important foundational work. As mentioned previously, significant work remains to be done to translate this into a clinically viable drug delivery option. Importantly, non-invasive ways to validate the delivery of therapeutics to the brain need to be developed. Assessment of BBB opening to MRI contrast agents (e.g.

Magnevist) is relatively straight forward as permeability of the BBB to Gd-DTPA results in an increased signal in the brain parenchyma on a T1-weighted image. While this is a useful step in assessing the effects of FUS on the blood brain barrier, it does not directly measure anything about the movement of actual drugs into the brain tissue. If possible, it would be desirable to know the kinetics and spatial distribution of the actual drugs into the brain.

Proposed One-Year and Long-Term Outcomes: The μB-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. Using the data obtained in this pilot project, grants will be submitted to the NIH, Ara Parseghian Medical Research Foundation. We are currently talking with investigators in the area of Parkinson's and Alzheimer's Diseases. Additional grants will also be submitted to foundations relevant to specific neurological disorders, e.g. the Michael J Fox Foundation.

Year End Progress Summary: Substantial progress has been made in each of the Specific Aims.
Aim 1: The MRgFUS technique has been developed by Michael Valdez to the point where safe BBB in mice can be achieved consistently. Experiments to date are carried out on the bench, where BBB opening is confirmed after the MRgFUS has been applied. The apparatus for being able to carry out the experiments while inside the magnet is being designed and assembled.
Aim 2: We have successfully generated liposome-conjugated μBs. Fluorescence microscopy has been used to verify the conjugation of fluorescein-loaded liposomes to our perfluorocarbon gas microbubbles. Remaining experiments will evaluate the ability to deliver the contents of the liposomes to the BBB with the MFgFUS technique.
Aim 3: Studies have been carried out using the FaCT/FastSPECT II instrument after BBB opening to assess level of BBB opening to radiolabeled compounds.

ARIZONA ALZHEIMER'S CONSORTIUM
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Calibrating blood oxygen level-dependent (BOLD) functional MRI by mapping venous anatomy and cerebro-vascular reactivity. Stephen M. Wilson, Ph.D. University of Arizona, Arizona Alzheimer's Consortium.

Specific Aims: The aim of this project is to develop a procedure to calibrate blood oxygen level-dependent (BOLD) functional MRI (fMRI) to account for important vascular factors, in order to obtain functional images that more closely reflect neural sources.

Our first specific aim is to identify draining veins and quantify voxel-wise cerebro-vascular reactivity (CVR), i.e. the capacity of blood vessels to dilate. We will use susceptibility-weighted imaging (SWI) and echo-planar imaging (EPI) to identify draining veins. Algorithms will be developed to derive maps of veins from these images. We will use a hypercapnia task (breath-holding) with fMRI to quantify voxel-wise CVR.

Our second specific aim is to calibrate BOLD fMRI data using this information about individual venous anatomy and voxel-wise CVR maps. Signal from veins will be masked out since it is not spatially specific, and parenchymal signal will be adjusted and expressed relative to local CVR.

This research will facilitate studies that aim to compare the neural substrates of cognitive processing between groups differing in age, neurological status, and/or cerebrovascular status, and studies concerned with precise localization of cognitive processes.

Background and Significance: Functional MRI is widely used to investigate the neural basis of cognitive, sensory, motor, social, affective and linguistic processes. Almost all studies rely on BOLD T2*-weighted signal as an index of neural processing, assuming a standard hemodynamic response function (HRF). Yet it is becoming increasingly clear that there are substantial differences between individuals in CVR, and hence there are differences in the amplitude, shape and time-course of the HRF[1]. In particular, there are differences in HRF as a function of age and various neurological diseases, which complicates the investigation of the effects of age and/or neurological diseases on the neural substrates of cognitive processes[2,3]. Even within a single individual, different tissue types and different brain regions show highly significant differences in HRF, for example, the BOLD response is much greater in draining veins than in gray matter, which is an impediment to precise spatial localization[4,5].

Preliminary Data: We studied 4 college-aged participants using fMRI. Data from a representative participant are shown. Veins appeared dark on susceptibility-weighted imaging (SWI) (**a**), and were successfully identified using an algorithm that searched for voxels that were darker than their neighbors (**b**). Veins were similarly identified on echo-planar imaging (EPI) (**c,d**). Most veins

a
Susceptibility-weighted imaging (SWI)

b

c
Echo-planar imaging (EPI)

d
Likelihood of vein
50   %   100

e

f
Breath-hold signal change
1%   10%

g
Grey matter segmentation

h
13.8-second breath-hold
Signal change (%)
Time past onset of breath-hold (s)
-4.6 0 4.6 9.2 13.8 18.4 23.0 27.6 32.2 36.8

i

j

k

were identified in both modalities (e.g. white arrowheads), whereas some were identified only in one modality (e.g. black arrowhead).

The breath-holding task to induce hypercapnia is shown in (**e**). The yellow ball moves along a sine wave, cueing participants to breathe in and out, then stays low to cue a breath-hold (right-hand side of image). Breath-holding resulted in a characteristic BOLD response localized primarily to gray matter and draining veins (**f**). The correspondence with gray matter can be seen by comparing (**f**) to the segmented gray matter (**g**). The BOLD response in gray matter is shown in gray for each participant and in black for the average of the 4 participants (**h**).

The algorithm for calibrating BOLD fMRI produced promising results. A typical vein is shown in (**i**), uncorrected functional activation data (narrative comprehension) in (**j**) and corrected activation data in (**k**). Note that the vein resulted in artifactual activation that has been successfully removed in the calibrated image.

Experimental Designs and Methods: We will study 8 participants aged 60-80 on a Siemens Skyra 3 Tesla scanner. We will acquire T1-MPRAGE, SWI, breath-hold fMRI, and narrative comprehension fMRI. The SWI and breath-hold fMRI images will be processed to obtain images of veins and CVR maps. These will be used to calibrate the narrative fMRI data. We anticipate greater cerebrovascular variability in the older cohort compared to the younger participants who we already scanned. We hypothesize that individuals' language regions will appear more similar to one another after calibration, since much of the variability is cerebrovascular rather than neural in origin.

Proposed One-Year and Long-Term Outcomes: The data obtained from this proposed project are expected to result in a publication, since no previous studies have collected the complete range of multimodal images that we believe are necessary to calibrate the BOLD signal. The findings will also serve as preliminary data in several grants from my own lab and potentially other labs (e.g. Beeson, Ryan, Alexander) that study aging populations or patients with cerebrovascular abnormalities (e.g. stroke) with fMRI.

Progress report: The overall goal of this project is to develop a procedure to calibrate blood oxygen level-dependent (BOLD) functional MRI (fMRI) to account for important vascular factors, in order to obtain functional images that more closely reflect neural sources.
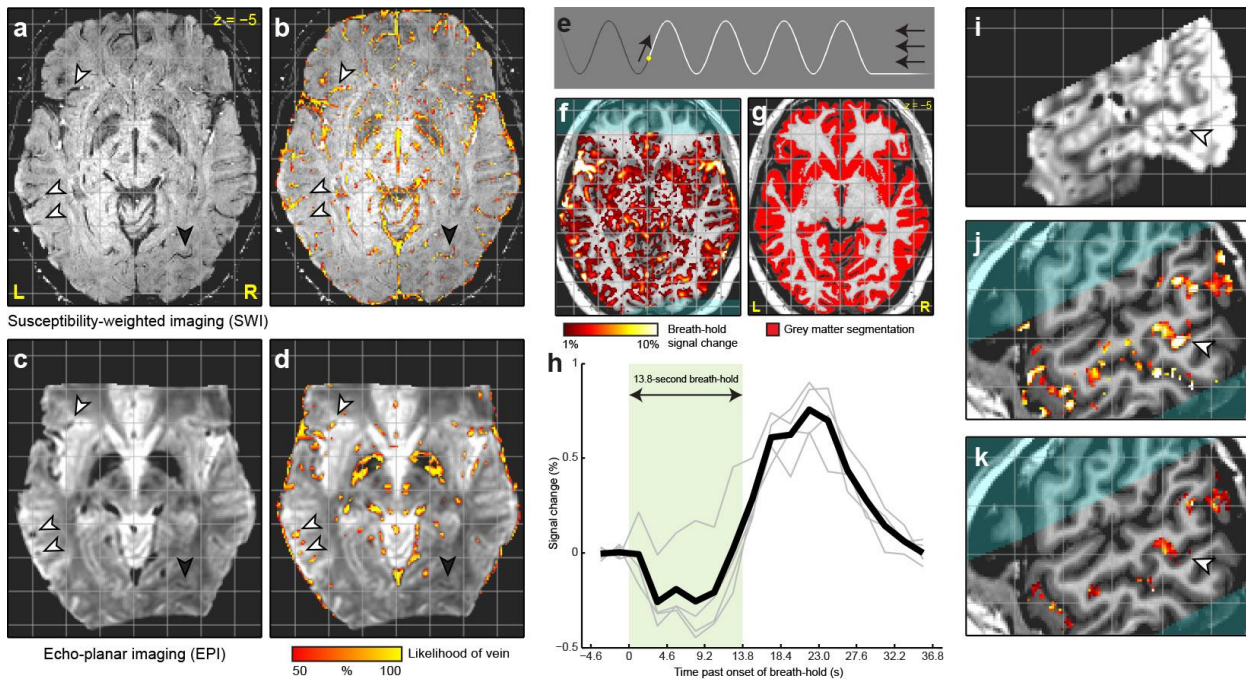
Our first specific aim is to identify draining veins and quantify voxel-wise cerebro-vascular reactivity, i.e. the capacity of blood vessels to dilate. We have succeeded in identifying draining veins using a combination of susceptibility-weighted imaging and echo-planar imaging (Wilson, 2014). We developed an algorithm to derive maps of veins from these images (Wilson, 2014). We have also succeded in quantifying voxel-wise cerebro-vascular reactivity using a hypercapnia task (breath-holding) (Wilson, 2014).

Our second specific aim is to calibrate BOLD fMRI data using this information about individual venous anatomy and voxel-wise cerebro-vascular reactivity maps. We have described a procedure for calibrating BOLD fMRI data using this vascular information, and shown how it allows a more precise localization of language regions (Wilson, 2014).

The published study (Wilson, 2014) describes results obtained in younger adults. Recruitment and scanning of older adults is ongoing, and we anticipate completing the collection and analysis of data from eight old adults as described in the proposal, by the end of the study period.

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2014 Publications and Manuscripts

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Yin J, Turner GH, Coons SW, Maalouf M, Reiman EM, Shi J. Association of amyloid burden, brain atrophy and memory deficits in aged Apolipoprotein ε4 Mice. Current Alzheimer Research 2014 (In print).

Current and Pending Grants

Current Grants

Ahern, Geoffrey (co-Investigator), Reiman, Eric (PI)   2012-2017
P30 AG19610-01 $15,755 Annual DC
NIA
Alzheimer's Disease Core Center – UAHSC Clinical Core

Ahern, Geoffrey (PI)   2013
Protocol # BAN2401-G000-201 $107,194/patient
Eisai
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.

Ahern, Geoffrey (PI)   2013
Protocol # H8A-MC-LZAX $32,863/patient
Lilly Pharmaceuticals
Effect of Passive Immunization on the Progression of Mild Alzheimer's Disease: Solanezumab (LY2062430) versus Placebo

Ahern, Geoffrey (PI)   2013
Protocol # EVP-6124-025 $27,944/patient
EnVivo Pharmaceuticals
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

Ahern, Geoffrey (PI)   2013
Protocol # 019-00 $37,069/patient
Merck Sharp & Dohme
A Phase III, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Clinical Trial to Study the Efficacy and Safety of MK-8931 (SCH 900931) in Subjects with Amnestic Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal AD).

Alexander, Gene (PI)   4/1/07-8/31/14 (NCE)
R01 AG025526 $360,713 Annual DC
NIA
Neuroanatomical Substrates of Aging & Cognitive Decline.

Alexander, Gene (PI)   07/01/13-06/30/14
ADHS14-052577 $92,575 Annual DC
State of Arizona, DHS
Risk Factors for Brain Aging and Cognitive Health.

Alexander, Gene (co-PI), Raichlen, David (PI)   06/01/12 – 6/30/14
University of Arizona Faculty Seed Grant $10,000 TC
Aerobic Exercise and the Evolution of Human Longevity

Barnes, Carol (PI)   07/01/09 – 06/30/14
5 R37 AG012609-20 $184,347 Annual DC
National Institute on Aging
Cell Assemblies, Pattern Completion and the Aging Brain

Barnes, Carol (PI)   05/01/10 – 04/30/15
5 R01 AG003376-29 (Barnes) $561,856 Annual DC
National Institute on Aging
Neurobehavioral Relations in Senescent Hippocampus

Barnes, Carol (co-PI)   09/01/10 – 07/31/15
5 R44 AG035446-04 $63,629 Annual DC
National Institute on Aging
Whole-brain fluorescence and brightfield imaging at single-cell level

Barnes, Carol (co-PI)   7/1/11 – 06/30/16
5 P30 AG019610-13 $12,611 Annual DC
National Institute on Aging
Arizona Alzheimer's Disease Core Center

Barnes, Carol (co-PI)   07/1/13 – 06/30/14
ADHS14-052577 $26,513 Annual DC
State of Arizona, DHS
Cognitive and neural consequences of gradual induction of hypertension in middle age: Potential
interaction with body weight loss

Hishaw, G. Alex (PI), Alexander, Gene (co-PI)   06/01/12 – 06/30/14
University of Arizona Faculty Seed Grant $9,935 TC
Effects of Mild Traumatic Brain Injury on the Aging Brain

Rapcsak, Steven (UA Site PI), Reiman, Eric (PI)   07/01/11 – 06/30/16
1 P30 AG019610 $69,216 Annual DC
NIH
Arizona Alzheimer's Disease Core Center - UA Clinical Core

Rapcsak, Steven (co-Investigator), Beeson, Pelagie (PI)   2/1/11-1-31-16
2 RO1 DC07646 $29,520
Developing Evidence-based Treatment Continuum for Spoken and Written Language

Rapcsak, Steven and Verfaellie, Mieke (multi-PI)   4/1/13-4/1/17
VA Merit Review $599,076 TC
Medial Temporal Lobe Contributions to Future Thinking: Evidence from Amnesia

Ryan, Lee (co-PI)   07/01/13-06/30/14
ADHS14-052577 $94,263 Annual DC
State of Arizona, DHS
The influence of hypertension on the compensation response in older adults

Scalf, Paige (co-PI)   07/01/13-06/30/14
ADHS14-052577 $20,000 Annual DC
State of Arizona, DHS
Age Related Changes in PRC and BA38 Influences on Perceptual Processing

Trouard, Theodore (PI)   6/15/11–5/31/14
R03 AG037806-02 $41,000 Annual DC
NIA
UTE MRI in Alzheimer's Mice

Trouard, Theodore (co-PI)   07/01/13-06/30/14
ADHS14-052577 $37,025 Annual DC
State of Arizona, DHS
Enhanced Delivery of Neurotherapeutics via FUS, MRI and SPECT

Wilson, Stephen (co-PI)   2013
Technology Research Initiative Fund (TRIF) Optics/Imaging Program $80,000
Equipment for stimulus presentation, response collection and patient monitoring

Wilson, Stephen (PI)   4/1/10-3/31/14 (NCE)
R03 DC010878 $383,454 TC
NIH NIDCD
Functional neuroimaging of language processing in primary progressive aphasia

Wilson, Stephen (co-PI)   07/01/13-06/30/14
ADHS14-052577 $9,996 Annual DC
State of Arizona, DHS
Calibrating blood oxygen level-dependent (BOLD) functional MRI by mapping venous anatomy and
cerebro-vascular reactivity

Weissig, V (Co-I; Migrino PI)   5/1/2013 – 4/30/2016
Department of Veterans Affairs (VA Health Care System) $500,000 (TDC)
Nano liposome-based treatment of amyloid protein (AL) toxicity.

Vallejo, J (PI)   7/1/2013 - 6/30/2014
MWU intramural grant $5000 (DC)
Role of caveolins and sphingolipids in the mechanism of insulin resistance.

Kaufman, J (PI)   7/01/2013-6/30/2014
MWU intramural grant $2000 (DC)
Combined CLARITY/MRI mapping of neuropathology in a mouse model of neurodegenerative disease.

Jones, T.B. (Hamm, Barrow Neurological Inst: PI)   9/1/2013 – 5/31/2018
NINDS R01 (subcontract to MWU) $4783 (TC sub)
Motoneuron pool plasticity following spinal cord injury.

Jentarra, G (PI)   7/01/2013-6/30/2014
Arizona Alzheimer's Consortium Pilot Grant $20,000 (DC)
Neuron structure and plasticity in young-adult APOE4 carriers and non-carriers.

Buhlman LM (PI)   7/1/2013 - 6/30/2014
MWU CHS Research Incentive Grant $5000 (DC)
Assessing the mechanism of nicotinic protection in Parkin loss-of-function heterozygous Drosophila
melanogaster.

Han, Peng Cheng (PI)   2013-2014
BNI-UA-Phoenix Joint Translation Neuroscience $50,000 (DC)
PACAP deficit in AD.

Shi, Jiong (PI)   2009-2014
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)   2013-2015
Avanir Pharmaceuticals, Inc $180,000 (TC)
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.

Shi, Jiong (PI)   2014-2016
Merck & Co. $460,500 (TC)
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 Amnestic Mild Cognitive Impairment
due to Alzheimer's Disease (prodromal AD).

Shi, Jiong (PI)   2010-2014
GE Healthcare $86,437 (TC)
A Principal Open-label Study to Assess the Prognostic Usefulness of Flutemetamol (18F) Injection for
Identifying Subjects with Amnestic Mild Cognitive Impairment Who Will Convert to Probable
Alzheimer's Disease.

Shi, Jiong (PI)   2012-2014
Navidea Biopharmaceuticals $307,625 (TC)
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.

Baxter, Leslie (co-PI; Theodore BNI PI; Sierkes PI)   9/25/12-9/24/14
Oligomeric Neuronal Protein Aggregates as Biomarkers $339,424
for Traumatic Brain Injury (TBI) and Alzheimer's disease (AD)   27,999 (BNI: DC)

Baxter, Leslie (co-PI; Corman PI)   4/1/2012- 12/26/2013
Defense Advanced Research Projects Agency (Co-PI) $1,519,881   (TC)
Toward Narrative Disruptors and Inductors: $88,184 (BNI DC)
Mapping the Narrative Comprehension
Network and its Persuasive Effects

Baxter, Leslie (co-PI; Reiman PI)   07/01/11 – 06/30/16
NIA AG019610 $53,272 (TC)
Arizona Alzheimer's Disease Core Center

Baxter, Leslie (PI)   07/01/11 - 06/30/12
State of Arizona/Barrow Subcontract $150,000 (TC)
Using multimodal MRI to investigate early brain changes $150,000 (BNI Match)
in presymptomatic APOE ε4 Carriers

Baxter, Leslie (Consultant; Wang PI)   NIA AG043760-01A1
"MRI Biomarker Discovery for Preclinical Alzheimer's disease with Geometry Methods"

Baxter, Leslie (Co-Pi PI: Pipe, Schmainda)   2012-2017
RO1 CA092500
"MRI contrast agent methods in GBM" $28,373 (DC)

Baxter, Leslie (PI)   07/01/11 - 06/30/14
State of Arizona/Barrow Subcontract $150,000 (TC)
Using multimodal MRI to investigate early brain changes $150,000 (BNI Match)
in presymptomatic APOE ε4 Carriers

Beach, Thomas
U24NS072026 (Beach)   9/1/11-6/30/16
NIH $1,077,546 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Beach, Thomas (Core Leader)
5 P30 AG019610 (Reiman)   7/1/11 to 6/30/16
NIH/NIA $154,794 (Annual DC)
Arizona Alzheimer's Disease Core Center

Beach, Thomas
GE Healthcare (Beach)   8/1/10 to 8/31/13
Postmortem Correlation for Amyloid Imaging Ligand GE-067-007 $89,724 (Beach TC)

Beach, Thomas
Schering-Bayer Pharmaceuticals, Inc. (Beach)   11/1/09 to present
Schering-Bayer Pharmaceuticals, Inc. $98,000 (Beach Total DC)
Postmortem Correlation for Amyloid Imaging Ligand Bay 94-9172

Beach, Thomas
Avid Radiopharmaceuticals, Inc. Beach (PI)   01/10/2009 to present
Avid Radiopharmaceuticals, Inc.
Postmortem Correlation for the Amyloid Imaging Ligand AV45-A07 and AV45-A16.

Beach, Thomas
MJFF (Adler)   9/1/11-8/31/14
Michael J. Fox Foundation for Parkinson 's Research $71,000 Annual DC
Transcutaneous Submandibular Gland Biopsy: A Diagnostic Test for Early Parkinson's Disease

Beach, Thomas
U01 (Scherzer)   9/30/12-8/31/17
Brigham and Women's Hospital $21,692 Annual DC
Biomarkers for early detection and intervention in Parkinson's disease

Beach, Thomas
MJFF (Adler/Beach)   1/01/12 – 12/31/14
Michael J. Fox Foundation for Parkinson's Research $25,000 total
Resources Utilization Grants Program Beach, Adler (co-PIs)

Beach, Thomas
MJFF Research Grant 2013 (Beach)   5/01/13 – 3/28/14
Michael J. Fox Foundation for Parkinson's Research $17,906 Annual DC
Search for Specific Retinal Biomarkers of Parkinson's Disease

Beach, Thomas
MJFF Research Grant 2011-2012 (Adler/Beach)   11/25/13-11/30/15
Michael J. Fox Foundation for Parkinson's Research $109,014 Annual DC
Evaluation of alpha-synuclein immunohistochemical methods for the detection of Lewy-type synucleinopathy in gastrointestinal biopsies.

Beach, Thomas
R21 (Sierks)   9/1/13-6/30/15
NIH via ASU $8,000 Annual DC
Nanobodies selective for oligomeric Tau species isolated from AD brain

Belden, Christine
P30 AG019610 (Reiman)   7/1/11-6/30/16
NIH/NIH $98,474 Annual DC Core
BSHRI
Arizona Alzheimer's Disease Core Center – Clinical Core

Belden, Christine
U24NS072026 (Beach)   9/1/11-6/30/16
NIH $1,077,546 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Coleman, Paul
R01 AG036400-01   9/15/09 to 8/31/14
NIH/NIA $339,377 Annual DC
DNA Methylation in Alzheimer's disease and normally aged brain.

DeCourt, Boris
NIRG-12-237512   10/1/12-9/30/14
Alzheimer's Association $45,455 Annual DC
Pre-clinical testing of lenalidomide as anti-amyloid treatment for AD

DeCourt, Boris
5P30 AG019610-12 (Reiman)   07/01/12-06/30/14
NIH/NIA ADC Pilot (DeCourt) $29,412 TC
Testing of platelet BACE1 mRNA and protein levels as biomarkers for AD

DeCourt, Boris
R01AG034155-01 (Sabbagh)   9/30/09 – 8/31/13
NIH/NIA $500,180 Annual DC
Study on Thalidomide as BACE1 inhibitor in Alzheimer's disease

DeCourt, Boris
AARC (Sabbagh)   7/1/13 – 6/30/14
State of Arizona and Sun Health Foundation (match) $51,480 Annual DC
Comparison of Alzheimer's disease and Down syndrome post-mortem brain markers.

Dugger, Brittany
1U24NS072026 (Beach)   9/01/11-6/30/13
NIH/NINDS $1,077,546 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Dugger, Brittany
Michael J. Fox Foundation for Parkinson's Research (Adler)   9/1/11-8/31/14
MJFF $71,000 Annual DC
Transcutaneous Submandibular Gland Biopsy: A Diagnostic Test for Early Parkinson's Disease

Dugger, Brittany
U24AG016976-15 (Kukull)   7/1/13 – 6/30/14
NACC– NACC Junior Investigator Award $25,000 TC
Relationship of cardiovascular risk factors to dementia subtypes

Dugger, Brittany
AARC (Reiman, Project PI Dugger)   7/1/13 – 6/30/14
State of Arizona and Sun Health Foundation (match) $51,480 Annual DC
Distribution of tau in peripheral tissues of Alzheimer's disease

Dugger, Brittany
Grant (Dugger)   10/1/13-9/31/15
Parkinson's Action Network $10,000 TC
2013 Parkinson's Action Network Postdoctoral Advocacy Award

Jacobson, Sandra
U24NS072026 (Beach)   9/1/11-6/30/16
NIH $1,077,546 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Jacobson, Sandra
P30 AG019610 (Reiman)   7/1/11-6/30/16
NIH/NIH $98,474 Annual DC Core B
Arizona Alzheimer's Disease Core Center – Clinical Core

Jacobson, Sandra
R01AG034155-01 (Sabbagh)   9/30/09 – 8/31/13
NIH/NIA $500,180 Annual DC
Study on Thalidomide as BACE1 inhibitor in Alzheimer's disease

Lue, Lih-Fen
MJFF Research Award (Lue)   8/1/11 to 9/30/13
Michael J. Fox Fdn for Parkinson's Research $72,589 Annual DC
Identifying peripheral inflammatory markers for Parkinson's disease with dementia

Lue, Lih-Fen
MJFF Cognition Biomarkers RFA (Lue/Walker/Caviness)   1/1/14 – 12/31/15
Michael J. Fox Fdn for Parkinson's Research $56,407 Annual DC
Validation of Novel and Traditional Quantitative EEG Biomarkers

Lue, Lih-Fen
R21AG034409-01A1 (Walker)   8/15/10-7/31/14
NIH $120,000 DC year 1
Are the suppressors of cytokine signaling involved in Alzheimer's disease?

Lue, Lih-Fen
1R21AG044068-01 (Walker)   9/30/12-8/31/14
NIH $150,000 Annual DC
Is Toll-like receptor-3 signaling involved in Alzheimer's disease?

Lue, Lih-Fen
AARC (Reiman, Project PI Walker)   7/1/13 – 6/30/14
State of Arizona and Sun Health Foundation (match) $57,000 Annual DC
Is Interluekin-34 a key regulator of microglia function in Alzheimer's disease?

Lue, Lih-Fen
AARC (Reiman, Project PI Lue)   7/01/13- 06/30/14
State of Arizona and Sun Health Foundation (match) $57,000 Annual DC
APOE4 genotype effect on blood cell-derived neural stem cell

Lue, Lih-Fen
ADHS13-031241 (Lue/Walker)   6/01/13 – 09/30/14
AZ DHS - Arizona Biomedical Research Commission (ABRC) $159,000 Annual DC
Longitudinal Changes in Circulating TAU Correlates with Changing Cognitive Performance

Mastroeni, Diego
R01 AG 036400 (Coleman)   9/15/09 to 8/31/14
NIH $339,377 Annual DC
DNA methylation in Alzheimer's disease and normally aging brain

Macias, Mimi
AARC (Macias)   7/1/13 – 6/30/14
State of Arizona and Sun Health Foundation (match) $51,480 Annual DC
The Role of Blood-Brain Barrier Dysfunction In Neurodegeneration.

Oddo, Salvatore
R01 AG037637 (Oddo)   8/1/11-7/31/16
NIH/NIA $166,930 Annual DC
Molecular interplay between Abeta, tau and mTOR: Mechanisms of neurodegeneration

Oddo, Salvatore
ADDF (Oddo)   8/1/2013-7/31/2015
Alzheimer's Drug Discovery Foundation $121,000 Annual DC
Reducing mTOR activity as a treatment for Alzheimer's disease

Oddo, Salvatore
CCAD (Oddo)   7/1/2013-6/30/2014
Charleston Conference on Alzheimer's Disease $50,000 Annual DC
Restoring cognition by remotely stimulating selective neuronal networks

Roher, Alex
1R21 AG035078-01 (Roher)   2/15/2010 – 1/31/2014
NIH/NIA $127,500 Annual Direct Costs
Beta-amyloid peptides in the oldest-old: A biochemical profile of successful aging

Roher, Alex
R01 AG19795-09A1 (Roher)   8/1/01-5/31/14
NIH $203,886 Annual Direct Costs
APP/Abeta/Tau biochemistry in transgenic mice, familial and sporadic AD

Sabbagh, Marwan
5P30 AG019610 (Reiman)   7/1/11-6/30/16
NIH/NIH $98,474 Annual DC Core B
Arizona Alzheimer's Disease Core Center – Clinical Core

Sabbagh, Marwan
U24NS072026 (Beach)   9/1/11-6/30/16
NIH $1,077,546 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Sabbagh, Marwan
R01 AG034155-01(Sabbagh)   9/30/09-8/31/13
NIH/NIA $500,180 Annual Direct Costs
Study on Thalidomide as BACE1 inhibitor in Alzheimer's disease

Sabbagh, Marwan
ADHS13-031241 (Lue/Walker)   6/01/13 – 09/30/14
AZ DHS - Arizona Biomedical Research Commission (ABRC) $159,000 Annual Direct Costs
Longitudinal Changes in Circulating TAU Correlates with Changing Cognitive Performance

Sabbagh, Marwan
2R01AG007367-21 (Rogers)   8/1/12 – 7/31/15
NIH/NIA subcontract (Sabbagh) $33,198 Annual DC
Alzheimer's disease: a blood diagnostic and biomarker of disease progression

Sabbagh, Marwan
NIRG-12-237512 (DeCourt)   10/1/12-9/30/14
Alzheimer's Association $45,455 Annual DC
Pre-clinical testing of lenalidomide as anti-amyloid treatment for AD

Sabbagh, Marwan
AARC (Sabbagh)   7/1/13 – 6/30/14
State of Arizona and Sun Health Foundation (match) $51,480 Annual Direct Costs
Comparison of Alzheimer's disease and Down syndrome post-mortem brain markers

Shill, Holly
IETF 2013   7/1/12-present
International Essential Tremor Foundation $35,000 Annual DC
A Feasibility study for an Essential Tremor Brain Bank at the Arizona Study of Aging and
Neurodegenerative Disorders

Shill, Holly
Grant (Shill)   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

Shill, Holly
Contract W81XWH-11-1-0310 (Adler/Shill)   7/1/12-3/31/13
USAMRAA via The Parkinson's Institute $18,729 Annual DC
Validating Diagnostic and Screening Procedures for Pre-Motor Parkinson's Disease

Shill, Holly
U24NS072026 (Beach)   9/1/11-6/30/16
NIH $1,077,546 Annual Direct
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Shill, Holly
Grant (Shill)   12/1/13 – present
Fountain Hills Walking Group PD support $15,000 total award costs

Shill, Holly
Grant (Shill)   1/1/14-12/31/14
Consolidated Anti-Aging Foundation $20,000 Annual Direct costs

Shill, Holly
Clinical Trial (Shill)   6/2013-present
UCB Biosciences
A multicenter, multinational, double-blind, placebo controlled, 3-arm, phase 4 study to evaluate the
efficacy of rotigotine on Parkinson's disease-associated apathy, motor symptoms and mood (BRIGHT)

Shill, Holly
18F-AV-133-B04 (Shill)   6/12-present
Avid Radiopharmaceuticals
An open label, multicenter study, evaluating the safety and efficacy of 18F-AV-133 PET imaging to identify subjects with dopaminergic degeneration among subjects presenting to a movement disorders specialty clinic with an uncertain diagnosis

Shill, Holly
Clinical Trial (Shill)   12/2013-present
Teva Neuroscience
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Add-on, Parallel Group Study to Assess the Effect of Rasagiline on Cognitive Abilities in Patients with Parkinson's Disease

Walker, Douglas
1R21AG044068-01   9/30/12-8/31/14
NIH $150,000 Annual Direct Costs
Is Toll-like receptor-3 signaling involved in Alzheimer's disease?

Walker, Douglas
R21AG034409-01A1   8/15/10-7/31/14
NIH $120,000 DC year 1
Are the suppressors of cytokine signaling involved in Alzheimer's disease?

Walker, Douglas
5U24NS072026 (Beach)   9/1/11-6/30/16
NIH – NINDS $1,077,546 Annual Direct
Costs
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Walker, Douglas
5 P30 AG019610 (Reiman)   7/01/12 – 06/30/16
NIH/NIA $154,794 dc/yr
(Neuropath Core)
Arizona Alzheimer's Disease Core Center

Walker, Douglas
AARC (Reiman)   7/1/13 – 6/30/14
State of Arizona and Sun Health Foundation (match) $57,000 Annual Direct Costs
Is Interleukin-34 a key regulator of microglia function in Alzheimer's disease?

Walker, Douglas
AARC (Reiman, Project PI Walker)   7/1/13 – 6/30/14
State of Arizona and Sun Health Foundation (match) $57,000 Annual Direct Costs
APOE4 genotype effect on blood cell-derived neural stem cell

Walker, Douglas
ADHS13-031241 (Lue/Walker)   6/01/13 – 03/31/14
AZ DHS - Arizona Biomedical Research Commission (ABRC) $159,000 Annual Direct Costs
Longitudinal Changes in Circulating TAU Correlates with Changing Cognitive Performance

Walker, Douglas
MJFF Cognition Biomarkers RFA (Lue/Walker/Caviness)   1/1/14 – 12/31/15
Michael J. Fox Fdn for Parkinson's Research $56,407 Annual Direct Costs
Validation of Novel and Traditional Quantitative EEG Biomarkers

Walker, Douglas
MJFF Research Award (Lue)   8/1/11 to 1/31/13
Michael J. Fox Fdn for Parkinson's Research $72,589 direct costs/year
Identifying peripheral inflammatory markers for Parkinson's disease with dementia

Chen, Kewei (PI)   7/1/13-6/30/14
AARC $76,357 Annual DC
State of Arizona
Advanced Image Analysis Techniques for the Detection and Tracking of Alzheimer's disease and its prevention

Chen, Kewei (Co Investigator)   4/1/12-3/31/17
NIH R01NS075075 $7,709 Annual DC
Determinants of Neurodegenerative Decline in Primary Progressive Aphasia

Dougherty, Jan   7/1/13-6/30/14
AARC $43,982 Annual DC
State of Arizona
Native American Outreach and Native American Clinical Core

Langbaum, Jessica (PI)   7/1/13-6/30/14
AARC $8,361 Annual DC
State of Arizona
Alzheimer's Prevention Registry

Langbaum, Jessica (PI)   7/1/13-6/30/14
Alzheimer's Disease Core Center Pilot $27,504 Annual DC
API APOE4 Genotyping and Disclosure Study

Reiman, Eric; Tariot, Pierre; Lopera, Francisco (Multi-PI) 5/18/12-4/30/17
NIH RF1AG041705 $12,302,690 Total DC
Alzheimer's Prevention Imitative

Reiman, Eric; Tariot, Pierre   9/20/13-8/31/18
NIH UF1AG046150 $22,280 Total DC
Alzheimer's Prevention Initiative APOE4 Trial

Reiman, Eric (PI)   7/1/11 - 6/30/16
NIA P30AG19610 $902,375 Annual DC
Alzheimer's Disease Core Center

Reiman, Eric (PI)   7/1/13-6/30/14
AARC $143,000 Annual DC
State of Arizona (Match from Banner Alzheimer's Foundation)
Alzheimer's Prevention Initiative

Reiman, Eric (PI)   4/1/12-3/31/14
NIH/NIA 5RO1AG031581 $868,038 Annual DC
PET, APOE, and the Preclinical Course of Alzheimer Disease

Reiman, Eric (PI)   7/1/03-6/30/14
TGEN Professional Services Agreement $26,550 Annual Costs

Reiman, Eric (Co-PI)   4/1/09-3/31/14
U01 AG032984 $8,529 Annual DC
Alzheimer's Disease Genomics Consortium

Reiman, Eric (Co Investigator)   9/30/09-8/31/14
NIH/NIA U01AG024904   Weiner (PI) $294,573 Annual DC
Amyloid Imaging, VMCI and Analysis, for ADNI

Reiman, Eric (Co Investigator)   3/1/09-8/31/14
Avid Clinical Study Agreement
Avid Radiopharmaceuticals, Inc.

Reiman, Eric (PI)   9/30/09-8/31/14
DOD W81XWH-12-5-0012 via N. Calif. Inst. Research & Education $24,570 Annual DC
Effects of traumatic brain injury and post-traumatic stress disorder
on Alzheimer's disease (AD) in Veterans using ADNI

Reiman, Eric (PI)   12/1/07-6/30/17
AstraZeneca
^{11}C-AZD2184 in the Assessment of Fibrillar Amyloid-β

Reiman, Eric   6/8/13-5/31/14
NIH UH2TR000967 via Yale University (Strittmatter/Van Dyck) $59,060 Annual Costs
Fyn Inhibition by AZD0530 for Alzheimer's Disease

Reiman, Eric   1/1/14-12/31/14
Flinn Foundation $450,000 Annual Costs
Alzheimer's Prevention Initiative Clinical Trials Arizona Infrastructure

Huentelman, Matthew
2 P30 AG019610   (Eric Reiman)   07/01/2011 - 06/30/2016
NIH $13,294
Arizona Alzheimer's Disease Core Center
The goal is to support and conduct research on Alzheimer's disease.
Role: Co-Investigator

Huentelman, Matthew
SU2C   (Jeffrey Trent)   04/01/2012 - 03/31/2015
American Association for Cancer Research $1,302,921
Personalized Medicine for Patients with BRAF wild-type (BRAFwt) Cancer
Role: Investigator

Huentelman, Matthew
Grant   (Matt Huentelman)   07/01/2013 - 06/30/2014
DHS
TGEN AARC FY 14: Novel biomarker and genetic risk factor identification in Alzheimer's disease
Principal Investigator

Huentelman, Matthew
R01   (Amanda Myers)   07/01/2013 - 04/30/2018
NIH $125,000
APOEomic: Searching for APOE interacting risk factors using omics data
Role: Co-Investigator.

Huentelman, Matthew
UH2/UH3   (Matthew Huentelman)   08/01/2013 - 07/31/2018
NIH/Trans-NIH Research $242,183
exRNA signatures predict outcomes after brain injury
Role: Principal Investigator

Dunckley, Travis
Grant   (Matt Huentelman)   07/01/2013 - 06/30/2014
AzDHS $40,000
TGEN AARC FY 14: Novel biomarker and genetic risk factor identification in Alzheimer's disease
Role: Co- Investigator

Dunckley, Travis
Grant   (Travis Dunckley)   12/13/2013 – 12/12/2004
MJFF $68,181
DNA Methylation as a Biomarker for Parkinson's Disease
Role: Principal Investigator

Dunckley, Travis
Grant   (Charles Alder)   10/10/2013 – 11/30/14
MJFF $38,591
A diagonostic test for early Parkinson's Disease
Role: Co-Investigator

Liang, Winnie
Contract   (John Carpten)   09/01/2011 -08/31/2019
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

Liang, Winnie
SU2C-AACR-DT0612   (Jeff Trent/ Patricia LoRusso)   04/01/2012 - 03/31/2015
American Association for Cancer Research $870,876
Personalized Medicine for Patients with BRAF wild-type (BRAFwt) Cancer
Role: Investigator

Liang, Winnie
1U01CA153060   (Nathan Ellis)   08/10/2010 - 07/31/2014
NIH $59,709
Genetic risk factors in African American colorectal cancer patients
Role: Investigator

Liang, Winnie
Grant   (Matt Huentelman)   07/01/2013 - 06/30/2014
AzDHS $15,000
TGEN AARC FY 14: Novel biomarker and genetic risk factor identification in Alzheimer's disease
Role: Investigator

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

Van Keuren- Jensen, Kendall
1 R01 NS076006   (Hollis Cline)   08/01/2011 - 07/31/2014
NIH $100,000
Transcriptome Analysis of Identified Cells in Developing X. laevis CNS
Role: Co-Investigator

Van Keuren- Jensen, Kendall
Grant   (Matt Huentelman)   07/01/2013 - 06/30/2014
AzDHS $39,998
TGEN AARC FY 14: Novel biomarker and genetic risk factor identification in Alzheimer's disease
Role: Investigator

Van Keuren- Jensen, Kendall
1UH2TR000891   (Matthew Huentelman)   08/01/2013 - 07/31/2015
NIH/Trans-NIH Research $242,183
exRNA signatures predict outcomes after brain injury
Role: Co-Investigator

Van Keuren- Jensen, Kendall
Grant   (Kendall Jensen)   10/01/2013 – 09/30/2014
Brain Aneurysm Foundation $25,000
Role: Principal Investigator

Van Keuren- Jensen, Kendall
Grant   (Johan Skog)   10/15/2013 – 10/14/2014
MJFF $61,422
Identification of enriched RNAs in AGO2 and exosome pellets compared to the RNA found in the whole sample
Role: Co-Investigator

Van Keuren- Jensen, Kendall
Grant   (Kendall Jensen)   04/03/2014 – 04/02/2015
MJFF $61,422
miRNA biomarkers of dementia
Role: Principal Investigator

Coon, D. W. (ASU Site PI)   09/30/2013-9/29/2016
U.S. Administration for Community Living (U.S. Administration on Aging).
                                                              $287,574 DC
Arizona Alzheimer's Disease Dementia Capability Project

Bimonte-Nelson, Heather (PI)
R01 AG028084 Renewal   9/01/13 - 5/31/18
National Institute on Aging $1,609,782 TC
Variations in hormones during menopause: effects on cognitive and brain aging

Bimonte-Nelson, Heather
National Science Foundation (NSF) Graduate Research Fellowship $32,000 per year (3 years)
Co-mentors: Bimonte-Nelson and Rachael Sirianni (BNI)
Student: Alesia Prakapenka
Development of targeted delivery of estrogen to examine its effect on cognitive function.

Bimonte-Nelson, Heather
Arizona State University   1/2014-12/14
CLAS NS-SS-GRG Seed Funding $21,700 TC
PI: Clive Wynne
Co-Investigators: Michael McBeath, Heather Bimonte-Nelson, Leslie Baxter
Adapting a commonly-used rodent maze task for use in the dog: Systematically testing an increasing working memory load during aging

Bimonte-Nelson, Heather (PI)   7/13-6/14
Alzheimer's Disease Core Center (Arizona) $30,000 TC
State of Arizona (ADHS14-052688) & NIH (5P30AG019610-13)
Bioidentical hormone therapy: effects on cognition as a function of transitional menopause progression.

Bimonte-Nelson, Heather
Institute for Mental Health Research   9/16/13 - 9/15/14
PI: Ryoko Hiroi $20,000 TC
Co-investigator: Heather Bimonte-Nelson
Sex-specific effects of an antidepressant treatment on cognition in aged rats

Bimonte-Nelson, Heather
K01AG037562   07/11-6/16
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 Aβ & Metabolism

Bimonte-Nelson, Heather (PI)
Arizona State University   1/13-1/14
CLAS NS-SS-GRG Seed Funding $25,000 TC
Impact of exogenous hormone treatment on age-related memory changes

Bimonte-Nelson, Heather
F32 MH093145 Postdoctoral NRSA   07/01/11 – 06/30/14
PI: Ryoko Hiroi $166,446 TC
Co-Mentors: Heather Bimonte-Nelson, Robert Handa
National Institute of Mental Health
Regulation of the Tryptophan Hydroxylase-2 Promoter by Estrogen

Bimonte-Nelson, Heather (PI)   5/14-8/14
CLAS Undergraduate Summer Enrichment Award (USE) $2,400
Provides funds to pay an undergraduate for research-related work done in the lab over the summer

Pending Grants

Alexander, Gene (PI)   07/01/14 - 06/30/17
Arizona Biomedical Research Commission $226,737 Annual DC
Title: Impact of Sleep and Blood Pressure Variation on Brain and Cognitive Health in the Elderly

Alexander, Gene (PI of UA Subcontract), Reiman, Eric (PI)
3 RO1 AG031581   07/01/13 – 06/30/18
NIA $11,788 Sub DC
PET, APOE and he Preclinical Course of Alzheimer's Disease

Alexander, Gene (PI)   09/01/14 -8/31/19
RO1 $499,920 Annual DC
NIA
NREM Sleep in the Aging Brain, Cognitive Decline & Preclinical Risk for AD

Alexander, Gene (PI of UA Subcontract), Cohen & Marsiske (PIs)   09/01/14 – 08/31/19
RO1 $358,510 Sub DC
NIA
Augmenting Cognitive Training in Older Adults

Barnes, Carol (PI)   08/01/13 – 07/31/18
1 RO1 AG049465-01 $512,412 Annual DC
National Institute on Aging
Neural System Dynamics & Gene Expression Supporting Successful Cognitive Aging

Barnes, Carol (PI)   9/1/14 – 8/31/19
2 RO1 AG012609-21A1 $250,000 Annual DC
National Institute on Aging
Cell Assemblies, Pattern Completion and the Aging Brain

Barnes, Carol / Liang, Rongguang (multi-PI)   09/1/14 – 08/31/17
1 UO1 MH106016-01 $152,561 Annual DC
National Institute of Mental Health
Mapping of Behavior Circuits: A Scalable Acquisition and Data Management System

Barnes, Carol (co-PI)   09/1/14 – 08/31/14
1 UO1 MH105928-01 $82,084 Annual DC
National Institute of Mental Health
A Molecular Census of Individual Cells and Circuits within Select Brain Regions

Barnes, Carol (co-PI)   04/01/15 – 03/31/17
1 R21 MH104979-01A1 $40,186 Annual DC
National Institute of Mental Health
Novel Confocal Fluorescence Microscope for Mapping Behavioral-Driven Brain

Coleman, Paul / Barnes, Carol/ Alexander, Gene (multi-PI)   08/01/13 – 07/31/18
1 RO1 AG049464-01 $375,894 Annual DC
National Institute on Aging
Epigenetic, Neuroimaging & Behavioral Effects of Hypertension in the Aging Brain

Huentelman, Matthew / Barnes, Carol (multi-PI)   09/15/14 – 09/14/18
1 RO1 AG048907-01 $207,753 Annual DC
National Institute on Aging
CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox

Ryan, Lee (co-Investigator), Latifi, Rifat (PI)   7/1/14-6/30/17
NSF $519,398 Total
Intraoperative Surgical Decision-Making

Ryan, Lee (PI of UA Subcontract), Huentelman, Matt (PI)   7/1/14-6/30/17
ABRC $286,850 TDC
Genetic Factors associated with family history for Alzheimer's disease

Trouard, Ted (Co-Investigator), Duncan PI   4/1/2014 – 5/31/2019
1 R01 HD079498-01 $451,781
NIH/NICHD
Intense physiotherapies to improve function in young children with cerebral palsy

Wilson, Steven (PI)   7/1/14-6/30/19 R01 DC013270
NIH NIDCD $2,193,837 TC
Neural correlates of recovery from aphasia after acute stroke

ABRC (PI: Shi) $749,874 (3 Yrs, TC)
PACAP: a novel biomarker for Alzheimer's disease

Valla, J (PI), Vallejo J/Jentarra G (Co-I)   9/1/2014 – 8/31/2018
NIA R01 $1,387,496 (TC)
Early brain changes associated with apolipoprotein E4-related neurological risk.
Olsen, Mark (Co-I; Wands: PI)   10/1/2014 - 9/30/2019
NCI R01 $514,625 (MWU TC)
ASPH as a therapeutic target for cancer

Beach, Thomas
ABRC BIG (Roher)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $226,923 Annual Direct Costs
Translating structural, hemodynamic and biochemical markers into comprehensive Alzheimer's dementia risk assessment tools

Beach, Thomas
ABRC BIG (Walker)   7/1/14 – 6/30/17
ABRC $226,504 Annual Direct Costs
Is Interleukin-34 the key cytokine for regulating inflammation in Alzheimer's and Parkinson's disease?

Beach, Thomas
ABRC BIG (Lue)   7/1/14 – 6/30/17
ABRC $209,737 Annual Direct Costs
Establishing patient-based stem cell biobank for neurodegenerative disease modeling and drug discovery

Beach, Thomas
ABRC BIG (Wu)   7/1/14 – 6/30/17
ABRC via Barrows Neurological Institute $54,357 Annual DC subaward
Alpha-synuclein - inflammasome signal pathway: A critical target for PD pathogenesis and therapeutics

Beach, Thomas
ADDF Challenge (Sierks)   1/1/14-12/31/14
Alzheimer's Drug Discovery Foundation $30,000 Annual Direct Costs
Selected toxic protein variants as early sensitive CSF and serum biomarkers for AD

Beach, Thomas
MJFF (Freeman)   7/1/14-6/30/19
Michael J Fox Foundation via Harvard University $12,800 Total Direct Costs
Synucleinopathy Biomarkers in the Skin

Beach, Thomas
R21 (Chen)   7/1/14-6/30/16
NIH via ICU $15,000 Total Direct Costs
Mitochondrial DNA deletion spectrum in brain tissues from donors with Alzheimer's disease

Beach, Thomas
R01 (Liang)   7/1/14-6/30/16
NIH via TGEN $12,043 Total Direct Costs
Characterization of posterior cingulate astrocytes and neurons in Alzheimer's disease

Beach, Thomas
R01 via St. Jude (Peng)   9/1/14-8/31/19
NIH $62,500 Total Direct Costs
An Integrated Platform for Clinical Proteomics

Beach, Thomas
R21 (Macias)   9/1/14-8/31/16
NIH $150,000 Annual Direct Costs
Is There a Vascular Signature for Alzheimer's Disease?

Beach, Thomas
ABRC ESI (Mastroeni)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $74,984 Annual Direct Costs
A Novel Compound to Protect Mitochondria against Oligomeric Abeta Toxicity, Implications for the Synapse

Coleman, Paul
ABRC BIG (Lue)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $209,737 Annual Direct Costs
Establishing patient-based stem cell biobank for neurodegenerative disease modeling and drug discovery

Coleman, Paul
NIRG (PI: Mastroeni, Co-PI Paul Coleman)   9/1/14-8/31/17
Alzheimer's Association NIRG $75,757 Annual Direct Costs
Underlying Mechanism in synaptic dysfunction in Alzheimer's Disease

Coleman, Paul
Grant (PI: Mastroeni, Co-PI Paul Coleman)   7/1/14-6/30/17
Bright Focus Foundation $100,000 Annual Direct Costs
Mechanisms that Drives a Synapse Mad in Alzheimer's Disease.

Coleman, Paul
NIH R01 (PI Alexander/Barnes/Coleman)   8/1/14-7/31/18
NIH
Project 4 Breakout: Epigenetic, Neuroimaging & Behavioral Effects of Hypertension in the Aging Brain

Coon, D. W. (PI)   12/1/2014-11/30/2019
National Institute on Aging $499,082 DC
EPIC: Translation of a Group Early-Stage AD Intervention into Diverse Communities

DeCourt, Boris
ADDF (Decourt)   2/1/14 – 1/31/16
Alzheimer's Drug Discovery Foundation $131,126 Annual DC
Using the anti-inflammatory drug lenalidomide to treat brain tau pathology: pre-clinical evaluation in transgenic mice

DeCourt, Boris
BF2013 (Sabbagh)   7/1/14 – 6/30/16
Bright Focus Foundation $100,000 Annual Cost
Florbetapir-PET, FDG-PET & MRI in DS with & without AD

DeCourt, Boris
K01 (DeCourt)   12/1/14 – 6/30/19
NIH $92,170 Annual DC
Pre-clinical testing of lenalidomide as pleitropic therapeutics for AD

Dugger, Brittany
ABRC ESI   7/1/14-6/30/17
Arizona Biomedical Research Commission $66,233 Annual DC
The effects of APOE genotype on APP/Aβ levels in human liver and brain

Dugger, Brittany
Arizona Alzheimer's Disease Core Center – Pilot Project 7/1/14-6/30/15
NIH/NIA $30,000 Annual DC
The effects of APOE genotype on APP/Aβ levels in human liver and brain

Dugger, Brittany
Parkinson's Study Group   7/1/14-6/30/14
Mentored Clinical Research Award $50,000 total project costs
Impact of Pathological Heterogeneity on Clinical Presentations in Parkinson's Disease

Dugger, Brittany
The Esther A. & Joseph Klingnstein Fund, Inc.   7/1/14-6/30/17
Fellowship Awards in Neurosciences $75,000 Annual DC
The effects of APOE genotype on amyloid beta metabolites in human liver and brain

Gaballa, Mohamed
ABRC BIG (Gaballa)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $225,002 Annual DC
Novel therapy for heart failure using epigentically-modified cardiac progenitor cells

Lue, Lih-Fen
IIRG (Lue)   9/1/13-8/31/16
Alzheimer's Association $72,727 Annual Direct Costs
How does microglial TREM2 function affect Alzheimer's disease?

Lue, Lih-Fen
R21 (Lue)   7/1/14 – 6/30/16
NIH $150,000 Annual Direct Costs
Is TREM2 abnormality in microglia a cause for Alzheimer's disease?

Lue, Lih-Fen
ABRC BIG (Lue)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $209,737 Annual Direct Costs
Establishing patient-based stem cell biobank for neurodegenerative disease modeling and drug discovery

Lue, Lih-Fen
ABRC BIG (Walker)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $226,504 Annual Direct Costs
Is Interleukin-34 the key cytokine for regulating inflammation in Alzheimer's and Parkinson's disease?

Lue, Lih-Fen
ABRC BIG via Barrows Neurological Institute (Wu)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $54,357 Annual DC subaward
Alpha-synuclein - inflammasome signal pathway: A critical target for PD pathogenesis and therapeutics

Lue, Lih-Fen
MJFF (Lue)   4/1/14 – 3/31/16
Michael J. Fox Fdn. For Parkinson's Research $163,296 Direct Costs
Enhancing microglial neuroprotective mechanisms through TREM2 phagocytic receptor

Lue, Lih-Fen
Merit Award (Cole)   10/1/14 – 9/30/19
Collaborator/Consultant   Fee per sample

Lue, Lih-Fen
IIRG   9/1/14-8/31/17
Alzheimer's Association - $75,757 Annual DC
Manipulating microglial TREM2-mediated mechanisms for neuroprotection in AD

Mastroeni, Diego
VENI 2014 (Mastroeni)   9/1/14 – 8/31/17
VENI International grant via Maastricht University $150,000 Annual DC
Effects of Oligomeric Amyloid-beta on the Triple E Status in Alzheimer's Disease: Energetics, Epigenetics and Expression of Synapse-related Genes

Mastroeni, Diego
ABRC ESI (Mastroeni)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $74,984 Annual DC
A Novel Compound to Protect Mitochondria against Oligomeric Abeta Toxicity, Implications for the Synapse

Mastroeni, Diego
NIRG (PI: Mastroeni, Co-PI Paul Coleman)   9/1/14-8/31/17
Alzheimer's Association NIRG $75,757 Annual Direct Costs
Underlying Mechanism in synaptic dysfunction in Alzheimer's Disease

Mastroeni, Diego
Grant (PI: Mastroeni, Co-PI Paul Coleman)   7/1/14-6/30/17
Bright Focus Foundation $100,000 Annual Direct Costs
Mechanisms that Drives a Synapse Mad in Alzheimer's Disease.

Macias, Mimi
R21 (Macias)   9/1/14-8/31/16
NIH $150,000 Annual DC
Is There a Vascular Signature for Alzheimer's Disease?

Oddo, Salvatore
ADDF (Decourt)   2/1/14 – 1/31/16
Alzheimer's Drug Discovery Foundation $131,126 Annual DC
Using the anti-inflammatory drug lenalidomide to treat brain tau pathology: pre-clinical evaluation in transgenic mice

Roher, Alex
ABRC BIG (Roher)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $226,923 Annual DC
Translating structural, hemodynamic and biochemical markers into comprehensive Alzheimer's dementia risk assessment tools

Sabbagh, Marwan
ABRC BIG (Sabbagh/Reiman/Chen)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $227,273 Annual DC
Longitudinal assessment of Florbetapir PET, FDG PET, and MRI in Down Syndrome Individuals with and without Alzheimer's Dementia

Sabbagh, Marwan
ABRC BIG (Roher)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $226,923 Annual DC
Translating structural, hemodynamic and biochemical markers into comprehensive Alzheimer's dementia risk assessment tools

Sabbagh, Marwan
ABRC BIG (Walker)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $226,504 Annual Direct Costs
Is Interleukin-34 the key cytokine for regulating inflammation in Alzheimer's and Parkinson's disease?

Sabbagh, Marwan
ABRC BIG (Lue)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $209,737 Annual Direct Costs
Establishing patient-based stem cell biobank for neurodegenerative disease modeling and drug discovery

Sabbagh, Marwan
ABRC BIG via ASU (Sierks)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $89,647 Annual DC
BSHRI subaward
Validation of oligomeric protein biomarkers for Parkinson's Disease

Sabbagh, Marwan
ADDF (Decourt)   2/1/14 – 1/31/16
Alzheimer's Drug Discovery Foundation $123,763 Annual DC/TC
Using the anti-inflammatory drug lenalidomide to treat brain tau pathology: pre-clinical evaluation in transgenic mice

Sabbagh, Marwan
BF2013 (Sabbagh)   7/1/14 – 6/30/16
Bright Focus Foundation $100,000 Annual DC/IDC
Florbetapir-PET, FDG-PET & MRI in DS with & without AD

Sabbagh, Marwan
R21 (Macias)   9/1/14-8/31/16
NIH $150,000 Annual DC
Is There a Vascular Signature for Alzheimer's Disease?
Shill, Holly
ABRC BIG via ASU (Sierks)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $89,647 Annual DC
BSHRI subaward
Validation of oligomeric protein biomarkers for Parkinson's Disease

Shill, Holly
ABRC BIG (Lue)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $209,737 Annual Direct Costs
Establishing patient-based stem cell biobank for neurodegenerative disease modeling and drug discovery

Shill, Holly
R15 via ASU (Krishnamurthi)   9/1/14 – 8/31/17
NIH $8,822 Annual Direct Costs
Real-time feedback to improve gait and posture in Parkinson's disease

Walker, Douglas
ABRC BIG (Walker)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $226,504 Annual Direct Costs
Is Interleukin-34 the key cytokine for regulating inflammation in Alzheimer's and Parkinson's disease?

Walker, Douglas
ABRC BIG (Lue)   7/1/14 – 6/30/17
Arizona Biomedical Research Commission $209,737 Annual Direct Costs
Establishing patient-based stem cell biobank for neurodegenerative disease modeling and drug discovery

Walker, Douglas
R21 (Lue)   7/1/14 – 6/30/16
NIH $150,000 Annual Direct Costs
Is TREM2 abnormality in microglia a cause for Alzheimer's disease?

Walker, Douglas
MJFF (Walker)   5/1/14-4/30/16
Michael J Fox Foundation $191,199 Annual Direct Costs
Endoglin and transforming growth factor signaling as an anti-inflammatory target for Parkinson's disease

Walker, Douglas
MJFF (Lue)   4/1/14 – 3/31/16
MJFF $163,286 Direct Costs
Enhancing microglial neuroprotective mechanisms through TREM2 phagocytic receptor.

Walker, Douglas
P30AG019610-15 Pilot (Dugger)   7/1/14 – 6/30/15
NIH via ADCC Pilot $30,000 Annual Direct Costs
The effects of APOE genotype on APP/AB levels in human liver and brain

Chen, Kewei   7/1/14-6/30/17
Arizona Biomedical Research Commission $740,021 Total Costs
Development of a Multi-Modal Image Analysis Tool with Improved Power to Track Alzheimer's disease
and evaluate Alzheimer's Prevention Therapies

Chen, Kewei (Co Investigator)   7/1/14-6/30/15
Arizona Biomedical Research Commission via ASU (Wang) $33,000 Total Costs
Early Cognitive Decline Association with Genetics and PET/MRI by Sparse Learning

Reiman, Eric (Co Investigator)   1/1/15-12/31/15
NIH SBIR via T3D $61,778 Total Costs
Phase 2a Clinical Trial of T3D959

Huentelman, Matthew
R01   (Eric Reiman)   04/01/2014 - 03/31/2016
NIH $88,561
Brain Imaging APOE & Preclinical Course of Alzheimer's Disease
Role: Investigator

Huentelman, Matthew
R01   (Kenro Kusumi)   04/01/2014 – 03/31/2019
NIH $27,966
Gene-Environmental mechanisms in the Development of Scoliosis
Role: Co- Investigator

Huentelman, Matthew
R01   (Gene Alexander)   07/01/2015 -06/30/2019
NIH $19,607
NREM Sleep in the Aging Brain, Cognitive Decline & Preclinical Risk for AD
Dr. Huentelman will use his expertise regarding APOE genotyping.
Role: Co-Investigator

Huentelman, Matthew
R01   (Matthew Huentelman)   09/15/2014 – 09/14/2018
NIH $66,898
CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox
Role: Multi-PI

Huentelman, Matthew
Grant   (Matthew Huentelman)   07/01/2014 – 06/30/2017
ABRC $114,901
Genetic factors associated with family history for Alzheimer's disease and their impact on cognition and brain function
Role: Principal Investigator

Huentelman, Matthew
Grant   (Douglas Walker)   07/01/2014 – 06/30/2017
ABRC $62,321
Is Interleukin-34 the key cytokine for regulating inflammation in Alzheimer's and Parkinson's Disease
Role: Co-Investigator

Huentelman, Matthew
Grant   (Leslie Baxter)   07/01/2014 – 06/30/2017
ABRC $45,389
Mapping Heterogeneous Behavior to the Brain in Autism Spectrum Disorder: Neural
Role: Co-Investigator

Huentelman, Matthew
K99   (Isabelle Schrauwen)   09/01/2014 – 08/31/2019
NIH $85,021
Molecular mechanisms of the normal impaired and regenerating inner ear
Role: Mentor

Huentelman, Matthew
R21   (Emily Rogalski)   09/01/2014 – 08/31/2016
NIH $26,778
Longitudinal and Neurobiologic Correlates of Cognitive SuperAging
Role: Co-Investigator

Huentelman, Matthew
Grant   (Matthew Hunetleman)   09/01/2014 – 08/31/2016
CART (American Federation for Aging Research) $101,582
The Genetics of Cognitive Performance in Non-Demented Subjects of First Degree Relatives with Alzheimer's Disease
Role: Principal Investigator

Huentelman, Matthew
R21   (Changiz Geula)   09/01/2014 – 08/31/2016
NIH $19,612
Exceptional Cognitive Aging: Cellular and Molecular correlates
Role: Co-Investigator

Huentelman, Matthew
R01   (Lalitha Madhavan)   09/01/2014 – 08/31/2017
NIH $3,129
Neural stem cells and the aging trajectory
Role: Co-Investigator

Huentelman, Matthew
U01   (Galbraith)   9/01/2014 – 08/31/2017
NIH $400,043
Transformative Approaches for Cell-Type Classification in the Brain
Role: Co-Investigator

Huentelman, Matthew
U01   (Rongguang Liang)   09/01/2014 – 08/31/2017
NIH $29,167
Mapping of Behavior Circuits: A Scalable Acquisition and Data Management System
Role: Co-Investigator

Liang, Winnie
R01-CA159871   (David Kaetzel)   12/01/2013 - 03/31/2014
NIH $72,684
Suppression of Melanoma Initiation and Progression by NM23-H1
Role: Staff Scientist

Liang, Winnie
UM1   (Pat LoRusso)   02/01/2014 – 01/31/2019
NIH $88,161
ViKTriY Early Clinical Trials Consortium (ECTC)
Role: Jr. Faculty Investigator

Liang, Winnie
(Aarthi Narayanan)   06/01/2014 – 05/31/2015
IARPA $297,578
Multi-omic Discovery of Host-derived Biomarkers of Venezuelan Equine Encephalitis Virus Exposure
Role: Lead Investigator

Liang, Winnie   07/01/2014 – 06/30/2015
Alz.DCC $30,000
Detection and characterization of circulating mitochondrial DNA in Alzheimer's disease
Role: Principal Investigator

Jensen, Kendall
Grant   (Ashkan Javaherian)   09/01/2014 – 08/31/2016
DoD $10,991
Exosome-Mediated Transmission of Neurodegeneration in Amyotrophic Lateral Sclerosis Using Patient Induced Pluripotent Stem Cell-Derived Neurons and Astrocytes
Role: Investigator

Jensen, Kendall
Grant   (Dr. Kalani)   07/01/2014 – 06/30/2017
Arizona Biomedical Research Commission $134,985
exRNA Signatures as Biomarkers for Stroke
Role: Investigator

Jensen, Kendall
Grant   (Robert Bowser)   07/01/2014 – 06/30/2017
Arizona Biomedical Research Commission $101,630
ALS Grant
Role: Investigator

Jensen, Kendall
Contract   (Aarthi Narayanan)   06/01/2014 – 05/31/2015
IARPA $211,000
Multi-omic Discovery of Host-derived Biomarkers of Venezuelan Equine Encephalitis Virus Exposure
Role: Lead Investigator

Jensen, Kendall
R01   (Kendall Jensen)   09/15/2014 – 09/14/2017
NIH $200,000
Characterization of extracellular vesicles derived from neurons
Role: Principal Investigator

Jensen, Kendall
R01   (Johanna DiStefano)   09/01/2014 – 08/31/2019
NIH $8,000
ROLE OF MICRORNAS IN THE DEVELOPMENT OF DIABETIC KIDNEY DISEASE
Role: Investigator

Jensen, Kendall
R01   (Ashkan Javaherian)   09/15/2014 – 09/14/2017
NIH $42,492
Exosome-Mediated transmission of neurodegeneration in amyotrophic lateral sclerosis
Role: Investigator

Jensen, Kendall
R01   (Robert Bowser)   09/01/2014 – 08/31/2019
Peptide and protein biomarkers for amyotrophic lateral sclerosis (ALS)
Role: Investigator

Arizona Alzheimer's Consortium
16th Annual Scientific Conference
Thursday, June 5, 2014

Banner Desert Medical Center
Mesa, Arizona

Poster Abstracts

Poster 1

BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) POLYMORPHISMS ARE ASSOCIATED WITH DIFFERENTIAL RATES OF AMYLOID ACCUMULATION AND COGNITIVE DECLINE IN COGNITIVELY NORMAL OLDER ADULTS. Acosta JI, Geda YE, Stokin G, Fleisher AS, Reschke C, Bauer R, Thiyyagura P, Lu B, Caselli RJ, Weiner M, Reiman EM, Chen K. Mayo Clinic Scottsdale; Arizona Alzheimer's Consortium; International Clinical Research Center, Brno, Czech Republic; St. Anne's University Hospital Brno, Brno, Czech Republic; Banner Alzheimer's Institute; Tsinghua University; University of California, San Francisco.

Background: Among cognitively unimpaired persons with florbetapir positron emission tomography (PET) evidence of significant fibrillar amyloid-β (Aβ) burden from the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study, carriers of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism were distinguished from non-carriers by greater 36-month rates of memory, language, executive function, and hippocampal volume declines. Here, Alzheimer's Disease Neuroimaging Initiative (ADNI) data were used to investigate whether baseline measurements and 24-month changes in fibrillar Aβ deposition and neuropsychologist test scores were differentially affected by BDNF-Met carrier status in cognitively unimpaired individuals.

Methods: 14 cognitively unimpaired BDNF-Met carriers, aged 76–94 years, and 20 non-carriers, aged 70–89 years, had baseline and 24-month follow-up clinical ratings, neuropsychological tests, florbetapir PET, and magnetic resonance imaging (MRI) scans. Standard uptake value ratios (SUVRs) with cerebellum reference region were used to quantify PET fibrillar Aβ burden. T-tests were used to compare baseline measurements and 24-month changes in mean cortical florbetapir SUVRs, hippocampal volumes, and performance on 10 neuropsychological tests.

Results: Except for age (carriers=82.52 ± 5.78, non-carriers=78.63 ± 4.49, $p=0.03$), at baseline, BDNF-Met carriers and non-carriers did not differ in their gender ratios, years of education, proportions of apolipoprotein (APOE) ε4 carriers, Mini-Mental State Examination scores, florbetapir SUVRs, or hippocampal volumes. Interestingly, for baseline Auditory Verbal Learning Test (AVLT) scores, BDNF-Met carriers exhibited greater memory retention relative to non-carriers with ($p=0.05$) or without ($p=0.03$) accounting for age. BDNF-Met carriers were, however, distinguished from non-carriers by greater 24-month mean cortical florbetapir SUVR increases with ages accounted for ($p=0.003$) or not ($p=0.02$). Similarly, the BDNF-Met carriers had greater 24-month decline on AVLT long-term recall scores again with ($p=0.009$) or without ($p=0.003$) co-varying out age (but uncorrected for multiple neuropsychological tests). The groups, however, did not differ significantly in their 24-month changes of hippocampal volume or other neuropsychological test performance scores ($p>0.05$).

Conclusions: This study raises the possibility that BDNF Val66Met allele is associated with accelerated rates of memory decline and greater amyloid deposition in cognitively normal adults. Additional studies are needed to confirm these preliminary findings and clarify the manner in which BDNF influences pathogenesis of Alzheimer's disease.

VIRTUALLY SUPPORTIVE: A FEASIBILITY PILOT STUDY OF AN ONLINE SUPPORT GROUP FOR DEMENTIA CAREGIVERS IN A 3D VIRTUAL ENVIRONMENT. Arizmendi B, O'Connor M. University of Arizona**;** Arizona Alzheimer's Consortium.

Background: Caregiver support groups effectively reduce stress from caring for someone with dementia. These same demands can prevent participation in a group. The present feasibility study investigated a virtual online caregiver support group to bring the support group into the home. While online groups have been shown to be helpful, submissions to a message board (vs. live conversation) can feel impersonal. The goal of this study was to investigate the use of a low cost computer-based platform for conducting live, yet anonymous support groups.

Methods: By using avatars, participants interacted via real-time chat in a virtual environment. Each group was moderated by one or both authors who followed the structure of an 8-week manualized caregiver support group protocol. Participants logged into the groups on their own computer thus they were able to join from the comfort of their own home.

Results: Data indicated lower levels of perceived stress, depression and loneliness across participants. Importantly, satisfaction reports also indicate that caregivers overcame the barriers to participation, and had a strong sense of the group's presence.

Conclusions: This study provides the framework for an accessible and low cost online support group for a dementia caregiver. The study demonstrates the feasibility of interactive group in a virtual environment for engaging members in meaningful interaction.

AGE RELATED DIFFERENCES IN HIPPOCAMPAL RESPONSE TO INCREASING DIFFICULTY IN AN ASSOCIATIVE MEMORY RETRIEVAL TASK: AN FMRI INVESTIGATION OF FUNCTIONAL COMPENSATION IN A FACE-NAME PAIRS TASK.
Baena E, Buckley T, Myhre JW, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Neuroimaging studies have shown that older adults engage bilateral frontal regions to a greater degree than young adults during memory tests, suggesting that older adults compensate for increasing task difficulty by relying to a greater degree on executive control processes. However, whether the compensation response occurs in other brain regions, such as hippocampus, is unclear.

Methods: The present study evaluated compensatory patterns of activation in younger (ages 18-30) and older (ages 65-91) adults in an associative memory task that engages hippocampus across three levels of difficulty. Participants studied face/name pairs and later completed a yes-no recognition test for previously presented pairs and recombined pairs. Difficulty was manipulated by increasing the set size (2, 4, and 6).

Results: Overall, younger adults were more accurate than older adults. Older adults showed linearly decreasing accuracy in response to increasing task difficulty, while younger adults maintained accuracy across set sizes. Linear increases in fMRI activation associated with increasing difficulty during successful retrieval were observed in bilateral hippocampus in young adults, as well as within ventral-visual cortical regions. In contrast, older adults showed linear increases in the left, but not right, hippocampus, as well as extensive regions of bilateral frontal and parietal cortex that were not observed in younger adults.

Conclusions: We suggest that younger and older adults engage different functional compensatory networks in response to increasing task difficulty. Increases in hippocampal activation, however, may be common across the two age groups, at least in the left medial temporal lobe.

STRATEGY USE IN NAVIGATING A HUMAN RADIAL-ARM MAZE: TRANSLATING SPATIAL COGNITION ACROSS SPECIES. Baxter LC, Grunfeld IS, Mennenga SE, Camp BW, Patten KJ, Bimonte-Nelson HA*, McBeath MK*. Arizona State University; Arizona Alzheimer's Consortium; Barrow Neurological Institute.
*equal contribution to this project

This study examines individual differences in navigational strategy in order to translate between domains of human and rodent research. We designed a 50-foot diameter, 11-arm walk-through human radial arm maze (HRAM) as a means of paralleling research done with rodent radial arm mazes (RAM). 157 participants were assessed on maze performance, a battery of neuropsychological and cognitive tests, and information regarding their strategy and cues used in navigating the maze. Our analyses examined participant performance (number and order of errors) as a function of self-reported cue use and strategy type. We grouped individuals into categories of strategy relevant to past human navigational research (systematic versus brute-force), into categories relevant to past rodent navigational research (whether internal or external cues were utilized), as well as by strategy consistency across maze testing sessions. Our findings revealed that those who used systematic strategies made fewer errors than those who used brute-force strategies, those who self-reported using external-reference cues performed better than the remaining participants, and those who were consistent in their strategy choice performed better than those that switched strategy between testing sessions. Within the participants who were inconsistent in their strategy choice, performance was better on the second testing session. The HRAM shows promise as a functional translational instrument for testing general memory and navigational principals commonly evaluated in rodents, and can be used to translate questions between rodents and humans. Testing humans using similar methodology to that used when evaluating rodent learning and memory provides a foundational tool to translate models of spatial cognition and reasoning across species.

RETINAL PATHOLOGY IN PARKINSON'S AND ALZHEIMER'S DISEASE: A-SYNUCLEINOPATHY BUT NOT Aβ OR TAU PATHOLOGY. Beach TG, Carew J, Serrano G, Adler CH, Shill HA, Sue LI, Sabbagh MN, Akiyama H, Cuenca N. Banner Sun Health Research Institute; Mayo Clinic Arizona; Tokyo Metropolitan Institute of Medical Science; Universidad de Alicante; Arizona Alzheimer's Consortium.

Background: Visual symptoms are relatively common in both Parkinson's disease (PD) and Alzheimer's disease. Optical coherence tomography has indicated possible retinal thinning in PD while retinal ganglion cell loss has been reported in AD. Still unclear is whether the characteristic proteinopathies of these diseases are present in the retina. Previous studies have generally reported negative findings (1). We sought to determine the presence or absence of pathological deposits of α-synuclein, Aβ and tau in the retinas of normal elderly subjects as well as those that had been neuropathologically diagnosed with PD and AD.

Methods: Retinal wholemounts were prepared from subjects with a primary clinicopathological diagnosis of PD, dementia with Lewy bodies, Alzheimer's disease, progressive supranuclear palsy as well as elderly normal control subjects. These were immunohistochemically stained with antibodies against α-synuclein phosphorylated at serine 129, which is a specific molecular marker of synucleinopathy as well as antbodies against Aβ and abnormally phosphorylated tau protein.

Results: In agreement with previous reports (1), we found no evidence of Aβ or tau pathology in any subject retinas. Phosphorylated α-synuclein-immunoreactive (p-syn IR) nerve fibers were present in 7/9 PD subjects and in 1/3 DLB subjects; these were sparsely distributed and superficially located near or at the inner retinal surface. The fibers were either long and straight or were branching, often with multiple en-passant varicosities along their length. The straight fibers most often had an orientation that was radial with respect to the optic disc. Together, these features are suggestive of either retinopetal/centrifugal fibers or of ganglion cell axons. In one PD subject there were sparse p-syn IR neuronal cell bodies with dendritic morphology suggestive of G19 retinal ganglion cells or intrinsically photosensitive ganglion cells. There were no p-syn IR features in any of the non-PD or non-DLB subjects.

Conclusions: Some of the observed visual function impairments in PD subjects might be due to α-synucleinopathy. It is possible that the p-syn IR fibers might allow an ophthalmological diagnostic test for PD should appropriate technology be developed for this. Like others, we found no evidence for pathological Aβ or tau deposition in the retinas of AD subjects.

1. Ho CY, Troncoso JC, Knox D, et al. Beta-amyloid, phospho-tau and alpha-synuclein deposits similar to those in the brain are not identified in the eyes of Alzheimer's and Parkinson's disease patients. Brain Pathol 2014;24:25-32

THEORETICAL IMPACT OF FLORBETAPIR (18F) AMYLOID IMAGING ON THE DIAGNOSIS OF ALZHEIMER'S DEMENTIA AND THE DETECTION OF PRECLINICAL CORTICAL AMYLOID. Beach TG, Schneider JA, Sue LI, Serrano G, Dugger BN, Monsell SE, Kukull W. Banner Sun Health Research Institute; University of Washington; Arizona Alzheimer's Consortium.

Background: The relative inaccuracy of the clinical diagnosis of Alzheimer's disease dementia (ADD) may be a major impediment to clinical trials of candidate therapeutic agents. A recent study (1) found sensitivity ranged from 70.9% to 87.3% while specificity ranged from 44.3% to 70.8%. In 2012, florbetapir (18F) (Amyvid) received US FDA approval as a diagnostic agent for the detection of cerebral cortex neuritic (amyloid) plaques (2). Although such approval is specifically not extended to the usage of florbetapir as a single definitive diagnostic test for ADD, it is of considerable importance to assess the potential improvement in diagnostic accuracy that might be so obtained.

Methods: To assess the theoretical impact of florbetapir on the diagnosis of ADD and the detection of preclinical cortical amyloid in cognitively normal subjects, we used data from two published studies. To estimate the fractions of subjects with specified densities of postmortem-identified neuritic plaques that are detectable by antemortem florbetapir imaging, we used the data of Clark et al (2), derived from 59 subjects. We then used these fractions to determine the proportion of florbetapir-positive cases that would meet neuropathological criteria for the presence of ADD, utilizing the data of Beach et al (1) from 919 subjects, derived from the National Alzheimer's Coordinating Center (NACC), which gathers information from the network of National Institute on Aging .Alzheimer's Disease Centers (ADCs).

Results: Assuming a positive florbetapir amyloid scan as the sole clinical diagnostic criterion for the presence of ADD, and the presence of moderate or frequent cortical CERAD neuritic plaque densities together with Braak neurofibrillary stage III-VI as the neuropathological definition of ADD, the sensitivity and specificity of a positive florbetapir amyloid scan for the detection of neuropathologically-defined ADD is estimated as 95% and 89%, respectively. From the same NACC dataset, 144 subjects had normal cognition; of these, 84 (56%) had neuritic plaques at autopsy and it is estimated that florbetapir imaging would detect 47/84 (56%).

Conclusions: The usage of florbetapir amyloid imaging or other comparable amyloid imaging agents would appear to greatly improve diagnostic accuracy and hence subject selection for ADD clinical trials, allowing smaller subject numbers and lower trial costs. Our calculations show that florbetapir amyloid imaging may detect only 56% of cognitively normal subjects with cortical neuritic plaques. This is encouraging but demonstrates that the very earliest stages of what might be termed "preclinical AD", with only sparse densities of cortical neuritic plaques, are still expected to be florbetapir-negative, at least when using equivalent methods as were used in the florbetapir trial.

1. Beach TG, Monsell SE, Phillips LE, et al. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. J Neuropathol Exp Neurol 2012;71:266-273.   2. Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. Lancet Neurol 2012;11:669-678.

ADMINISTRATION OF A SELECTIVE β2 ADRENERGIC RECEPTOR ANTAGONIST EXACERBATES NEUROPATHOLOGY AND COGNITIVE DEFICITS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE. Branca C, Hartman LK, Shaw DM, Farrell EK, Caccamo A, Oddo S; Banner Sun Health Research Institute; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Currently, there are no available approaches to cure or slow down the progression of Alzheimer's disease (AD), which is characterized by the accumulation of extracellular amyloid-β (Aβ) deposits and intraneuronal tangles composed of hyperphosphorylated tau. β2 adrenergic receptors (β2ARs) are expressed throughout the cortex and hippocampus and play a key role in cognitive functions. Alterations in the function of these receptors have been linked to Alzheimer's disease; however these data remain controversial as apparent contradicting reports have been published. Given the current demographics of growing elderly population and the high likelihood of concurrent beta-blocker use for other chronic conditions, more studies into the role of this receptor in AD animal models are needed.

Methods: To determine the effects of chronic administration of selective β2AR antagonist on Aβ and tau pathology, we treated 8-month-old female 3xTg-AD and NonTg mice with 1 mg/kg ICI 118,551, a selective β2AR antagonist, which was delivered via daily intraperitoneal (i.p.) injections for 6 weeks.

Results: Here we show that administration of ICI 118,551, a selective β2AR antagonist, exacerbates cognitive deficits in a mouse model of AD, the 3xTg-AD mice. Neuropathologically, ICI 118,551 increased Aβ levels and Aβ plaque burden. Concomitantly, ICI 118,551-treated 3xTg-AD mice showed an increase in tau phosphorylation and accumulation. Mechanistically, these changes were linked to an increase in amyloidogenic APP processing.

Conclusions: These results suggest that under the conditions used here, selective pharmacological inhibition of β2ARs has detrimental effects on AD-like pathology in mice. Overall, these studies strengthen the notion that the link between β2ARs and AD is likely highly complex and suggest caution in generalizing the beneficial effects of beta-blockers on AD.

Poster 8

AN INVERSE RELATIONSHIP BETWEEN LONGITUDINAL CHANGES IN FASTING SERUM GLUCOSE AND CEREBRAL GLUCOSE METABOLISM IN ALZHEIMER'S DISEASE RELATED BRAIN REGIONS. Burns CM, Kaszniak AW, Chen K, Lee W, Bandy DJ, Reschke C, Caselli RJ, Reiman EM. University of Arizona**;** Banner Alzheimer's Institute**;** Mayo Clinic Scottsdale; Arizona Alzheimer's Consortium.

Background: Positron emission tomography (PET) has been utilized to demonstrate a cross sectional relationship between elevated indicators of insulin resistance and reduced regional cerebral metabolic rate for glucose (rCMRgl) in AD related brain regions of cognitively healthy adults. Studying this relationship across time will permit us to draw a stronger causal inference between factors that affect glucose control and risk associated with the development of AD.

Methods: This is a longitudinal study (4.4 ± 1.0 years) of 80 cognitively normal, non diabetic persons aged 61 ± 5 years, with a first-degree history of AD, including 42 APOE-ε4 non carriers and 38 carriers. An automated brain-mapping algorithm characterized and compared correlations between increases in fasting serum glucose levels and decreases in [18F] –fluorodeoxyglucose PET rCMRgl measurements. Associated changes in a select set of neuropsychological tests measuring memory, attention and processing speed were also studied with linear regression.

Results: There was a negative correlation between changes in fasting serum glucose levels across time and changes in rCMRgl in brain regions preferentially affected by AD. There was no interaction between APOE-e4 status and the fasting serum glucose/ CMRgl longitudinal relationship, suggesting an independent risk associated with serum glucose levels. Furthermore, increases in fasting serum glucose were associated with a decline in a measure of visuospatial memory (Rey-Osterrieth Complex Figure Test, Delayed Recall).

Conclusions: Findings suggest that increases in fasting serum glucose levels across time may be associated with the development of AD related pathophysiology and changes in cognitive performance. These findings underscore the importance of the study of risk related to glucose control and further support the use of neuroimaging measurements as a more efficient manner to identify and track metabolic processes involved in AD development.

GENETIC REDUCTION OF MTOR AMELIORATES ALZHEIMER'S DISEASE-LIKE COGNITIVE AND PATHOLOGICAL DEFICITS BY RESTORING HIPPOCAMPAL GENE EXPRESSION SIGNATURE. Caccamo A, De Pinto V, Messina A, Branca C, Oddo S. Banner Sun Health Research Institute; University of Catania; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Elevated mammalian target of rapamycin (mTOR) signaling has been found in Alzheimer's disease (AD) patients and is linked to diabetes and aging, two known risk factors for AD. However, whether hyperactive mTOR plays a role in the cognitive deficits associated with AD remains elusive.

Methods: Here, we genetically reduced mTOR signaling in the brains of Tg2576 mice, a widely used animal model of AD.

Results: We found that suppression of mTOR signaling reduced amyloid-β deposits 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: Our results implicate hyperactive mTOR signaling as a previous unidentified signaling pathway underlying gene-expression dysregulation and cognitive deficits in Alzheimer's disease. Furthermore, hyperactive mTOR signaling may represent a molecular pathway by which aging contributes to the development of AD.

Poster 10

ASSESSMENT OF GERIATRIC PARTICIPANT'S RETENTION OF A PHARMACIST-PROVIDED WARFARIN EDUCATION CLASS. Carroll K, Gerber DK. Midwestern University; Arizona Alzheimer's Consortium.

Background: Warfarin therapy is efficacious in preventing blood clots, but it is not without risks- namely bleeding. Many risk factors for bleeding complications are common in older patients, such as multiple comorbidities, polypharmacy, history of hypertension, insufficient social support, and reduced functional status. Fear of major bleeding remains high among prescribers, which can lead to underuse in the elderly. One study looked at bleeding rates of elderly patients prescribed anticoagulation with warfarin and found that insufficient education was a major factor in predicting bleeding. Furthermore, in a quasi-systemic review, between 50% and 80% of older patients were found to have inadequate knowledge about the basic aspects of warfarin therapy. At the Banner Health Center anticoagulation clinics, patients have the opportunity to participate in a pharmacist led warfarin education class. This study aims to determine the retention of education provided to those geriatric patients. This study also aims to assess if baseline characteristics, such as cognitive function or comorbid conditions, affect warfarin education retention, and if subjects with higher Oral Anticoagulation Knowledge (OAK) test scores have a more therapeutic and consistent control of INRs.

Methods: Prior to the education, the subjects' cognitive function will be evaluated as a baseline characteristic using a cognitive screening tool, the clock-drawing test. The subject will then listen to a presentation prepared by a pharmacist about warfarin. This presentation is updated to reflect the most current information. After the presentation the subject will complete the validated OAK test as the first intervention. At a follow up anticoagulation clinic visit within the following 3-8 weeks, the subject will be administered the same OAK test as the second intervention. The primary population to be evaluated in this study is geriatric subjects. The study will include all genders, race, and age $\geq$ 65 years old.

Data collection is ongoing at the time of abstract submission.

Preliminary results will be presented at the conference.

PREDICTIVE TESTING FOR ALZHEIMER'S DISEASE: SUICIDAL IDEATION AMONG HEALTHY PARTICIPANTS. Caselli RJ, Langbaum J, Marchant GE, Lindor RA, Hunt KS, Henslin BR, Dueck AC, Robert JS. Mayo Clinic Arizona; Banner Alzheimer Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: People undergoing predictive genetic testing for Alzheimer's disease are at risk for suicidal ideation.

Methods: A survey developed from interviews with focus groups of healthy individuals enrolled in an AD research program was completed by 316 members of the Arizona APOE Cohort.

Results: 83.5% were interested in obtaining genetic test results: 64 wanted them only if testing was free, 28 only within the context of research, and 167 were willing to personally pay at least \$100. Univariate analyses revealed that those wanting genetic testing (compared to those who did not) had higher Personality Assessment Inventory (PAI) Paranoia (T score 43.9 v 41.8, p=.038) and Neuropsychiatric Inventory Questionnaire (NPIQ) total (1.36 v 0.63, p=.015) scores, lower Selective Reminding Test (SRT) immediate free recall (89.6 v 94.6, p=.014), and more divorces per person (.67 v .34, p=.009). In a multivariate model containing these 4 terms SRT (OR=1.055, p=.011) and divorce (OR=.469, p=.015) remained significant. 6% endorsed they would seriously consider suicide if found to be at high risk for AD. In univariate analyses those endorsing suicide were older (70.7 v 65.2 +/- 10.7 years, p=.032), more likely to be unmarried (11.5% v 4.1%, p=.026), endorsed greater feelings of nonsupport (PAI-NON T score 53.5 v 46.3 +/- 8.4, p=.005) and suicidal rumination (PAI-SUI T-score 50.9 v 46.8 +/- 5.7, p=.018), had a higher NPIQ total score (2.6 v 1.2 +/- 1.8, p=.002), and performed better on WAIS-R information (age scaled score 13.8 v 12.5 +/- 2.3, p=.020), WAIS-R similarities (age scaled score 14.1 v 12.9 +/- 2.0, p=.019), and vegetable fluency (items in 1 minute, 18.0 v 15.5 +/- 4.2, p=.018). Personality factors (NEO 5 factor model) and depression scores did not differ between the groups, and there was no cognitive measure on which those endorsing suicide performed less well. In a multiple regression model containing these 8 items, vegetable fluency (OR=1.197, p=.024) and marital status (OR=6.012, p=.020) remained significant.

Conclusions: Our cohort members endorsing suicidal ideation were older and less likely to be married but seemed neuropsychiatrically healthy on all cognitive, psychiatric, and personality measures.

NOVEL METHOD FOR BEHAVIOR-DRIVEN MOLECULAR AND STRUCTURAL INVESTIGATION IN RODENT WHOLE BRAIN. <u>Chawla MK, Gray DT, Comrie AE, Barnes CA</u>. University of Arizona; Arizona Alzheimer's Consortium.

<u>Background</u>: Currently methods for identifying the regional distribution of neuronal activity within the brain during specific behaviors is not only time consuming, but also labor intensive. To circumvent the need to serial section, stain, obtain confocal images of the tissue, then reconstruct large parts of brain by using algorithms that can montage tissue sections back together, we are currently developing a method that allows behavior-induced activity markers to be imaged in intact brain. This involves combining a recently developed whole brain clarification method (CLARITY; Chung et al., 2013) that provides the capacity to image deep into an intact brain, with a gene expression, cellular activity marker method (catFISH) that labels only those cells active in a given behavioral experience.

<u>Methods</u>: Brain from a young rat was extracted after maximal electro-convulsive shock treatment (that enables rapid transcription of immediate early genes) and quick frozen in isopentane that was cooled in a dry-ice ethanol slurry. The frozen brain was then placed in a 50 ml centrifuge tube containing hydrogel solution for post-fixation which allows cross linkage with formaldehyde in the presence of hydrogel monomers, covalently linking tissue elements to monomers that are then polymerized into a hydrogel mesh. An electric field (25 volts) was applied across the sample in ionic detergent in a electrophoretic chamber which actively transports micelles through the tissue, which removes brain lipids, leaving the fine structure and cross linked biomolecules in place. The cleared brain tissue (~2 mm slab) was then processed for in situ hybridization using full length Arc digoxigenin tagged cRNA probe (Chawla et al., 2005) followed by CY3 TSA amplification. Tissue was counterstained with DAPI and submerged in 85% glycerol for imaging.

<u>Results</u>: Images were collected using an advanced intravital multi-photon microscope and a 3-D rending of the collected images was performed. Cell nuclei with Arc transcription foci and cytoplasmic Arc were clearly visible up to ~300 μm deep in the tissue.

<u>Conclusion</u>: These results provide evidence for the first time that we can combine Arc catFISH with CLARITY methods in a slab of cleared brain. Future experiments will be carried out in whole brain of animals that have undergone exploratory behaviors.

Chawla, M.K., Gray, D.T., Comrie, A.E., and Barnes, C.A. (2014) Novel method for behavior-driven molecular and structural investigation in rodent whole brain. The 2014 Arizona Alzheimer's Consortium Annual Conference, June 2014.

IMPROVING THE POWER TO TRACK FIBRILLAR AMYLOID PET MEASUREMENTS AND EVALUATE AMYLOID-MODIFYING TREATMENTS USING A CEREBRAL WHITE MATTER REFERENCE REGION-OF-INTEREST. Chen K, Roontiva A, Thiyyagura, P, Lee W, Liu X, Ayutyanont N, Protas H, Landau S, Luo J, Bauer R, Reschke C, Bandy D, Koeppe R, Fleisher AS, Caselli RJ, Jagust WJ, Weiner MW, Reiman EM, and the Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; University of Arizona; Mayo Clinic Arizona; University of California, Berkeley; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: We postulated that variability in longitudinal positron emission tomography (PET) measurements of fibrillar amyloid-β (Aβ) burden might be partly attributable to the combined effects of between-scan differences in head positioning and the use of inferior reference regions-of-interest (ROIs) in the computation of cerebral-to-reference ROI standard uptake value ratios (SUVRs). We used florbetapir PET images from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to demonstrate improved power to track longitudinal fibrillar Aβ changes and evaluate Aβ-modifying treatments using a cerebral white matter (WM) ROI.

Methods: Baseline and 24-month follow-up florbetapir PET scans from 31 probable Alzheimer's dementia (pAD) patients, 187 mild cognitive impairment (MCI) patients and 113 cognitively normal controls (NCs) were used to compare the power of automatically generated cerebellar, pontine, and WM (eroded corpus callosum/centrum semiovale) reference ROIs to track SUVR changes and evaluate Aβ-modifying treatment effects. Data were analyzed in Aβ+ and Aβ- pAD, MCI, and NC and cognitively normal apolipoprotein E4 (APOE4) carrier and non-carrier sub-groups.

Results: In contrast to use of cerebellar or pontine reference ROIs, the WM reference ROI permitted us to consistently detect significant longitudinal SUVR increases in the Aβ+ pAD, MCI, and NC and normal APOE4 carrier sub-groups, to consistently detect significantly greater SUVR increases in these groups than in their respective Aβ- or non-carrier controls, and to detect an overall correlation between longitudinal SUVR increases and longitudinal Mini-Mental State Examination (MMSE) score declines. Using the WM reference ROI, we estimate the need for far fewer pAD, MCI, Aβ+ NC, and APOE4-carrying NC subjects to detect an amyloid-modifying treatment effect in a 12-month placebo-controlled trial.

Conclusions: A WM white matter reference ROI can help improve the power to track longitudinal fibrillar Aβ increases, relate them to longitudinal cognitive decline, and evaluate Aβ-modifying treatments with improved statistical power.

DIFFERENTIAL EFFECTS OF CONTEXT SHIFTS ON OBJECT RECOGNITION AND SOURCE MEMORY IN OLDER ADULTS. Cooke KA, Kawa K, Memel MB, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Context shifts between study and test can result in substantial declines in object recognition. For example, in young adults, recognition accuracy decreases by approximately 15% when objects are studied in a semantically-related scene and subsequently tested on a white background, suggesting an obligatory binding between an object and its context (Hayes et al., 2007). Naveh-Benjamin (2000) proposed that older adults do not engage in associative binding to the same extent as younger adults. Paradoxically, this would suggest that older adults should not show the same decrease in object recognition when context shifts occur.

Methods: In a series of three experiments, photographs of unique objects either embedded in a semantically-related scene or on a white background were presented in an incidental learning paradigm. Various context manipulations were performed in which participants were asked to make judgments about objects whose backgrounds had been changed between encoding and retrieval.

Results: Experiment 1 demonstrated that, contrary to the associative binding hypothesis, older and younger adults show similar decrements in recognition when context shifts occur. Experiment 2 varied the specificity vs. familiarity of the context. Once again, older and younger adults showed similar patterns – recognition was best for objects tested in the identical context, decreased for objects tested in a familiar context, and decreased further for objects tested in a completely novel context. Experiment 3 investigated context shifts in source memory. In contrast to object recognition, only younger adults showed a context effect, while context shifts had no impact on source memory judgements for older adults.

Conclusions: Our results suggest that older adults engage in successful binding of objects and contexts, conferring a benefit to recognition memory. However, they may be less capable of accessing contextual information to aid in source memory judgements.

Poster 15

AN INTERNET-BASED STUDY OF OVER 25,000 INDIVIDUALS DEMONSTRATES SIGNIFICANT EFFECTS OF AGE, GENDER, EDUCATION, AND ALZHEIMER'S DISEASE FAMILY HISTORY IN PAIRED ASSOCIATE LEARNING. Corneveaux J, Schrauwen I, Siniard A, Peden J, Turk M, De Both M, Richholt R, Mueller M, Langbaum J, Reiman EM, Caselli RJ, Coleman P, Barnes C, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University of Arizona; LeaseHawk; Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute.

Background: The demographic and health/disease risk factors associated with learning of various cognitive tasks are of significant scientific interest because of the myriad of disorders that include cognitive deficits as part of their core symptomatology. Much of the existing data on learning performance is based on studies that were underpowered to detect all but the strongest effectors of learning due to their size or demographic risk factor recruitment bias. To address these concerns we developed a web-based paired associate learning (PAL) task that was coupled with 20 demographic and health/disease risk factor questions at mindcrowd.org. To date over 65,000 unique visitors have viewed our site with over 25,000 of them consenting into our study and completing the entire test. This large sized cohort spanning demographic and risk factor ranges will allow us to perform the most in-depth investigation of PAL and the factors that may influence it.

Methods: Paired associate learning test (PAL): Subjects were presented with a list of 12 word pairs sequentially with each pair shown on screen for two seconds. During the recall period, the subject is shown one half of the word pair and must enter the other paired word. This cycle repeats an additional two times for a total of three trials. Data-analysis: Strict filtering criteria were used to clean the data prior to analysis, which lead to a total of 19,202 unique entries. First, to ensure a full capacity to learn and exclude bias from the ceiling effect, the third round was excluded, and learning over round 0-1-2 was calculated. A multiple regression model was fitted with score as the dependent value, and main effects, testround, and interaction testround:demographic as independent effect. Significance of the interaction was tested by analysis of variance of a model with and without the interaction term. In a second model, bias due to the ceiling effect was corrected by removing individuals with a start score >4, to allow a full capacity to learn over the 3 rounds (1-2-3) (N=5,275). To test learning ability over the 3 testrounds, a random intercept model was fitted with score as dependent valuable, all main effects, testround and the interaction term testround:demographic as fixed effects, and ID as random effect. A Kenward-Roger approximation was used to compare models with and without the interaction term to detect significant different slopes over the different rounds depending on the demographic. Regression diagnostics and the fit of the models were carried out by visual inspection of several residual plots, testing the presence of high influential data points and/or outliers, and by testing autocorrelation of the residuals and the presence of multicollinearity.

Results: Our results show that learning ability over the testrounds is mostly influenced by Age, Gender and Education. The difference in learning ability between genders is present at every age and is highest in the 60s ($p < 2.2 \times 10^{-16}$), which is consistent with what was found with overall PAL performance. The decline in learning per age group is more extensive at the older ages, and the decline is more pronounced in males (70s; testround:gender $p < 2.2e-16$). We also found a decreased learning ability in younger individuals (<20s) with a first-degree Alzheimer's relative (p=0.001).

Conclusions: We found that learning in the PAL task is significantly influenced by Age, Gender and Education. In addition, first-degree Alzheimer's relatives also show a significant decrease in learning at young age (20s). These data suggest that similar factors associated with overall PAL performance also

influence PAL. The use of our web-based recruitment approach is feasible and identified novel factors associated with PAL. These findings further highlight the importance of large studies of cognitive performance that span multiple demographic factors. Future work will investigate additional non-heritable as well as heritable factors that are associated with PAL.

SANGER SEQUENCING EXONS OF BDNF GENE DERIVED FROM A LATINO SAMPLE.
Dawit S, Krell-Roesch J,Acosta J, Champion MD, Velgos SN, Shaibi G, Mandarino LJ, Cevette NM, Caselli RJ, Geda YE. University of Kansas Medical Center; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Little is known about BDNF gene sequencing amongst Latinos. The aim of this study is to conduct Sanger sequencing of three targeted exon regions of the Brain Derived Neurotrophic Factor (BDNF) gene within a Latino sample.

Methods: We obtained blood samples from 357 Latinos (234 females). The mean (SD) age was 41.7 (8.3) and 41.5 (9.4) years for men and women, respectively. Participants included self-identified Latino persons recruited between 2009 and 2011 for a cardiometabolic disease study. Informed consent for future DNA research was obtained. Participants underwent extensive medical evaluation, including a self-administered survey on physical activity. The mean (SD) BMI for those who reported physical exercise was 29.5(4.9), and for those who did not report exercise was 31.9(7.5). In order to determine whether previously identified polymorphisms associated with disease were also carried in the genomes of our population, we conducted Sanger sequencing of three targeted exon regions of the BDNF gene. Custom python scripts were developed to convert raw sequencing reads and quality metrics to trimmed reads which were then aligned to the BDNF reference sequence using the (BWA) package. Polymorphisms were identified and characterized using IGV.

Results: A known SNP, (rs2353512) associated with addiction and neuropsychiatric morbidity was found in our sample. Although our sample was overweight or obese, we did not find a well-known polymorphism associated with Obesity (Val66Met [G->A/C->Trs6265]). No variations between sequence and reference were observed in region 2 (aln 136-582) or region 3 (aln 25-223).

Conclusions: A well-known polymorphism that is associated with obesity was not observed in our Latino sample, suggesting that sequence variations responsible for the obesity phenotype in our sample are in a region of the gene/genome that we did not sequence. It is also possible that other non-BDNF genomic regions are responsible for the obesity phenotype in our sample. Therefore, future sequencing efforts will focus on whole-genome assessment of our sample.

Poster 17

"INCIDENTAL" BRAIN PATHOLOGIES IN PROSPECTIVELY FOLLOWED NORMAL ELDERLY BRAIN BANK VOLUNTEERS. Dugger BN, Hentz JG, Adler CH, Sabbagh MN, Shill HA, Jacobson S, Caviness JN, Belden C, Driver-Dunckley E, Davis KJ, Sue LI, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: We recently investigated the clinicopathological outcomes of initially normal elderly subjects who enrolled in our brain and body donation program (Dugger et al. J Neuropathol Exp Neurol. 2014). In addition to the defining histopathology for certain neurodegenerative disorders, other pathologies may exist within the brain, including cerebral white matter rarefaction (CWMR), argyrophilic grains (Arg), cerebral amyloid angiopathy (CAA), and glial tauopathies. Furthermore, deposits of proteins that define certain diseases, such as TAR DNA binding protein-43 (TDP-43), may exist but cases lack corresponding clinical features during life.

Methods: We sought to determine the frequencies of these pathologies in a prospectively-assessed, community-based autopsy series.
We utilized the same 119 cases from our previous study, all having normal cognitive and movement disorder assessments at study entry and examined these for the following pathologies: CWMR, Arg, CAA, glial tauopathies, and abnormal TDP-43 deposits.

Results: Of these cases, 52% were female, median age at study entry was 83.5 years (range 67 to 99), and median duration from first visit until death was 4.3 years (range 0-10). All 119 cases contained at least one of the examined pathologies. With respect to the 87 subjects who were still clinically normal at death, 47 (54%) had CWMR, 22 (25%) Arg, 37 (43%) CAA, 8 (9%) glial tauopathies, and 41 (47%) TDP-43. Of the 30 who converted to a clinicopathologically defined neurodegenerative disease by the time of death, 27 cases (90%) had CWMR, 12 (40%) with Arg, 19 (63%) with CAA, 6 (20%) with glial tauopathies, and 15 (50%) with TDP-43. Pathology groups are not mutually exclusive; particular overlap was found.

Conclusions: Although limited by a relatively small sample size, these other pathologies found within initially normal elderly subjects represent a rough estimate of the incidence that exist within brains of elderly individuals over a defined time period.

Poster 18

THE PRESENCE OF TOTAL TAU IN PERIPHERAL TISSUES OF ALZHEIMER'S DISEASE.
Dugger B, Whiteside C, Maarouf C, Beach TG, Dunckley T, Meechoovet B, Roher AE. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Tau is one of the main protein aggregates within the brains of Alzheimer's disease (AD) patients; however, tau has not been extensively examined within human peripheral organs. Previous work from our laboratory demonstrated tau deposits to be present within the spinal cord of over 95% of AD and nearly 50% of elderly non-demented cases (ND). The purpose of our study was to determine the levels of total tau in areas amendable for biopsy as compared to the brain.

Methods: We chose cases from a previously published report (Dugger et al. J Alzheimers Dis. 2013 PMID: 23246918) that contained phosphorylated tau deposits through the extent of their spinal cord (18 AD and 2 ND cases). Total tau in the abdominal skin, liver, scalp, sigmoid colon, and submandibular gland was quantified by Western blot and enzyme-linked immunosorbent assay. Frontal gray matter was used as a frame of reference for each case.

Results: Western blot analyzes revealed that total tau was detectable in all peripheral areas analyzed but only a fraction of that compared to that found within the brain. enzyme-linked immunosorbent assays revealed the brain to have the highest levels of total tau (7889 ± 2742ng/mg, average$\pm$stdev), followed by the submandibular gland (120 ± 25.9ng/mg), sigmoid colon (22 ± 8.96ng/mg), abdominal skin (21 ± 16.1ng/mg), scalp (14 ± 5.68ng/mg), and liver (13 ± 4.61ng/mg).

Conclusions: These results demonstrate that tau is present in measurable quantities within these peripheral tissues but not to the levels that are detected within the brain. Future studies investigating different phosphorylated species of tau are planned.

COMPREHENSIVE PROFILING OF DNA METHYLATION DIFFERENCES IN PATIENTS WITH ALZHEIMER'S AND PARKINSON'S DISEASE. Dunckley T, Meechoovet B, Caselli R, Driver-Dunckley E. Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Many complex sporadic neurodegenerative disorders are the phenotypic expression of interactions between environmental influences and an individual's inherent genetic risk. Specific molecular mechanisms mediating the differential impact of environmental factors on susceptible individuals leading to the development (and prevention) of neurodegenerative disease remain unclear. Epigenetic changes to DNA methylation patterns at specific genomic loci have been found in individuals with AD and PD, even in peripheral tissues such as blood. A more complete genome-wide characterization of the methylation events in AD and PD could add new insights into the etiology of these disorders.

Methods: Methylation profiles were obtained on blood samples from 15 neurologically normal controls, from 15 AD and from 15 non-demented PD patients using the Illumina Infinium 450K Methylation BeadChip. We obtained robust data on over 480,000 CpG methylation sites in the form of beta values, which represent the ratio of methylated CpG to the sum of methylated plus nonmethylated CpG at a given site. Thus, these values range from 0 (unmethylated) to 1 (fully methylated).

Results: We identified 84 methylation sites in AD vs controls with statistically significant changes to the beta value greater than 0.2. In PD vs controls, there were 83 sites with a beta value larger than the 0.2 threshold. However, of these sites, only 7 were shared between AD and PD. Thus, patients with either AD or PD exhibit numerous unique methylation events in peripheral blood DNA.

Conclusions: Methylation profiles in the blood of individuals with AD or PD and healthy controls show distinct differences in the patient sample sets examined. Further validation efforts on larger sample sets, and characterization of methylation status in patients at varying stages of disease, will help to establish whether methylation status at specific loci could be leveraged as therapeutic targets or biomarkers to track disease progression or aid in disease diagnosis.

FRONTAL CORTICAL GAMMA FREQUENCY SLOWING IN AGING: CAN C6 RESCUE CORTICAL SYNCHRONY AND DECISION SPEED? Espinoza AI, Uprety AR, Lipa P, Thome A, Hindley TR, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Behavioral data from older individuals suggest that the normal elderly show behavioral and cognitive slowing compared to young controls. Biological explanations for this slowing have revolved around the possibility that action potential conduction velocity may be altered in the aged brain due to defective myelination or to changes in cognitive strategies used by older individuals that are less efficient. A complementary possibility has been proposed recently. Insel et al. (2012) suggest that this slowing may be caused by altered interactions between cell assemblies, a hypothesis supported by data showing that gamma frequency is significantly reduced in prefrontal cortex of aged rats. This slowed gamma oscillation in the anterior cingulate cortex (ACC) was correlated both with slower decision and behavioral speeds. Furthermore, Insel et al. (2012) found that when cross correlation analysis was applied to simultaneously recorded excitatory-inhibitory cell pairs, the interval between the excitatory drive on to inhibitory cells was lengthened in the older rats. They therefore proposed that the change in communication within these cell circuits may contribute to the altered gamma synchrony within medial frontal cortical networks. Because the synchrony provided by neuronal oscillations may facilitate the organization of information, modifying these oscillations pharmacologically provides an opportunity to attenuate age related cognitive slowing. Methyl 3,5-diphenylpyridazine-4-carboxylate (C6; AgeneBio, Inc., Carmel, IN), a GABAA α5 receptor agonist, has been shown to improve the cognition of aged rats in hippocampus-dependent memory tasks (Gallagher et al., 2012).

Methods: The hypothesis tested in the present experiment is that C6 may rescue age-related cognitive decline by restoring synchronization among inhibitory-excitatory cells in frontal cortex that make up theta and gamma local field potential oscillations. Multiple-single unit recordings in the ACC of aged rats were conducted, while animals performed a cued decision-making task on a three-armed maze.

Results: Preliminary results demonstrate that C6 results in a significant alteration of the power but not frequency of the theta and gamma oscillations.

Conclusions: Further experiments are ongoing to better understand these effects at the individual neuron spiking level and to illuminate effects of C6 on ACC-dependent behavior.

PRAS40 AS A NOVEL THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE. <u>Farrell EK, Hartman LK, Branca C, Shaw DM, Caccamo A, Oddo S.</u> Banner Sun Health Research Institute; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Reducing the mammalian target of rapamycin (mTOR) activity increases lifespan and health span in a variety of organisms. Alterations in protein homeostasis and mTOR activity and signaling have been reported in several neurodegenerative disorders, including Alzheimer disease (AD); however, the causes of such deregulations remain elusive. We have previously shown that mTOR is a potential molecular link between Aβ, tau and cognitive decline. Specifically, we showed that Aβ oligomers increase mTOR signaling, an event that correlates with the phosphorylation of the proline-rich AKT substrate 40 kDa (PRAS40), a key regulator of mTOR activity. Here we show the involvement of amyloid-β (Aβ) and PRAS40 in regulating mTOR activity and show preclinical preliminary data indicating PRAS40 a new therapeutic target for AD

Methods: Non-transgenic (non-Tg) and 3xTg-AD mice were injected with one of several cocktails: with amyloid-precursor protein (APP), Aβ, anti- Aβ antibody, or Aβ-containing conditioned media with or without a Pim1 or akt kinase inhibitor. Activity of mTOR was measured via a commercially available ELISA kit. PRAS40 and phosphorylated PRAS40 were measured from cell extracts via Western Blot.

Results: Here, we show that mTOR activity and signaling are increased in cell lines stably transfected with mutant APP and in brains of 3xTg-AD mice, an animal model of AD. In addition, we show that in the 3xTg-AD mice, mTOR activity can be reduced to wild type levels by genetically preventing Aβ accumulation. Similarly, intrahippocampal injections of an anti-Aβ antibody reduced Aβ levels and normalized mTOR activity, indicating that high Aβ levels are necessary for mTOR hyperactivity in 3xTg-AD mice. We also show that the intrahippocampal injection of naturally secreted Aβ is sufficient to increase mTOR signaling in the brains of wild type mice. The mechanism beyond the Aβ-induced mTOR hyperactivity is mediated by the proline rich Akt substrate 40 (PRAS40), as we show that the activation of PRAS40 is necessary for the Aβ-induced mTOR hyperactivity. Notably, we also show that treatment with a small molecule inhibitor of Pim1, an upstream PRAS40 kinase, decreases PRAS40 phosphorylation and ameliorates mTOR hyperactivity in mice.

Conclusions: Aβ accumulation, which has been suggested to be the culprit of AD pathogenesis, causes mTOR hyperactivity by increasing PRAS40 phosphorylation. This suggests that reducing PRAS40 phosphorylation is a valid therapeutic approach for reducing mTOR hyperactivity. A preclinical trial is underway to examine the effects of a Pim1 inhibitor, a kinase known to phosphorylate PRAS40.

Poster 22

SEX DIFFERENCES IN ANATOMICAL MODIFICATIONS AND PATHOLOGY BURDEN OF ALZHEIMER'S DISEASE.

Filon JR, Serrano GE, Intorcia AJ, Carothers K, Carew JJ, Dugger BN, Fornwalt BE, Pullen JC, Saxon-LaBelle MM, Scott S, Scroggins AM, Sue LI, Sabbagh MN, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Previous studies suggest that females are affected by Alzheimer's disease (AD) more severely and at a higher prevalence than males. However, these studies remain controversial due to differences in life expectancy between genders and a lack of pathological evidence confirming clinical diagnosis. In this study, we wanted to explore if AD affects females more severely than males, in terms of the inferred loss of cerebral volume and brain weight as well as amyloid plaque and tangle density.

Methods: This is a case-control study of AD and non-demented (ND) control subjects participating in the Brain and Body Donation Program (BBDP) in Sun City, AZ. Subjects were systematically selected. Subjects' brains were weighed, sliced and photographed at time of autopsy. Cerebral volume was obtained by tracing photographed coronal slices using AxioVision Rel. 4.8 software. Amyloid plaque and tangle density was determined by the neuropathologist of the BBDP. Data on subjects' height, age of onset and expired age were retrieved from multiple research visits and private medical records.

Results: We found that subjects' brain weights directly correlated with postmortem cerebrum volume obtained through tracing (R=0.71; p<0.001). Compared to control subjects, decreased cerebral volume and brain weight was observed in AD males and AD females, but only reached statistical significance for females (p<0.01). When compared to their ND counterparts, brain weights in AD males were lower by approximately 6% and cerebral volumes by 3%. In contrast, AD females brain weights and cerebral volumes were 16% (p<0.01) and 14% lower (p<0.05), respectively. We found no significant sexual dimorphism in amyloid and neurofibrillary tangle load.

Conclusions: This suggests that females with a clinicopathological diagnosis of Alzheimer's disease might have more brain volume loss than males despite equivalent densities of the characteristic histopathological lesions. The reasons for this are unclear but a number of hypotheses could be generated. More quantitative histopathological studies might reveal differences that we are not observing with our standard semiquantitative scores.

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PLAQUES, NOT TANGLES RELATED TO ABDOMINAL CIRCUMFERENCE AT AUTOPSY IN ELDERLY BRAIN BANK INDIVIDUALS. Fornwalt BE, Scroggins AM, Saxon-LaBelle MM, Carew JJ, Pullen JC, Filon JR, Intorcia AJ, Scott S, Sue LI, Beach TG, Dugger BN. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Measures of weight, such as body mass index (BMI), have been known to be associated with many health conditions, including Alzheimer's disease (AD). Studies suggest that higher BMI in midlife increases the risk for AD in late life, while once AD begins, the affected subjects lose weight. In subjects with AD, BMI has an inverse linear relationship to AD pathologies. Although BMI may be a reliable measure, abdominal circumference mayprovide an independent prediction of risk over and above that of BMI.

Methods: Abdominal circumferences of 237 demented and non-demented elderly individuals weremeasured at autopsy. Semi-quantitative plaque and tangle scores for each individual were recorded from each different brain region (frontal, temporal, parietal, hippocampal, and entorhinal); the cases were subdivided by Braak neurofibrillary tangle stage and total CERAD plaque densities. A series of multiple linear regression models were performed to understand the relationship of plaque and tangle findings to abdominal circumference, having abdominal circumference as the outcome variable adjusting forgender and age at death.

Results: Abdominal circumference at death was inversely correlated with plaque densities in every brain region (all p values < 0.01) except the hippocampus (p=0.17). There wereno significant associations with any neurofibrillary tangle measures (all p values > 0.21).

Conclusions: These data suggest that plaques, not tangles are statistically associated with weight changes in AD. Understanding the specific mechanism(s) behind this association may be of some importance.

RELATIONSHIPS BETWEEN BEHAVIORAL DECLINES, HYPEREXCITABILITY, AND INHIBITORY NETWORKS IN THE MEDIAL TEMPORAL LOBE OF AGED RHESUS MACAQUE. Gray DT, Thome A, Erickson CA, Lipa P, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Hippocampal neurons have been shown to encode features of episodic memory in multiple animal models. The representation of these scenes relies on complex neural codes, and basic electrophysiological characteristics of neurons in the hippocampus have been suggested to underlie the ability of these networks to encode and retrieve information. In rodent models, activity of neurons in specific subregions of the hippocampus increases with age, and this hyperexcitability correlates with performance deficits in various medial temporal lobe-dependent behaviors. While the origins of this increased neural output remain poorly understood, several studies suggest that inhibitory circuits in select hippocampal regions change with age. It is unknown whether similar age-related alterations occur in non-human primates. Furthermore, no study to date has examined the relationship between the behavioral, electrophysiological, and molecular components of these deficits.

Methods: To address these questions, three middle aged and two aged rhesus macaques were behaviorally characterized in a delayed nonmatching-to-sample task, which has been shown to partially rely on the integrity of the hippocampus. In these same animals, ensemble single unit electrophysiological recordings were obtained from the CA3 region of the hippocampus and perirhinal cortex, along with quantification of the density of parvalbumin- and somatostatin-expressing GABAergic interneurons.

Results: Investigating the interactions between these three levels of analysis revealed hyperexcitability in CA3 neurons which correlated with both a decrease in the density of somatostatin-containing interneurons as well as behavioral deficits. These relationships were not observed in the perirhinal cortex.

Conclusions: Together, these findings are consistent with data suggesting that age-related declines in episodic memory are due, at least in part, to network dysfunction in specific regions of the medial temporal lobe which arise from losses in a specific class of interneuron. This suggests that therapies aimed at restoring or preserving somatostatin-containing interneurons may be a promising intervention for age-related cognitive decline.

Keywords: Geriatric, Aging, Hippocampus, Interneurons, Somatostatin, Parvalbumin, Excitability

Gray, D.T., Thome, A., Erickson, C.A., Lipa, P., and Barnes, C.A. (2014) Relationships between behavioral declines, hyperexcitability, and inhibitory networks in the medial temporal lobe of aged rhesus macaque. The 2014 Arizona Alzheimer's Consortium Annual Conference, June 2014.

Poster 25

PITUITARY ADENYLATE CYCLASE ACTIVATING POLYPEPTIDE IN ALZHEIMER'S DISEASE. Han P, Baxter LC, Liang WS, Tang Z, Yin J, Beach TG, Caselli RJ, Reiman EM, Shi J. Barrow Neurological Institute; The First Hospital of Kunming Medical University; Translational Genomics Research Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) is a neurotrophin. There is growing evidence of its efficacy in reducing Alzheimer's pathology in animal models but human studies are lacking. We investigated the relevance of PACAP in Alzheimer's disease (AD).

Methods: We investigated the expression of PACAP mRNA and protein in the brains of pathologically confirmed late onset AD patients compared with age matched cognitively normal controls (n=33 for mRNA, n=23 for protein).

Results: We discovered reduced levels of both in the brain regions susceptible to Alzheimer's pathology, including the entorhinal cortex (ENT), the middle temporal gyrus (MTG), the superior frontal gyrus (SFG) and the primary visual cortex (PVC), This reduction inversely correlated with amyloid burden (CERAD plaque density) in the ENT, MTG and SFG but not the PVC, a region spared in most cases of AD. PACAP expression is significantly decreased in the advanced Braak Stage (V-VI) in the moderate stage (III-IV).

Conclusions: The close inverse relationship between PACAP reduction and AD pathological features suggests that downregulation of PACAP mRNA and protein expression may contribute to AD pathogenesis.

PACAP DEFICIT IN ALZHEIMER'S DISEASE AND PROTECTION AGAINST BETA-AMYLOID TOXICITY. Han P, Tang Z, Yin J, Beach T, Reiman E, Shi J. Barrow Neurological Institute; The First Hospital of Kunming Medical University; Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: This study was aimed to quantify a neuropeptide, pituitary adenylate cyclase activating polypeptide (PACAP) in AD and non-AD brains, to evaluate the protective effects of PACAP against beta-amyloid toxicity, and to provide an insight on the pharmacological mechanism.
PACAP is intrinsically expressed in mammals and is considered to be a potent neurotrophic and neuroprotective peptide. The change of PACAP level in Alzheimer's disease (AD) remains unclear. We quantified the level of PACAP in AD brain to compare it with cognitively normal non-AD brain (CN). We further tested whether PACAP reduced beta-amyloid toxicity in primary cultured neurons, a post-mitotic cell population modeling AD pathological conditions.

Methods: We examined PACAP in human postmortem AD cortex and compared it with CN cortex. We used cultured primary neuron to establish in vitro model of beta-amyloid toxicity, to introduce genetic manipulation to knock down or over-express proteins and to analyze mitochondrial functions.

Results: PACAP expression was reduced in human AD cortex. This deficiency was linked to beta-amyloid plaque burden and Braak Stage. We also observed similar PACAP reduction in the brains of 3T×AD mice. In the cultured neurons, treatment with PACAP effectively protected neurons against beta-amyloid toxicity. PACAP stimulated mitochondrial Sirtuin 3 (SIRT3) production. Similar to PACAP, SIRT3 was reduced in AD and 3T×AD transgenic mice. Knocking down SIRT3 compromised the neuroprotective effect of PACAP, and this was reversed by over-expressing SIRT3.

Conclusions: PACAP is reduced in AD and the reduction is related to the severity of AD pathology. PACAP protects against beta-amyloid induced toxicity. The neuroprotective effects are mediated by SIRT3 and enhanced mitochondrial function. These results suggest that PACAP may be a potentially effective therapeutic approach for AD.

GENETIC SUPPRESSION OF β2-ADRENERGIC RECEPTORS AMELIORATES TAU PATHOLOGY IN A MOUSE MODEL OF TAUOPATHIES. Hartman LK, Branca C, Shaw DM, Farrell EK, Caccamo A, Oddo S. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Accumulation of the microtubule-binding protein tau is a key event in several neurodegenerative disorders referred to as tauopathies, which include Alzheimer's disease, frontotemporal lobar degeneration, Pick's disease, progressive supranuclear palsy, and corticobasal degeneration. Thus, understanding the molecular pathways leading to tau accumulation will have a major impact across multiple neurodegenerative disorders. The beta-2 adrenergic receptors (β2ARs) play a role in learning and memory and have been linked to AD. Toward this end, the number of β2ARs is increased in brains of AD patients and epidemiological studies show that the use of beta blockers decreases the incidence of AD. The mechanisms underlying these observations, however, are not clear.

Methods: To elucidate the link between tau pathology and β2ARs, we removed the gene encoding the β2ARs from a mouse model overexpressing mutant human tau.

Results: We show that the tau transgenic mice lacking the β2AR gene had a reduced mortality rate compared to the parental tau transgenic mice. Removing the gene encoding the β2ARs from the tau transgenic mice also significantly improved motor deficits. Neuropathologically, the improvement in lifespan and motor function were associated with a reduction in brain tau immunoreactivity and phosphorylation. Mechanistically, we provide compelling evidence that the β2AR-mediated changes in tau were linked to a reduction in the activity of GSK3β and CDK5, two of the major tau kinases.

Conclusions: These studies provide a mechanistic link between β2ARs and tau and suggest the molecular basis linking the use of beta-blockers to a reduced incidence of AD. Furthermore, these data suggest that a detailed pharmacological modulation of β2ARs could be exploited to develop better therapeutic strategies for AD and other tauopathies.

Poster 28

RELATION OF MRI WHITE MATTER HYPERINTENSITY SEVERITY TO NOCTURNAL BLOOD PRESSURE VARIATION AND HYPERTENSION IN HEALTHY COGNITIVE AGING.

Haws K, Hishaw GA, Totenhagen JW, Torre GA, Gillespie WL, Reid BA, Nguyen LA, Fitzhugh MC, Lines JW, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: White matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) provide a marker of the white matter changes associated with healthy aging. Hypertension in the elderly is a risk factor for cerebrovascular disease and cognitive impairment. Blood pressure (BP) in healthy individuals typically exhibits normal diurnal variation, with nighttime systolic reductions of 10%-20%. Having sustained levels of diurnal BP, without nocturnal dipping, has been associated with increased risk for cardiovascular disease. We sought to investigate the effects of diurnal BP variation and hypertension on MRI WMH severity in otherwise healthy elderly to evaluate the potential impact of these vascular risk factors on cognitive brain aging.

Methods: We studied 86 neurologically healthy adults, 70-89 years of age (mean ± sd age = 79±5 yr; 43M/43F; mean ± sd Mini-Mental State Exam = 28.6±1.4). Subjects underwent physical and neurological examinations, 24-hour ambulatory BP monitoring with measurements obtained hourly, and 3T MRI scans. The severity of WMHs was assessed using FLAIR MRI scans and a standardized visual rating scale (Scheltens et al., 1993). Thirty-six subjects had treated hypertension and 50 subjects had no history of hypertension diagnosis or treatment. Systolic BP nocturnal dipping was determined from the percent difference in average nocturnal relative to diurnal systolic BP and subjects were grouped into dippers (>10% nocturnal reductions; n=45) and non-dippers (<10% nocturnal reductions; n=41) for analysis.

Results: Analysis of variance (ANOVA) was used to investigate the effects of hypertension and nocturnal dipping status on severity of WMHs which included semiquantative ratings of periventricular, white matter, basal ganglia and infratentorial signal hyperintensities. The results showed main effects for dipping status on periventricular ($p < 0.031$) and basal ganglia ($p < 0.009$) WMHs with nocturnal non-dippers showing greater severity of WMHs. There were no significant main effects for hypertension in this sample. There was, however, a significant hypertension by nocturnal dipping interaction for infratentorial ($p < 0.013$) WMHs with the non-dipping hypertension group showing greater severity of WMHs than the other groups.

Conclusions: In neurologically healthy older adults, non-dipping nocturnal BP is associated with greater WMHs in the periventricular and basal ganglia and among non-dipping hypertensives in the cerebellar region. Sustained diurnal systolic BP without normal nocturnal reductions is an important vascular risk factor that may influence the course of cognitive brain aging in individuals with and without hypertension.

NEXT-GENERATION PROFILING TO IDENTIFY THE MOLECULAR ETIOLOGY OF PARKINSON'S DEMENTIA. Henderson-Smith A, Phillips L, Corneveaux J, Liang WS, Huentelman M, Beach T, Dunckley T. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Parkinson's disease (PD) is characterized by degeneration of mid-brain dopaminergic neurons and a high prevalence of dementia associated with the spread of degenerative pathology to vulnerable cortical regions, including the posterior cingulate cortex. RNA sequencing (RNA-seq) is an attractive approach to uncovering the etiology of this and other complex neurodegenerative diseases.

Methods: The present mRNA-seq study includes differential gene expression and alternative splicing analyses of the posterior cingulate cortex from neurologically normal control patients, patients with Parkinson's disease (PD), and patients with Parkinson's Dementia (PD-D).

Results: Genes overexpressed in both disease states were predictably involved with an immune response, while shared underexpressed genes function in signal transduction or as a component of the basal keratinocyte cytoskeleton. Alternative splicing analysis produced a clear pattern of cytoskeletal activity disturbance. Genes with the greatest degree of differential expression did not overlap with genes exhibiting the highest alternative splicing activity.

Conclusions: Resulting variation from the two types of expression analyses indicates the importance of broadening expression studies to include exon-level changes since there can be significant splicing activity with potential structural consequences, a subtlety that is not detected when examining whole gene differential expression or is under-represented with probe-limited arrays.

DEVELOPMENT OF A NOVEL CENTRIFUGAL-OPTICAL DIAGNOSTIC DEVICE FOR ALZHEIMER'S DISEASE. Hsia A, Procopio C, Perkins M, Valla J. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common form of dementia, characterized by progressive cognitive and functional impairments. There is currently no cure for AD, and disease management typically involves medications for symptomatic treatment. AD cannot yet be diagnosed in its early stages, and accurate diagnosis requires a specialized neurological examination or expensive imaging. Based on past research showing reduced mitochondrial enzyme activity in platelets in patients with AD, we have developed a functional assay system that could serve as an early diagnostic.

Methods: This assay utilizes a reduction-oxidation active indicator molecule to mark cytochrome oxidase (ETC Complex IV) activity in platelets. Following this staining, the platelets are measured densitometrically, and this requires a suitable small-volume, engineered centrifugal-optical device. A prototype device was developed in a computer-aided design program. To assess hysteresis and structural failure, finite element analysis (FEA) was performed on the device while it was exposed to a simulated high centrifugal force environment. Structural displacement and Von Mises stress at critical points, where sensitive densitometric measurements would be performed, were monitored throughout the simulation to indicate for any signs of physical alterations to the prototype. General High/Medium Polystyrene was the chosen material for the prototype because of its high tensile strength and optical clarity.

Results: Results indicated that the generated Von Mises stress from centrifugation of the device would not surpass that of General High/Medium Flow Polystyrene. Additionally, no sign of structural displacement or material failure were found at the critical points after centrifugation.

Conclusions: This assay system can currently provide a measure of the activity of cytochrome oxidase in blood cells from AD patients. However, maximal enzyme velocity may not yet have been achieved, and high velocity is required to fully differentiate the disordered patient from control. While the simulation results are limited to the assumption of a controlled environment with no inherent defects in the device's material and changes to the centrifugation force, the centrifugal-optical device design is functional. Limitations due to the injection molding process maintain a requirement for a larger initial sample. We continue to explore design modifications to reduce this need.

ALTERED EXPRESSION OF GENES INVOLVED IN SYNAPTIC PLASTICITY AND MITOCHONDRIAL ENERGY METABOLISM, IN THE PCC OF YOUNG-ADULT APOE4 CARRIERS. <u>Jentarra G</u>, Chavira B. Midwestern University; Arizona Alzheimer's Consortium.

<u>Background:</u> The APOE4 allele is a known risk factor for Alzheimer's disease (AD) and is associated with bioenergetic declines in various brain regions including the PCC (posterior cingulate cortex), even in young adult carriers. We hypothesized that early bioenergetic declines in the brains of young adult APOE4 carriers are due to reductions in the activity and plasticity of neurons, leading to a lower demand for energy from the mitochondria. To examine this idea, we studied the expression of genes involved in both neuronal plasticity and in mitochondrial function.

<u>Methods:</u> RNA was extracted from the superficial layers of the posterior cingulate cortex (PCC) of young adult (avg. age <30 years) APOE4 carriers (heterozygotes) and non-carriers (n=8 per group). SA Biosciences qPCR arrays were then used to measure the expression of genes essential to either neuronal plasticity or mitochondrial energy metabolism (84 genes per array).

<u>Results:</u> A small subset of genes involved in neuronal plasticity was significantly altered in the APOE4 carriers. Particularly notable was a 1.5 fold upregulation of brain derived neurotrophic factor (BDNF, $p < 0.01$)). The transcription of BDNF is regulated by the MECP2 protein, which is associated with Rett syndrome. A separate qPCR reaction run to assess MeCP2 gene expression levels found that it was also upregulated by 1.5 fold ($p < 0.01$). In addition, a protein phosphatase inhibitor involved in synaptic plasticity (PPP1R14A) was down-regulated 2.5 fold ($p < 0.01$) and TNF alpha, a pro-inflammatory cytokine previously linked to AD, was down-regulated 3 fold ($p = 0.05$). The mitochondrial metabolism array identified small changes in the expression of only 3 genes, indicating a lack of widespread dysregulation of genes involved in the electron transport chain. A collaborator (Dr. Jon Valla) previously found that APOE4 carriers show an upregulation of the hexokinase-1 and GLUT-3 proteins, which are involved in glucose uptake by cells. Therefore, we also examined the expression of the hexokinase-1 and GLUT-3 genes. The genes were both upregulated by 1.6 fold in APOE4 carriers, indicating a potential difference in glucose usage. These data were in agreement with the protein expression changes seen by Dr. Valla.

<u>Conclusions:</u> Changes in the expression of BDNF, MeCP2, PPP1R14A, and TNF alpha are expected to alter the growth and function of neurons, particularly in regards to synaptic plasticity. This could present a neurological vulnerability that may make APOE4 carriers more likely to develop AD. While we did not find changes in electron transport chain genes, we did discover upregulation of gene expression for hexokinase-1 and GLUT-3 which are involved in transporting and trapping glucose in cells. This could reflect an increased demand for glucose needed for energy production through the electron transport chain, or perhaps low glucose availability to the cells.

CHOLINERGIC DYSFUNCTION AND MUSCARINIC RECEPTOR UNCOUPLING IN ALZHEIMER'S DISEASE. Jones DC, Potter PE, Bills M, Killpack L, HamadanM, Sue L, Beach TG. Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The major purpose of this study was to characterize the mechanism underlying muscarinic receptor uncoupling in Alzheimer's disease (AD) using brain tissue from AD and a neuroblastoma cell model (SH-5YSY cells). 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. We also found that as plaque levels and β-amyloid increased, levels of the G-protein coupled receptor kinase (GRK-2) were significantly decreased, and Gq/11 protein was shifted from the cytosol to the membrane fraction.

Methods: In the current study, levels of β-arrestin, a protein involved in receptor recycling, 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). First, 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. Second, using western blot analysis, we demonstrated that β-arrestin, levels were decreased in both non-demented groups with neuritic plaques as well as in those with Alzheimer's disease, compared to the control group.

Results: Finally, preliminary data in SH-5YSY 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.

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 very important to attempt to circumvent impairment of signal transduction by addressing cholinergic dysfunction in the treatment of Alzheimer's disease.

Poster 33

PRELIMINARY ATTEMPTS AT REPLICATING THE CLARITY METHOD FOR IMAGING THICK BRAIN SPECIMENS. Kaufman J, Castro M, Chavira B, Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.

Background: CLARITY is a recently-proposed method for deep imaging of neural tissue, with reported specimen thickness ranging from 1mm blocks to intact adult mouse brains (Chung et al., 2013). Briefly, the process involves impregnation of neural tissue with an acrylamide hydrogel scaffold, followed by optical clearing with an ionic surfactant (SDS) that removes lipids but preserves proteins and nucleic acids bound to the hydrogel. The resulting hydrogel-tissue hybrid is reported to be compatible with immunofluorescence and confocal microscopy. We attempt to replicate the CLARITY method and characterize its challenges.

Methods: Wild-type mice were perfused with PBS followed by hydrogel monomer solution. The brains were extracted and further incubated in hydrogel monomer. After polymerization, the brain was cut into 1.5mm coronal blocks and passively cleared with SDS clearing solution. Blocks were tagged using parvalbumin immunofluorescence and imaged on a confocal microscope.

Results: We were able to achieve successful hydrogel embedding and optical clearing, producing tissue blocks that are nearly transparent. Parvalbumin immunofluorescence demonstrates specific tagging of a subset of GABA-ergic inhibitory neurons, including Purkinje neurons of the cerebellum. Clearing was sufficient to acquire optical sections through several hundred microns of tissue, depending on the region. However, penetration and diffusion of the antibody was inconsistent.

Conclusions: Our preliminary tests of the CLARITY protocol demonstrate its potential as well as its challenges. Although the process produces a surprising amount of swelling and shrinkage of the hydrogel/tissue specimen, the end result yields unmistakable cytoarchitectural morphology. Immunopositive tagging could be visualized through thicknesses of several hundred microns, indicating that the procedure has significant potential for imaging intact neural specimens. However, the application of immunohistochemistry to the clarified tissue remains a difficult challenge. In order for CLARITY to be useful for studying neurodegenerative disorders like Alzheimer disease, it will be necessary to achieve successful immunostaining of pathology-specific biomarkers.

Poster 34

THE EFFECTS OF KIBRA, APOE, AND HYPERTENSION STATUS ON MEASURES OF MEMORY FUNCTIONING IN OLDER ADULTS. Underline Kawa K, Stickel A, Walther K, Glisky EL, Hackett N, Huentelman MJ, Ryan L. University of Arizona; Ludwig Maximilians University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

.Background: As the older adult population increases relative to the rest of the population, it is critical to investigate factors that influence cognitive functioning in aging. One such factor that has received much attention in the field of cognitive aging is genetics. The focus of the present study was on the effects of KIBRA and APOE on memory functioning in an older adult sample (n = 213). Although the effects of KIBRA (Papassotiropoulos et al., 2006; Preuschhof et al., 2010) and APOE (Caselli et al., 2009; Ryan et al., 2011) have been investigated independently in separate studies, few studies have investigated the combined effects of KIBRA and APOE (Corneveaux et al., 2010; Laukka et al., 2012). Thus, the purpose of the present study was to investigate how the interactions between KIBRA and APOE as well as pre-existing health conditions such as hypertension may moderate the effects of KIBRA on memory functioning.

Methods: Our sample included 213 older adults who were well-matched on age and education across KIBRA (T-carriers (n = 109); CC homozygotes (n = 104)) and APOE (ε4 non-carriers (n = 166); ε4 carriers (n = 47)) genotypes.

Results: Given that previous research has shown worse performance on measures of episodic memory in KIBRA CC homozygotes (Papassotiropoulos et al., 2006; Schaper et al., 2008) and APOE ε4 allele carriers (Caselli et al., 2009; Ryan et al., 2011), we hypothesized that KIBRA CC homozygotes and APOE ε4 carriers in our sample would likewise perform worse than KIBRA T-carriers and APOE ε4 non-carriers. Additionally, we hypothesized that hypertensive individuals would perform worse than normotensive individuals on measures of memory and that hypertension status would interact with KIBRA and APOE genotypes. Surprisingly, once hypertension and APOE status were considered, the effects of KIBRA were in the opposite direction than hypothesized, with KIBRA T-allele carriers having lower scores than non-carriers on measures of memory functioning. As expected, APOE ε4 carriers and hypertensive participants had significantly lower scores on measures of memory functioning. Furthermore, all two-way interactions between KIBRA, APOE, and hypertension were nonsignificant, although the interaction between KIBRA and APOE trended toward significance.

Conclusions: These results demonstrate the need to consider the influences of multiple genetic and health factors in order to understand age-related memory changes. They also suggest that KIBRA may in fact have minimal, or even different effects, in older adults compared to young adults.

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MULTIFUNCTIONAL RADICAL QUENCHERS: THERAPEUTIC AGENTS FOR MITOCHONDRIAL AND NEURODEGENERATIVE DISEASES. Khdour OM, Alam MP, Arce PM, Chen Y, Roy B, Dey S, 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 Huntington's disease. However, the links between mitochondrial dysfunction and the onset and progression of some of these and other neurodegenerative diseases is still incompletely understood. In diseases where this link is already established, drugs developed to target mechanisms involved in mitochondrial dysfunction may be useful to treat these diseases. Previously we have shown that coenzyme Q10 analogues can protect against amyloid beta induced neuronal toxicity in a differentiated SH-SY5Y model. The hypothesis tested is that coenzyme Q10 analogues can be designed and prepared to suppress oxidative stress, and diminish the degradation of cellular macromolecules, in addition to supporting ATP synthesis in a broader range of mitochondrial and neurological diseases. Because they suppress one-electron trafficking in dysfunctional mitochondria, with multiple beneficial effects, we denote them multifunctional radical quenchers (MRQs). It was therefore of interest to extend these latter studies to identify compounds having the same efficacy but with sufficient metabolic stability to be useful in vivo. Compounds with such properties may find utility in treating mitochondrial and neurodegenerative diseases such as FRDA and Alzheimer's disease.

Methods: A number of coenzyme Q10 analogues (MRQs) were prepared and tested for their ability to suppress ROS formation, restore ATP production and confer protection in several different cell lines from a wide spectrum of mitochondrial and neurological disease patients. Metabolic stability of the compounds was evaluated in vitro using bovine liver microsomes.

Results: The coenzyme Q10 analogues were found to be excellent ROS scavengers, and to protect the cells from oxidative stress induced by glutathione depletion. The metabolic stability of an analogue containing an azetidine group has afforded a promising candidate for studies in animal models of neurodegenerative and mitochondrial diseases.

Conclusions: We have succeeded in preparing coenzyme Q10 analogues that protect against oxidative stress and preserving mitochondrial function, while retaining metabolic stability in microsomes. Agents with such properties may find utility in treating mitochondrial and neurodegenerative diseases such as FRDA and Alzheimer's disease.

PHYSICAL EXERCISE IN MIDLIFE VERSUS LATE-LIFE MAY HAVE DIFFERENTIAL IMPACT ON THE OUTCOME OF INCIDENT MILD COGNITIVE IMPAIRMENT: THE MAYO CLINIC STUDY OF AGING. Krell-Roesch J, Acosta JY, Stokin GB, Bartley MM, Roberts RO, Knopman DS, Christianson TJ, Pankratz VS, Petersen RC, Geda YE. Mayo Clinic Arizona; Mayo Clinic Rochester; International Clinical Research Center and St. Anne's University Hospital Brno; Arizona Alzheimer's Consortium.

Background: Physical exercise is associated with possible benefits for neurocognitive health. However, there is a lack of prospective cohort studies that examined the association between timing of engagement in physical exercise in cognitively normal persons and the outcome of incident mild cognitive impairment (MCI) in late-life.

Methods: We conducted a prospective cohort study derived from the population-based Mayo Clinic Study of Aging. The participants were 1,830 cognitively normal persons at baseline. They underwent neurological evaluation, risk factors ascertainment, and neuropsychological testing. Additionally, physical exercise in midlife and late-life were measured by using a validated survey with ordinal responses. An expert consensus panel classified participants as being cognitively normal or having new onset MCI after reviewing neurological, cognitive, and other pertinent data and according to published criteria. We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using Cox proportional hazards model, after adjusting for age, sex, and education.

Results: The cohort was followed forward in time for a median of 3.2 years to the outcomes of incident MCI or censoring variables. Of 1,830 cognitively normal persons at baseline, 389 developed incident MCI at follow-up. Light (HR = 0.58; 95% CI, 0.43–0.79) as well as vigorous (HR = 0.78; 95% CI, 0.63-0.97) midlife physical exercise were associated with decreased risk of incident MCI. However, the association with moderate midlife physical exercise (HR = 0.85; 95% CI, 0.67-1.09) was marginally significant. With regard to physical exercise in late-life, we observed that light (HR = 0.75; 95% CI, 0.58-0.97) and moderate (HR = 0.81; 95% CI, 0.66-0.99) but not vigorous (HR = 0.90; 95% CI, 0.66-1.25) physical exercise were associated with decreased risk of incident MCI.

Conclusions: Light physical exercise in midlife and late-life were associated with decreased risk of incident MCI. Additionally, vigorous midlife as well as moderate late-life physical exercise were associated with decreased risk of incident MCI. These findings indicate that (1) most elderly individuals may not engage in vigorous physical exercise in late-life and that (2) the intensity of physical exercise in midlife versus late-life may have a differential impact on the outcome of incident MCI.

Poster 37

AGE-RELATED CHANGES IN ENTORHINAL-HIPPOCAMPAL DYNAMICS. Lester AW, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Backround: The hippocampus and entorhinal cortex are critical for encoding new memories and are highly susceptible to both pathological and non-pathological age-associated brain changes. Both afferent projections from the entorhinal cortex as well as intrinsic hippocampal connections are substantially altered in Alzheimer's disease, but also show more subtle changes with advanced age. The ensemble activity generated by the cells in the temporal lobe is believed to underlie a "cognitive map" of space, providing an invaluable tool for studying episodic memory and the neural correlates of impaired memory-guided behavior. As with older adults, aged rats are impaired in many spatial navigation tasks. These impairments are accompanied by age-related changes in the "realignment" of place fields in familiar or changed environments. Such alterations may arise from circuit disruptions at multiple stages of the hippocampal processing pathway, and could have the effect of either slowing external cue processing or weakening the ability of these cues to influence firing field alignment. To identify the loci, timing and effect of network changes in aging, spatial processing within the hippocampus, as well as the content of spatial input to the hippocampus from the medial entorhinal cortex, must be assessed concurrently.

Methods: We are currently refining existing extracellular recording technology to perform simultaneous high density recordings from both layer II medial entorhinal cortex and the CA3 region of the hippocampus as rats navigate through space. To gain control of the external cues rats can use to orient in space, a novel behavioral apparatus has been developed that allows instantaneous rotation of all orienting cues.

Results: With the methods outlined, we plan to: 1) investigate how spatial representations are updated both at very short time-scales (i.e., tens of milliseconds) and over longer time intervals, 2) how different processing stages within the hippocampal formation are affected by age; 3) and will then use these measurements to systematically isolate the influence that age has on spatial tuning to better understand the implications of altered network dynamics for representations within this critical medial temporal lobe memory system.

Conclusions: The results of this study will provide a better understanding of what functional changes contribute to the realignment impairments in aged animals, as well as the anatomical source of these impairments.

Keywords: aging, hippocampus, entorhinal cortex, place cells, grid cells

Lester, A.W. and Barnes, C.A. (2014) Age-related changes in entorhinal-hippocampal dynamics. The 2014 Arizona Alzheimer's Consortium Annual Conference, June 2014.

MULTIVARIATE REGIONAL NETWORK OF GRAY MATTER VOLUME ASSOCIATED WITH HEALTHY COGNITIVE AGING. Lines J, Totenhagen J, Haws K, Fitzhugh M, Hishaw G, Torre G, Gillespie W, Chen K, Rieman E, Trouard T, Moeller J, Alexander G. University of Arizona; Arizona Alzheimer's Consortium; Banner Alzheimer's Institute; Columbia University.

Background: We previously reported patterns of magnetic resonance imaging (MRI) gray matter 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) and Statistical Parametric Mapping (SPM) voxel-based morphometry (VBM) in individuals over a wide age range, 20 to 84 years of age.

Methods: In this study, we sought to further investigate age-related differences in MRI gray matter in 50 healthy middle-aged to elderly adults, 50 to 89 years of age (mean±SD = 69.3±10.6, 25M/25F), by extending the application of the multivariate SSM to VBM performed with the Advanced Normalization ToolS (ANTS; Avants et al., 2010) program, which includes a highly accurate spatial normalization algorithm (Klein et al., 2009). All subjects were medically screened to exclude neurological or psychiatric conditions, hypertension, and diabetes. T1-weighted volumetric 3T MRI scans were processed for VBM using a stream developed for ANTS, including brain extraction, bias field correction, tissue segmentation, high-dimensional warping, and smoothing to produce regional gray matter volume maps. Multivariate analysis of the ANTS VBM gray matter maps was performed with SSM to determine the best combination of component patterns associated with age in the sample.

Results: The SSM analysis identified a linear combination of four component patterns predicting age (p < 0.000001). The combined pattern included areas of reduced gray matter mainly in bilateral frontal, parietal, and lateral temporal brain regions with relative preservation in the occipital cortex and in the vicinity of the hippocampal regions. Greater expression of the age-related SSM pattern was associated with poorer performance on cognitive measures of processing speed (0.001 < p < 0.04) and executive function (0.03 < p < 0.05).

Conclusions: In healthy middle-aged to elderly adults, a regional network pattern of gray matter volume is observed that is associated with individual differences in cognitive abilities known to be affected during healthy aging. These findings provide further support for the use of multivariate network analysis methods combined with VBM to investigate the regionally distributed effects of healthy aging on the brain and associated age-related cognitive decline.

A MULTICOMPONENT INTERVENTION FOR MILD COGNITIVE IMPAIRMENT IMPROVES MOOD AND COGNITION IN PATIENTS AND CAREGIVERS. Locke DEC, Fields JA, Cuc AV, Fowler A, Young J, Caselli M, Hoffman Snyder C, Chandler Greenaway M, Smith GE. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Objective: This study sought to examine the impact of a multicomponent intervention program on mood, cognition and behavior in patients with MCI and their caregivers.

Participants and Methods: Newly diagnosed MCI patients referred to HABIT (Healthy Action to Benefit Independence and Thinking) attended a 10-day program that included memory compensation training, mind-body movement, brain fitness training, group therapy, and wellness education. One hundred forty-nine participant/caregiver dyads completed mood, quality of life (QOL), functional ability, patient self-efficacy, and caregiver burden surveys at baseline and 3 months post program. These surveys were also collected at baseline and 3 months later from 66 control dyads, i.e., individuals with MCI and their partners who did not go through HABIT.

Results: Mixed-model analyses of variance showed that HABIT MCI participants showed significant improvement in depression (p=.002), anxiety (p<.01) and QOL (p<.0001) and experienced fewer and less severe neuropsychiatric symptoms (p<.01 and p=.04, respectively) 3 months post intervention. MCI controls showed no change on any of these variables except for a trend towards improvement in depression (p=.06). HABIT MCI caregivers showed significant reductions in depression (p<.01), anxiety (p<.0001), and distress (p<.02) and a trend towards improved QOL (p=.07). Caregivers of MCI controls showed no change. Furthermore, higher memory compensation learning scores for MCI participants who completed the HABIT program were significantly associated (p<.001) with higher scores on a measure of instrumental ADLs that assesses memory, language, visuospatial abilities, and executive functioning.

Conclusions: Multicomponent behavioral interventions such as HABIT can help individuals with MCI and their caregivers adjust to the disease and its consequences on cognition and well-being, potentially leading to reduced healthcare costs and extended time to nursing home placement.

PRIORITIZATION OF TREATMENT OUTCOMES BY PARTNERS OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT. Locke DEC, Gonzalez P, Smith G. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: The impact of treatments in meeting caregivers' needs are generally not evaluated (Berger G, et al. 2004). Our aim is to identify which are the most important behavioral outcomes to care partners of people with mild cognitive impairment. This permits later evaluation of the contributions clinical interventions actually have in meeting patient and partners' priorities.

Methods: 33 partners (91% female; Mean age= 71; 54% college graduates) from the Mayo Healthy Actions to Benefit Independence and Thinking (HABIT) program consented to an interview (over the telephone or in person) focused on rank ordering the 12 patient/partner centered outcomes assessed in the program. Rank ordering was on scale of 1= most important to 12= least important.

Results: 30% of partners reported that quality of life for the patient was the most important treatment outcome. Among the 33 caregivers, this outcome also obtained the highest median rank. Patient self-efficacy in handling their MCI (Median Rank= 4) ranked second. Partner quality of life was the highest ranking partner outcome (Median Rank=4). Obtaining median ranks from 5 to 8 were: daily function, memory based activities, patient's anxiety, partner's self-efficacy, patient's depression and distressing behaviors, and partner's anxiety. Partner depression (Median Rank= 10) and burden (Median Rank=10) were of least importance among all treatment outcomes, and ranked last in more than 25% of partner.

Conclusions: Results reveal that at the MCI stage, concerns about patient quality of life and patient self-efficacy, predominate. Psychosocial stressors like anxiety, depression, and burden, are not yet a priority in the opinion of partners contrasting to findings in more advanced stages of dementia (Mittleman, et al. 2004). This validates that with MCI, partners are focused in patients' opportunities to improve quality of life and gain skills that may sustain self-esteem and compensate for their cognitive decline.

WHERE, NOT HOW MUCH. INCREASED CYTOPLASMIC AND DECREASED NUCLEAR LOCALIZATION OF A KEY EPIGENETIC MOLECULE IS AN EARLY EVENT IN ALZHEIMER'S DISEASE WITH MAJOR IMPLICATIONS FOR GENE EXPRESSION.
Mastroeni D, Delvaux E, Nolz J, Oddo S, Coleman PD. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Expression of many hundreds of genes is altered in Alzheimer's disease. Coordinated changes in expression of many hundreds of genes has been associated with epigenetic mechanisms during development of the nervous system.

Methods: We have quantified numbers of neurons exhibiting ectopic cytoplasmic H3k4me3 in Alzheimer's and control brains as a function of Braak stage and also in relation to a series of markers of tau phosphorylation and conformation.

Results: Our evidence is consistent with ectopic cytoplasmic and decreased nuclear localization of H3k4me3 being an early event in the cellular pathophysiology of Alzheimer's disease (AD).

Conclusions: The H3k4me3 histone modification is associated with expression of large numbers of genes known to be affected in Alzheimer's disease. We propose that absence of H3k4me3 in the neuronal nucleus in Alzheimer's disease may be a mechanism for the widespread alteration in gene expression known to occur in Alzheimer's disease.

NOVEL COENZYME Q10 ANALOGUE PROTECTS MITOCHONDRIA FROM OLIGOMERIC AB. <u>Mastroeni D, Khdour OMC, Arcec PM, Hecht SM, Coleman PD</u>. Banner Sun Health Research Institute; Maastricht University Medical Centre; Arizona State University; Arizona Alzheimer's Consortium.

While oligomeric amyloid beta (Aβo) is strongly implicated in the etiology of Alzheimer's disease (AD), the actual mechanism(s) by which it exerts its effects are not completely understood. Presently, we demonstrate a strong correlation between changes in the expression of epigenetic chromatin modifying enzymes in AD brain and in Aβo treated differentiated neuroblastoma cells. Aβo treatment was also found to alter the structure of chromatin in the regulatory region of a representative epigenetic gene, KAT6B. Because the epigenome requires constant consumption of energy in the form of ATP, and Aβo has been strongly linked to a decrease in mitochondrial function, two Coenzyme Q10 analogues were designed to protect the mitochondria. In addition to supporting respiratory chain function, the two coQ10 analogues employed in this study suppress ROS and lipid peroxidation, and confer cytoprotection to cultured cells under conditions of induced oxidative stress. These findings suggest a cascade of events which starts with oligomeric abeta and its inhibitory actions on mitochondrial function, followed by downstream effects on epigenetic molecules which regulate chromatin structure.

ALZHEIMER'S DISEASE IS ASSOCIATED WITH DYSREGULATED EXPRESSION OF IMMUNE RESPONSE AND MITOCHONDRIAL GENES IN POSTERIOR CINGULATE ASTROCYTES. McDonald J*, Sekar S*, Cuyugan L, Aldrich J, Kurdoglu A, Adkins J, Serrano G, Craig DW, Beach TG, Reiman EM, Liang WS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Banner Sun Health Research Institute; Banner Alzheimer's Institute.

*contributed equally

Background: Alzheimer's disease (AD) is characterized by CMRgI (cerebral metabolic rates of glucose) deficits in the posterior cingulate and precuneus in carriers of the APOEε4 allele, decades prior to the onset of measureable cognitive deficits, and as well as in AD subjects. To understand the molecular basis of these alterations and to understand cell-specific contributions to disease, we previously performed expression profiling of PC neurons microdissected from AD subjects and controls and identified widespread decreased expression of electron transport chain genes.

Methods: For this study, we expanded our analysis to characterize expression changes in PC astrocytes using RNA sequencing given the role of astrocytes in energy storage and metabolism, and immunity in the brain. We laser capture microdissected cortical astrocytes from the PC of AD patients (n=10) and healthy elderly controls (n=10). RNA sequencing libraries were prepared for each subject and paired end sequenced on the Illumina HiSeq.

Results: We generated over 5.22 billion reads and 295.10G of Q30 data. Analysis of AD subjects compared to controls led to the identification of 226 differentially expressed genes (corrected $P<0.05$). Pathway analysis of these genes indicated that the most significantly affected pathway is immune responses processes. Comparison of APOE4 carriers compared to non-carriers, irrespective of disease status, led to the identification of 681 differentially expressed genes (corrected $P<0.05$). Pathway analysis indicated that the most significantly impacted pathway is DNA damage responses. We further evaluated expression of mitochondrial genes, defined as mitochondrially-encoded genes and MitoCarta genes, and identified altered expression of 9 genes in the AD versus control analysis and 31 genes in the APOE stratified analysis.

Conclusions: Results from this study highlight transcriptomic alterations that characterize PC astrocytes in AD and also provide evidence of more significant mitochondrial changes in these cells in APOE4 carriers. This study also improves our understanding of astrocytic alterations in a metabolically affected brain region in AD and demonstrates the need to consider differential contributions of different cell types to disease pathogenesis. Lastly, we provide this data as a resource to the research community through the NCBI dbGaP resource.

A TEST OF THE SENSITIVE WINDOW FOR HORMONE THERAPY INITIATION DURING TRANSITIONAL MENOPAUSE: CONJUGATED EQUINE ESTROGENS IMPAIR MEMORY AFTER, BUT NOT BEFORE, OVARIAN FOLLICULAR DEPLETION. Mennenga SE, Acosta JI, Garcia AN, Hewitt LT, Kingston ML, Tsang CWS, Camp BW, Mayer L, Dyer C, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium; SenesTech, Inc.

Menopause, typically occurring in the fifth decade of life, is characterized by loss of circulating ovarian-derived estrogen and progesterone as well as several negative health consequences, including hot flashes, bone density loss, vaginal atrophy, and cognitive decline (Curtis et al., 2004). Many women take hormone therapy (HT) to alleviate some symptoms of menopause; conjugated equine estrogens (CEE, tradename Premarin) are the most commonly prescribed HT in the US (Hersh et al., 2004). In rats whose ovaries have been surgically removed (Ovariectomy, Ovx), CEE HT has been shown to benefit spatial working and reference memory (Acosta et al., 2009) as well as non-spatial working memory (Walf & Frye, 2008). Importantly, while the Ovx model is useful for isolating the effects of individual hormones, abrupt surgical loss of ovarian hormones models <13% of women; the majority of women undergo natural, transitional menopause. Using the VCD model to produce follicle-deplete, ovary-intact rats with hormone profiles similar to that of naturally menopausal women (Flaws et al., 1994; Springer et al., 1996; Springer, McAsey, et al., 1996; Springer, Tilly, et al., 1996; Borman, et al., 1999; Kao et al., 1999; Hu, et al., 2001; Hu, Christian et al., 2001; Hu et al., 2002; Mayer, et al., 2002; Mayer et al., 2004; Mayer et al., 2005), our lab has previously shown that, while CEE benefits spatial working and reference memory following Ovx, it impairs performance when administered after transitional hormone loss (Acosta et al., 2010). Several studies have given rise to the critical window hypothesis (Khoo et al., 2010; MacLennan et al., 2006; Maki, 2006; Maki & Sundermann, 2009; Resnick & Henderson, 2002; Zandi et al., 2002), suggesting a narrow window of time during which HT can benefit memory around menopause. In naturally menopausal women, HT initiated post-menopause was detrimental to cognitive performance, whereas HT initiated prior to menopause was beneficial (Greendale et al., 2009) and use of HT at perimenopause enhanced memory and hippocampal activation in women (Maki et al., 2011). The goal of the present study is to determine whether the cognitive impact of CEE HT is influenced by the timing of treatment initiation during transitional menopause. On the working and reference memory water radial-arm maze task, CEE administered after transitional follicular depletion produced working and reference memory impairments, whereas CEE administration initiated at the beginning of follicular depletion transiently benefitted memory only during the learning phase of testing. This work suggests that CEE's effects on cognition vary depending on the timing of treatment initiation during the menopause transition.

ESTRADIOL ONLY IMPROVES PERFORMANCE WHEN WORKING MEMORY LOAD IS VERY HIGH: ALTERNATIVE INTERPRETATIONS OF POOR PERFORMANCE ON AN EASY TASK. Mennenga SE, Gerson JE, Koebele SV, Hewitt LT, Jordan AS, Mousa AA, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

17β-Estradiol (E2) is the most potent naturally circulating estrogen, and is the most common estrogen evaluated in rodent learning and memory studies. There is evidence that E2 treatment induces cognitive benefit following ovariectomy (Ovx) in rats; however, this benefit seems to be limited to conditions involving a high working memory load. The Water Radial Arm Maze (WRAM) assesses spatial working and reference memory; there are several WRAM variations, including differences in the number of reinforcers subjects are required to locate within a testing session. The number of reinforcers animals are required to find within a session corresponds to the working memory load that the task requires. We hypothesize that the cognitive benefits of E2 treatment in young animals are specific to working memory tasks with a high memory load and, in fact, performance indicative of impaired memory may be seen in animals treated with E2 when the working memory demand is not high enough. Here, in two studies, the cognitive effects of tonic E2 administration were evaluated in young Ovx rats under different working memory loads. Study I assessed the cognitive effects of low, medium, and high doses of E2 using the WRAM with hidden platforms in 4 of 8 arms, requiring a lower working memory load. Study II assessed the cognitive effects of low and high doses of E2, with hidden platforms in 7 of the 8 arms, requiring a higher working memory load. For each study, animals were given 12 testing days, followed by a delay test. Results showed that, in young animals tested under the current parameters, E2-induced enhancements were only evident when requirements necessitated a high working memory load. There were no differences in reference memory errors regardless of the behavioral task, indicating that effects were specific to the working memory domain. Our data suggest that in young animals, the benefits of E2 treatment become apparent only at high working memory loads, and that the benefits of E2 are not realized on tasks that do not sufficiently tax the working memory system. These results indicate task difficulty as a factor to be considered when evaluating the impact of female steroids on cognition.

Poster 46

UNDERSTANDING THE COGNITIVE IMPACT OF THE CONTRACEPTIVE ESTROGEN ETHINYL ESTRADIOL: TONIC AND CYCLIC ADMINISTRATION IMPAIRS MEMORY, AND PERFORMANCE CORRELATES WITH BASAL FOREBRAIN CHOLINERGIC NEURONS. Mennenga SE, Gerson JE, Koebele SV, Kingston ML, Tsang CWS, Engler-Chiurazzi EB, Baxter LC, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium; Barrow Neurological Institute.

Ethinyl estradiol (EE), a synthetic, orally bio-available estrogen, is the most commonly prescribed form of estrogen in oral contraceptives, and is found in at least 30 different contraceptive formulations currently prescribed to women as well as hormone therapies prescribed to menopausal women. Thus, EE is prescribed clinically to women at ages ranging from puberty to reproductive senescence. Here, in two separate studies, the cognitive effects of cyclic or tonic EE administration following ovariectomy (Ovx) were evaluated in young female rats. Study I assessed the cognitive effects of low and high doses of EE, delivered tonically via a subcutaneous osmotic pump. Study II evaluated the cognitive effects of low, medium, and high doses of EE administered via a daily subcutaneous injection, modeling the daily rise and fall of serum EE levels with oral regimens. Study II also investigated the impact of low, medium and high doses of EE on the basal forebrain cholinergic system. The low and medium doses utilized here correspond to the range of doses currently used in clinical formulations, and the high dose corresponds to doses prescribed to a generation of women between 1960 and 1970, when oral contraceptives first became available. Here, we evaluate cognition using a battery of maze tasks tapping several domains of spatial learning and memory and basal forebrain cholinergic function by using immunohistochemistry and unbiased stereology to estimate the number of cholinergic cells in the medial septum and vertical/diagonal bands. At the highest dose, EE treatment impaired multiple domains of spatial memory relative to vehicle treatment, regardless of administration method. When given cyclically at the low and medium doses, EE did not impact working memory, but transiently impaired reference memory during the learning phase of testing. Of the doses and regimens tested here, only EE at the highest dose impaired several domains of memory; tonic delivery of low EE, a dose that corresponds to the most popular doses used in the clinic today, did not impact cognition on any measure. Both medium and high doses of EE reduced the number of cholinergic cells in the basal forebrain and cell population estimates in the vertical/diagonal bands negatively correlate with working memory errors. Together these results suggest that EE may act through a different mechanistic pathway than natural 17beta-estradiol.

THE FREQUENCY AND DISTRIBUTION OF BDNF IN A LATINO SAMPLE IN PHOENIX, ARIZONA. Miller EA, Krell-Roesch J, Acosta JY, Shaibi G, Mandarino LJ, Velgos SN, Cevette NM, Hentz JG, Coletta DK, Caselli RJ, Geda YE. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Brain Derived Neurotrophic Factor (BDNF) is implicated in neurogenesis, survival of neurons, physical activity, and cognitive function. A common polymorphism in the BDNF gene (CT) produces an amino acid substitution of valine by methionine at codon 66 (Val66Met). This substitution alters the intracellular trafficking and regulated secretion of BDNF. The current study examined the frequency and distribution of serum BDNF and the BDNF genotype (rs6265) as well as BDNF's association with physical activity in a Latino sample taken from the community-based participant registry and biobank for the investigation of cardiometabolic phenotypes in Phoenix, AZ.

Methods: Between 2009 and 2011, we assembled a registry of self-identified Latino individuals for the purpose of investigating cardiometabolic phenotypes. The participants underwent medical evaluation, including a self-administered survey on physical activity. The investigators banked plasma, DNA, RNA, and immortalized lymphoblastoid cell lines. Mean BDNF levels for subjects that reported physical activity were compared to the mean for subjects who did not report physical activity, using a two-sample t test. Multivariable associations were assessed by using a general linear model. Comparisons of other variables were made by using the two sample t-test or Pearson chi-square test. Associations between BDNF and the other continuous variables were quantified by using the Pearson correlation coefficient.

Results: Data were available for 349 subjects. 195 subjects (56%) indicated regular physical activity. The physical activity group had a smaller proportion of women and a lower mean body mass index (BMI). The mean BDNF levels did not differ substantially between the physical activity and non-physical activity groups ($\Delta - 1$, 95% CI -4 to 3). Adjusting for age, sex, BMI, fasting glucose, or 2 hour glucose did not alter the mean difference between the physical activity and non-physical activity groups. The rs6265 genotype was available for 343 subjects. 225 subjects (64%) were CC, 109 (31%) were CT and only 9 (3%) were TT. Mean BDNF also did not differ between the CC and CT genotypes. BDNF levels were weakly associated with glucose levels and age. Higher glucose level and older age were associated with higher BDNF level. Mean BDNF levels did not differ between men and women.

Conclusions: BDNF levels were not significantly associated with physical activity or the rs6265 polymorphism. BDNF levels were weakly positively associated with glucose level and age. The frequency and distribution of methionine carriers (CT and TT) is consistent with studies that reported BDNF genotype distributions in primarily non-Hispanic white samples. The BMI of all study participants (including those who reported physical activity) is at overweight or obese levels. This may in part explain the absence of correlation between BDNF and physical activity. Limitations of the study are that physical activity was not objectively measured. Future studies should objectively measure energy expenditure and examine its association with BDNF, and neurocognitive function.

AGESIST STEREOTYPES ABOUT MEMORY MAY NOT AFFECT ALL OLDER ADULTS.
Moseley SA, Edwards CL, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

Background: Activation of ageist stereotypes has proven detrimental to memory performance of older adults in several studies. Less research, however, has focused on how to overcome the effects of stereotype threat, especially in the context of memory and aging. The current study tested whether a self-affirmation intervention would eliminate decrements in older adults' memory performance resulting from the threat posed by the negative stereotype that older adults have poor memories.

Methods: Participants were 48 older adults (17 male), with a mean age of 73.1 and 16.6 mean years of education. Participants were assigned to one of four conditions in a 2 (high vs low threat) x 2 (self-affirmation vs control) between-subjects design. Tests of immediate, short delayed and long delayed free recall as well as measures of perseverations and intrusions served as dependent variables.

Results: A 2 X 2 ANOVA of memory performance failed to reveal a significant main effect for threat, affirmation, or their interaction on any of the dependent measures. The sample was dichotomized into younger and older subsets. Although the data revealed a main effect of age on immediate recall, no effects of the experimental manipulations were significant in either age group.

Conclusions: Stereotype threat did not affect the memory performance of older adults. Consistent with other studies that have failed to produce stereotype threat effects in this population, findings suggest that sample demographics may have played a role. High social and mental engagement, and/or high levels of education may produce inoculating effects to ageist stereotypes.

AQUATIC THERAPY AND ALZHEIMER'S DISEASE - A CASE REPORT. <u>Myers KW, Capek D, Shill H, Sabbagh M</u>. Midwestern University; Royal Oaks Retirement Community; Banner Sun Health Research Institute; University of Arizona College of Medicine, Phoenix; Arizona Alzheimer's Consortium.

Background: Aquatic therapy (AT) aquatic therapy has been used for decades to provide physical therapy for patients with lower extremity deformities. Recently, investigators also have shown potential benefits for patients with neurological conditions such as balance disorders, Parkinson's disease and post stroke effects.

Results: This case report documents a patient with severe Alzheimer's disease who responded well to Halliwick-concept and AT.
Subjective and objective evidence is presented to document his improvement.

Conclusions: This case suggests a need to further investigate the potential for aquatic therapy to improve quality of life of patients with dementia.

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FACEBOOK FOR SENIORS: THE EFFECTS OF ONLINE SOCIAL NETWORKING ON COGNITIVE FUNCTION IN HEALTHY OLDER ADULTS. Myhre JW, Woolverton C, Robbins R, Polsinelli A, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

Background: Previous research suggests that older adults who remain socially active and cognitively engaged have better cognitive function than older adults who are socially isolated and disengaged. Learning to use an online social network service, like Facebook.com, may tap into both social and cognitive processes, enabling increased social engagement and support, and potentially enhancing cognitive abilities in older adults. This study aimed to examine the efficacy of an online social networking website as an intervention to maintain or enhance cognitive function in older adults.

Methods: Participants were 41 older adults (12 male), with a mean age of 79.4 and 16.45 mean years of education. Participants were assigned to learn how to use Facebook (n = 14), an online diary website (active control, n = 13), or placed on a waitlist (no treatment control, n = 14). There were no between group differences on age, education, or gender. Participants assigned to learn a website attended three 2-hour classes over the period of one week. Following the class, participants used the website at home for seven weeks. Two tests previously shown to measure "updating and monitoring of working memory representations" (Miyake et al., 2000) were administered before and after this 8-week period and performance on these two tasks were put into a composite score called "Updating."

Results: A 2 x 3 mixed ANOVA of the composite Updating measure revealed a significant Time x Group interaction, $F(2,37) = 6.482$, $p = .004$. Participants in the Facebook group showed a significant increase in performance compared to no significant change in the other two groups, paired samples t-test for 1) Facebook: $t(12) = 3.517$, $p = .004$, 2) Active Control: $t(12)=.782$, $p>.05$, and 3) Waitlist: $t(13) = -1.91$, $p>.05$. There were no significant group differences at baseline, $F(2,37) = .300$, $p = .743$.

Conclusions: Participants assigned to learn Facebook showed improvements on tasks requiring the dynamic updating of working memory compared to the active and no treatment control group participants. These results suggest that learning and using Facebook may be one way for older adults to bolster specific aspects of cognitive function. Additionally, this study supports the idea that we can maintain or improve cognitive function as we age through continued learning and socializing.

DEVELOPMENT OF THERAPEUTIC AREA-SPECIFIC DATA STANDARDS FOR ALZHEIMER'S AND PARKINSON'S DISEASES. <u>Neville J, Kopko S, Tolk C, Odenkirchen J, Broadbent S, Romero K, Stafford B, Hartley E, LeRoy B, Avilés E, Stephenson D.</u> Coalition Against Major Diseases**;** Critical Path Institute; Clinical Data Interchange Standards Consortium; National Institute of Neurological Disorders and Stroke.

<u>Background</u>: Critical Path Institute (C-Path) has played a leadership role in both consensus data standards and precompetitive data sharing for multiple disease areas including Alzheimer's disease (AD) and Parkinson's disease (PD). Both of these factors are key to success of clinical trials in the future. Working with the Clinical Data Interchange Standards Consortium (CDISC), C-Path has successfully developed consensus data standards for AD and PD, and a version 2.0 of the AD CDISC standards has been recently completed aimed at biomarkers and early stages of the AD spectrum. These therapeutic area specific standards represent the preferred format by regulatory agencies for submitting new drug applications. Importantly, CDISC standards will be required by FDA for regulatory submission as early as FY 2017. Thus, these standards serve two main purposes: integration of existing data and the prospective collection of clinical trial data.

<u>Methods</u>: A coalition of industry members, regulatory agencies, academic experts, government agencies and patient groups collectively developed data standards in partnership with the Clinical Data Interchange Standards Consortium (CDISC).
With input from clinical subject matter experts (SMEs), NINDS (for PD) and ADNI (for AD), working groups of data modelers mapped clinical concepts relevant to AD and PD to the CDISC Study Data Tabulation Model (SDTM) and developed controlled terminology to support the construction of standardized databases for research and regulatory submission in AD and PD.

<u>Results</u>: CDISC therapeutic-area data standards implementation guides were developed for AD and PD in collaboration with CDISC as supplements to the CDISC SDTM, a standard recognized by FDA. The AD user guide represents the first ever therapeutic area CDISC standard developed. The remapping of legacy clinical trial data to the AD standard played a critical role in developing an integrated database of legacy clinical trials, which in turn was a key foundation for the development of the first-ever regulatory-endorsed clinical trial simulation tool. Concepts covered by the AD CDISC user guide include CSF biomarkers, ApoE genotype, volumetric MRI, amyloid PET imaging, and more than 10 clinical outcome assessment scales, including ADAS-Cog, MMSE and CDR. Concepts covered by the PD CDISC user guide include MRI, PET-SPECT, Deep Brain Stimulation, Neuropathology, and a variety of clinical outcomes assessments including both UPDRS and MDS-UPDRS.

<u>Conclusions</u>: The use of consensus data standards maximizes efficiency in regulatory review and facilitates analyses across diverse studies. CDISC standards allow for integrating and pooling data across various stakeholders' systems in a platform-independent manner. Implementation of CDISC standards, particularly in the biomarkers arena, promises to facilitate improved efficiencies and harmonization in clinical trials.

THE RELATIONSHIP BETWEEN ANKLE DORSIFLEXION RANGE OF MOTION AND ELDERLY FALL RISK PREDICTORS. Nithman RW. Midwestern University; Arizona Alzheimer's Consortium.

Purpose/Hypothesis: The purpose of this pilot study was to investigate the relationship between ankle range of motion and fall risk, overall mobility, and lower extremity strength in older adults with cognitive disorders who reside in assisted living facilities (ALF). The investigator hypothesized that improvements in ankle range of motion gained over a three week intervention period would correlate with concurrent improvements in balance and overall mobility as measured by Performance Oriented Mobility Assessment/Tinetti Assessment Tool (POMA) and Timed Up and Go (TUG) scores.

Background/Significance: The sequelae of injurious falls among community dwelling older adults is a multi-factorial, public health problem requiring further investigation. In 2000, the total direct cost of all fall injuries for people 65 and older exceeded $19 billion. Loss of functional independence leads to institutionalization, and as many as 3 out of 4 nursing home residents fall each year. That is twice the rate of falls for older adults living in the community. Whether institutionalized or community-dwelling, older adults with Alzheimer's disease (AD) fall more than twice as often as those without dementia. Residents of ALF's are underrepresented in the rehabilitation literature, and this patient demographic is posing unique challenges to physicians and care managers.
Although many fall risk factors are outside of the control of the healthcare team, a heightened awareness of ankle contracture prevention and management can have tremendous impact on preventing injurious falls. Ankle DF contractures will impact an individual's center of gravity, quality of gait, righting reactions, and transfer ability. There has been minimal research on the impact of DF range of motion (ROM) as it correlates with standardized fall risk screening tools or self/caregiver-reported fall history.

Subjects: 23 residents from an ALF in Glendale, AZ participated in this study. All participants except two had physician confirmed presence of some form of dementia. The mean age was 79.6 (SD 11.63) ranging from 57-94 years of age. Of the 23 participants, 19 were female, 4 were male. At baseline, the mean TUG score for both groups was 42.9 seconds. The mean Tinetti POMA for both groups was 14.8. Both screening tools confirm that sampled participants posessed very high fall risks. 19/23 participants had a baseline ankle plantarflexion contracture defined as one or more ankles limited to 0 degrees or less DF.

Materials/Methods: Upon IRB approval, 30 ambulatory residents of an ALF were recruited for participation in this study. Participants received the following pre- and post-tests from the same examiners: 1) ankle DF ROM with the knee extended and flexed, 2) ankle dorsiflexion, plantarflexion, and knee extension strength (MMT), 3) the TUG, and 4) the Tinetti POMA. After the baseline evaluations, research participants were randomly assigned into either the control or treatment group. Participants selected for the intervention group were scheduled to receive stretching to the gastrocnemius and soleus muscles of both ankles 3 days/week for 3 weeks. Treatment consisted of 6-8 minute stretching sessions performed in the seated or supine position with each stretch lasting 20-30 seconds, 5 repetitions bilaterally.

Results: The differences among pre- and post-test TUG and POMA scores, LE MMT, and ankle ROM variables where calculated among both the control and intervention groups. Results indicate statistical significance (p <.05) only for right lower extremity (RLE) ankle DF ROM with the knee extended and flexed. Although unable to reject the null hypothesis for the remaining variables, the mean change in pre-

/post-test scores for the TUG (-10.5seconds), POMA Gait (+1.45), POMA Balance (+1.45), POMA Total (+2.91), and MMT scores indicate positive outcome trends with the intervention group.

Conclusions: Screening for ankle contractures and prophylactic ankle flexibility exercises has the potential to prevent falls and enhance the overall mobility status of older adults as measured by the TUG and POMA. Variability of this study's participants and the limited sample size prohibited further statistical inferences. A follow-up study which includes a larger sample size with stricter inclusion criteria such as accounting for the large variability in age, comorbidities, and overall functional status of ALF residents is needed with future investigations. Results also reveal a possible connection between ankle contractures and limb dominance that is worthy of further investigation.

Clinical Relevance: ALF's and Personal Care Homes (PCH) are partnering with home health agencies, traveling physician and nurse practitioner groups, and independent consultants to meet the health needs of their residents. Healthcare providers should consider ankle ROM as an important impairment to consider as relates to functional outcomes including but not limited transfer abilities, ADL participation including functional reach, and performance on outcome tools such as the TUG and POMA, for example. In conjunction with other factors that predispose an older adult to falls, qualified healthcare professionals should train patients, caregivers, and family members on recognition of ankle contractures and their potential impact on fall risks; it is recommended that caregivers and families be educated on gastrocnemius and soleus exercises as a part of routine fall prevention best practices with older adults. Passive ankle stretching exercises are generally well-tolerated and can be performed on older adults who have difficulty following one-step commands.

MITOCHONDRIAL ABNORMALITIES AND NICOTINE TREATMENT IN A FAMILIAL MODEL OF PARKINSON'S DISEASE. Odumosu M, Call GB, Buhlman LM. Midwestern University; Arizona Alzheimer's Consortium.

Background: Parkinson's disease (PD), a neurodegenerative disorder, is characterized by the death of dopaminergic neurons in the substantia nigra pars compacta. Mutations in the PARK2 gene are a primary cause of familial PD and have been shown to promote mitochondrial fission that preceds mitophagy. Patients with PARK2 mutations may have increased neuronal death, possibly due to a deficiency in the ability to dispose of dysfunctional mitochondria that are major sources of oxidative stress. A reduction in mitochondrial respiratory chain complex I function has been detected in patients with Parkin mutations and implicated in sporadic PD. This combination of decreased mitochondrial function and an inability to dispose of non-functioning mitochondria also may promote cell death in PD patients. Several studies suggest nicotine may be protective against the onset and incidence of PD. Previous studies in Drosophila park25 heterozygotes, a Parkin loss-of-function model, show that nicotine increases median lifespan, longevity and rescues climbing and flying deficits. The present study focuses on determining the effects of adult park25 heterozygous mutation and nicotine pretreatment on Drosophila mitochondrial mass and shape. We also examine the effects of adult park25 heterozygous mutation and nicotine pretreatment on Drosophila mitochondrial respiratory chain complex I function. Our results indicate park25 mutants show no impairment of mitochondrial complex I function and/or mitochondrial turnover; however, nicotine pretreatment reduces complex I activity only in control flies. Although we detected no effect of genotype on mitochondrial function or morphology in our park heterozygotes, our data support that of a previous study suggesting nicotine can affect NADH dehydrogenase activity in rat brain mitochondria. Aberrant mitochondrial function has been detected in Drosophila with homozygous park mutations. Evidence suggests that our heterozygous mutant model may have a less severe pathology; perhaps our methods cannot detect the potentially less-dramatic changes in mitochondrial morphology and function.

Methods: Mitochondrially-enriched fractions from control and park25 flies pretreated with or without nicotine are run on a denaturing gel, after which time the gels are incubated in buffer containing NADH and nitrotetrazolium, blue, which turns blue when reduced, thus indirectly measuring NADH dehydrogenase activity. Secondly, shape of fluorescently labeled mitochondria from ovarian nurse cells from flies of the same conditions is quantified using fluorescence microscopy and image analysis.

Results: Nicotine pretreatment decreases NADH dehydrogenase activity, but only in control flies. We have detected no effect of genotype on mitochondrial morphology or complex 1 activity.

Conclusions: Previously, we have shown that exposure to nicotine improves the phenotype of heterozygous Drosophila park mutants. Although we detected no effect of genotype on mitochondrial function or morphology in our park heterozygotes, our data support that of a previous study suggesting nicotine can affect NADH dehydrogenase activity in rat brain mitochondria. Aberrant mitochondrial function has been detected in Drosophila with homozygous Parkin mutations. Evidence suggests that our heterozygous mutant model may have a less severe pathology; perhaps our methods cannot detect the potentially less-dramatic changes in mitochondrial morphology and function.

KETOGENIC THERAPY IN ALZHEIMER'S DISEASE: POTENTIAL MECHANISM FOR FAILURE IN APOE4+ PATIENTS. Pangle P, Shonebarger D, Perkins M, Valla J. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) has been shown to manifest with region-specific declines in brain energy metabolism. This same pattern of metabolic decline has been observed in young subjects who are at genetic risk for future AD development because they carry the apolipoprotein E4 gene allele (APOE4+). A recent clinical study of a ketogenic medicinal food demonstrated efficacy in improving AD cognition. However, this positive effect was generated entirely by the APOE4- subjects; APOE4+ patients showed no improvement over placebo. To understand this, we have begun a series of studies to understand the full profile of metabolic changes in the APOE4+ brain.

Methods: Postmortem posterior cingulate cortex (PCC) samples from 12 APOE4+ and 12 APOE4- young adults (mean age=29.2 years; mean post mortem interval (PMI) = 14.8 hours) were analyzed via Western blotting in order to determine protein expression in several energy metabolism pathways.

Results: In the postmortem PCC of APOE4+ young adults, glucose phosphorylation (hexokinase), ketone catabolism (SCOT) and OXPHOS protein expression was significantly upregulated in the APOE4+ subjects compared to the APOE4-. Glucose transport (GLUT1) showed no change. However, monocarboxylate transport (MCT1) was significantly downregulated in APOE4+ subjects.

Conclusions: APOE4+ young adults demonstrate significant bioenergetic alterations in the PCC. Given the upregulation of several enzymes of energy metabolism, but decline in monocarboxylate transport, we speculate that the APOE4+ brain may be compensating for chronic energy insufficiency due to impaired ketone flux. This effect could lead to the failure of response to ketogenic therapy previously reported in APOE4+ AD patients.

OLDER ADULTS' AUTOBIOGRAPHICAL MEMORIES SUGGEST IMPORTANCE OF SOCIAL INTERACTIONS AND THIRD PERSON PERSPECTIVE IN MAINTENANCE OF POSITIVE AFFECT. Polsinelli AJ, Rentscher KE, Martinez T, Sherman NC, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

Background: It is suggested that older, compared to younger, adults are better at maintaining positive affect (i.e., socioemotional selectivity theory [SEST]) and social engagement may be particularly important for older adults' emotional, physical, and cognitive wellbeing. The current study examined whether content of autobiographical memories (AMs) supports these claims. It was hypothesized that older adults would use a) less negative and more positive affect words and b) more socially-related words and third-person pronouns (i.e., a marker of taking another's perspective) in the context of recalling positive AMs.

Methods: Older (n=45) and younger (n=25) adults reported three negative and three positive AMs. These AMs were audio-recorded, transcribed and analyzed with the Linguistic Inquiry and Word Count software which generated proportional scores for emotional, social, and pronoun word usage.

Results: Overall, younger adults used more negative affect words across both AM categories and more first person pronouns, particularly when recalling positive AMs. Older adults used more social language and third person pronouns, particularly when recalling positive AMs.

Conclusions: The results suggested reduced saliency of negative affect in older adults and an increase in focus on social experiences and others' perspectives when recalling positive AMs. These results are consistent with the shift in goal-focus that is proposed to occur in later-life. According to SEST, older adults strive to sustain positive affect and maintain pre-existing relationships with others that generate positive experiences. Results of the current study suggest that personal memories that are perceived as positive are more likely to focus on relationships with and perspectives of others.

NEUROPSYCHIATRIC SYMPTOMS, APOEE4 AND THE RISK OF INCIDENT DEMENTIA: THE MAYO CLINIC STUDY OF AGING. Pink A, Acosta JI, Roberts RO, Mielke MM, Christianson TJ, Pankratz VS, Stokin GB, Boeve BF, Petersen RC, Geda YE. Mayo Clinic Arizona; Mayo Clinic Rochester; International Clinical Research Center and St. Anne's University Hospital Brno; Paracelsus Medical University; Arizona Alzheimer's Consortium.

Background: There is a need to examine the population-based risk of incident dementia by baseline neuropsychiatric symptoms and ApoEe4 status among subjects with prevalent mild cognitive impairment (MCI).

Methods: We prospectively followed 332 participants with prevalent MCI (aged 70 years and older), enrolled in the Mayo Clinic Study of Aging for a median (inter-quartile range [IQR]) of 3.0 (2.5, 5.3) years. The diagnoses of MCI and dementia were made by an expert consensus panel based on published criteria, and after reviewing neurological, cognitive, and other pertinent data. Neuropsychiatric symptoms were determined at baseline using the Neuropsychiatric Inventory Questionnaire (NPI-Q). We estimated the risk of incident dementia by calculating hazard ratios (HR) and 95% confidence intervals (95% CI) by using Cox proportional hazards models, with age as a time scale. Models were adjusted for sex, education, and medical comorbidity. We also examined the interactions between each neuropsychiatric symptom and ApoEε4 in predicting risk of dementia.

Results: Baseline agitation (HR=1.97; 95% CI, 1.13-3.42), nighttime behaviors (HR=1.68; 95% CI, 1.02-2.78), depression (HR=1.63; 95% CI, 1.10-2.41) and apathy (HR=1.62; 95% CI, 1.03-2.54) significantly predicted incident dementia. We observed synergistic interactions between ApoEε4 and depression (joint effect HR=2.21; 95% CI, 1.24-3.91; test for additive interaction, $p<0.001$); ApoEε4 and apathy (joint effect HR=1.93; 95% CI, 0.93-3.98; test for additive interaction, p=0.031). Anxiety (HR=0.93; 95% CI, 0.54-1.61), irritability (HR=1.00; 95% CI, 0.61-1.67), and appetite/eating (HR=1.59; 95% CI, 0.86, 2.95) were not associated with increased risk of incident dementia.

Conclusions: Among prevalent MCI cases, baseline agitation, nighttime behaviors, depression and apathy elevated the risk of incident dementia. The risk of dementia was higher for participants with depression or apathy who were ApoEε4 carriers.

IS MUSCARINIC RECEPTOR UNCOUPLING IN ALZHEIMER'S DISEASE RELATED TO A DECREASE IN BETA-ARRESTIN? Potter PE, Bills M, Killpack L, Jones D, Hamada M, Sue L, Beach TG. Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The purpose of this study was to characterize the mechanism underlying muscarinic receptor uncoupling in patients with Alzheimer's disease. We found previously 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. We also have found that as plaque levels and β-amyloid increased, levels of the G-protein coupled receptor kinase GRK-2 were significantly decreased, and Gq/11 protein was shifted from the cytosol to the membrane fraction.

Methods: In the current study, levels of β-arrestin, a protein involved in receptor recycling, were examined in four groups: patients diagnosed with Alzheimer's (AD), age matched controls with many plaques (MP), age matched controls with sparse plaques (SP), and age-matched controls with no plaques (NP). The amount of plaque formation was correlated with loss of cholinergic neurons as assessed by choline acetyltransferase (ChAT) activity. Levels of signal transduction markers were measured using Western blot. Levels of β-amyloid were measured using ELISA.

Results: We found that β-arrestin levels were decreased in both non-demented groups with neuritic plaques as well as in those with Alzheimer's disease, compared to the control group.

Conclusions: It is likely that alterations in GRK, coupled with a decrease in β-arrestin, could impair muscarinic receptor recycling. Loss of recycling could lead to downregulation or uncoupling of the receptors. Thus, it may be very important to attempt to circumvent impairment of signal transduction by addressing cholinergic dysfunction in treatment of Alzheimer's disease.

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EARLY-FRAME PIB PET PERFUSION AND FDG PET GLUCOSE METABOLISM COMPARISON IN COGNITIVELY NORMAL PERSONS AT THREE LEVELS OF GENETIC RISK FOR ALZHEIMER'S DISEASE. Protas HD, Chen K, Luo J, Rausch JT, Bauer III R, Goodwin S, Richter N, Bandy D, Caselli R, Fleisher AS, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Arizona State University; University of California, San Diego; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: While Pittsburgh Compound B (PiB) positron emission tomography (PET) is commonly used for assessing fibrillar beta-amyloid deposition, its early frames can also be used for evaluating cerebral perfusion (pPiB). Recent reports showed a significant association between pPiB measured cerebral blood flow and fluorodeoxyglucose (FDG) measured cerebral metabolic rate for glucose in patients with Alzheimer's dementia (AD). This current study characterizes the relationship between regional pPiB and FDG PET measurements in cognitively normal apolipoprotein-E (APOE) e4 homozygotes (HM), heterozygotes(HT) and noncarriers(NC).

Methods: Dynamic PiB-PET and FDG-PET scans were acquired with a between-scan interval of less than 6 months in 10 APOE-e4 HM, 18 HT, and 21 NC, 64±6 years of age. pPiB images were computed from frames acquired 1.0-6.5 min, and FDG-PET images from frames acquired 30-60 min after injection, each normalized for the count variation using a cerebellar gray matter reference region. SPM8 was used to characterize and compare differences in regional PET measurements among the three groups. Voxel-wise linear regression was used to characterize the relationship between regional pPiB and FDG-PET measurements.

Results: In comparison with the HT and NC groups, the APOE-e4 HMs had significantly lower pPiB and FDG PET measurements in the vicinity of the precuneus, posterior cingulate, parieto-temporal cortex, and prefrontal regions (P<0.005, uncorrected). There was a close correlation between voxel-based pPiB PET and FDG PET measurements for all subjects ($R2=0.94±0.02$, max=0.97, min=0.84) and a close correlation between voxel-based pPiB-PET and FDG-PET differences among the HM, HT and NC groups ($R=0.71$, $p<1.1e-16$).

Conclusions: PiB-PET and FDG-PET measurements are roughly comparable in their ability to characterize regional differences between cognitively normal persons at differential risk for AD. Further studies are indicated to assess the power of pPiB in the tracking of preclinical AD and in the evaluation of preclinical AD treatments.

PREVALENCE OF AGE-RELATED PERIPHERAL PATHOLOGIES IN ALZHEIMER'S DISEASE AND NON-DEMENTED CONTROLS. Pullen JC, Saxon-LaBelle MM, Serrano GE, Carew JJ, Filon JR, Fornwalt BE, Dugger BN, Intorcia AJ, Scott S, Scroggins AM, Sue LI, Sabbagh MN, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Previous studies from our group showed that a small number of clinically-diagnosed health conditions, such as renal and congestive heart failure, are less prevalent in subjects with Alzheimer's disease (AD) when compared to non demented controls (ND). In order to corroborate and extend those findings, we compared the occurrence of autopsy diagnoses between AD and ND subjects.

Methods: All subjects were enrolled and autopsied at the Brain and Body Donation Program (BBDP) in Sun City, AZ (AD=86 and ND=49). Age did not differ between groups (mean was 83 years old; $p=0.50$). Hematoxlyin and Eosin sections from different peripheral organs were examined by a pathologist; some of the observed pathologies were grouped by common terminology. Fisher's tests were used to analyze the difference in prevalence between the most common pathological diagnoses in AD and ND subjects.

Results: The total number of autopsy diagnoses per subject in AD and ND ranged between four to twenty, with an average of twelve diagnoses in both groups. Liver atrophy, general inflammation, bronchopneumonia ($p<0.05$) and nephrosclerosis ($p=0.06$) were more prevalent in AD subjects than in ND. Likewise, abdominal adhesions and splenomegaly were more prevalent in ND controls than in AD subjects ($p<0.05$).

Conclusions: These findings suggest interactions between brain and peripheral disorders. The majority of the subjects used in this study had multiple pathological findings, but a group of these pathologies were more common in AD subjects. Higher prevalence of peripheral inflammation and peripheral organ atrophy observed in AD might be influenced by the brain inflammation and/or brain atrophy observed in this disease. Chronic inflammation and/or decreased body mass index (BMI) might lead to organ atrophy. Further studies should investigate if inflammation or decreased BMI observed in AD influence peripheral organ pathology through any specific mechanism.

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BRAIN IMAGING AND BLOOD BIOMARKER ABNORMALITIES IN CHILDREN AT GENETIC RISK FOR AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE IN THE PRESENILIN 1 E280A KINDRED. Quiroz YT, Schultz A, Chen, K, Brickhouse M, Fleisher AS, Langbaum JBS, Thiyyagura P, Protas H, Fagan AM, Shah AR, Muniz M, Arboleda-Velasquez JF, Munoz C, Velilla L, Tariot PN, Dickerson BC, Lopera F, Sperling RA, Reiman EM. Massachusetts General Hospital and Harvard Medical School; Universidad de Antioquia; Alzheimer's Prevention Initiative; Banner Alzheimer's Institute; Washington University; Boston University; Harvard Medical School; Brigham & Women's Hospital, Boston, MA; Arizona Alzheimer's Consortium.

Background: We have previously characterized brain and fluid biomarkers in young adults carrying a high-penetrance autosomal dominant mutation that causes early-onset Alzheimer's disease. To gain further knowledge on the preclinical phase of Alzheimer's disease, we sought to characterize structural and functional MRI, and plasma biomarkers in a cohort of children at genetic risk for autosomal dominant Alzheimer's disease in the presenilin-1 (PSEN1) E280A kindred.

Methods: Thirty-seven 9-17-year-old PSEN1 E280A mutation carriers and non-carriers from the Colombian Alzheimer's Prevention Initiative Registry in Medellín Antioquia, Colombia had structural and functional MRI during a memory task and resting state, and venepunctures. Outcome measures were task-dependent precuneus or posterior cingulate cortex (PCC) deactivations, resting functional connectivity, regional grey matter reductions, cortical thickness in the AD-signature, plasma Aβ (1-42) concentrations and Aβ (1-42):Aβ(1-40) ratios. Structural and functional MRI data were compared using automated brain mapping algorithms and search regions related to Alzheimer's disease. Resting state fMRI data were analyzed by means of seed-based analysis.

Results: The carrier and non-carrier groups did not differ significantly in their intellectual ability, behavioral performance, or proportion of apolipoprotein E (APOE) ε4 carriers. Similar to what we previously found in young adults at genetic risk for early-onset AD, children with the PSEN1 E280 mutation had elevated levels of Aβ(1-42) in plasma, and less fMRI task-related deactivation in parietal regions, compared to age-matched non-carriers. Paradoxically, they showed increased functional connectivity between the PCC and bilateral medial temporal lobe regions, greater gray-matter volume and thicker cortex in temporal and parietal regions,

Interpretation: Children at genetic risk for autosomal dominant Alzheimer's disease have task-related functional MRI findings and plasma biomarker findings consistent with Aβ (1-42) overproduction. Although the extent to which the underlying brain changes are either neurodegenerative or developmental remain to be determined, this study shows some of the earliest biomarker changes in children at genetic risk for autosomal dominant Alzheimer's disease.

GENE EXPRESSION PROFILING OF HUMAN ASTROCYTES TREATED WITH BEXAROTENE AND RELATED COMPOUNDS. Richholt RF, Coffey PM, Piras IS, Persico AM, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University Campus Bio-Medico.

Background: Characteristic features of Alzheimer's Disease (AD) include the accumulation of amyloid plaques in the brain. Impaired clearance of beta-amyloid (Aβ), the major constituent of these plaques, is critical in their formation, and possibly in eventual neuronal cell death. Recently, in an AD mouse model, treatment with the RXR agonist bexarotene resulted in rapid Aβ plaque clearance and restored cognitive, social and olfactory deficits. RXR and LXR activation has been shown to increase expression of the cholesterol transporters ABCA1 and ABCG1, as well as APOE. These increases in expression, particularly in that of APOE, were attributed to the rapid plaque clearance. The interactions of these molecules to facilitate amyloid clearance is not fully understood, therefore we decided to investigate bexarotene and related RXR/LXR agonists in human astrocytes in culture to examine their influence on gene expression patterns.

Methods: Human primary astrocyte cultures (Lonza) were treated for 48 hours at doses from 100-200nM with the following RXR/LXR agonists - bexarotone, honokiol, 9-cis retinoic acid (RA). RNA and protein were collected at the following time points 3, 6, 12, 24, and 48 hours and analyzed for APOE, ABCG1, and ABCA1 gene expression levels via q-RTPCR.Transcriptome wide gene expression analysis was conducted with Illumina HumanHT-12 v4 Expression BeadChips. 3 biological replicates for each treatment and time point.

Results: Bexarotene increased ABCA1 expression (LFC 1.44; P-Value 1.39E-16) and ABCG1 expression (LFC 1.59; P-value 1.00E-5). APOE expression was not significantly altered during the time course by any drug treatment. Related compounds, 9-cis retinoic acid (an RAR agonist), and honokiol (an RXR agonist) show mixed results. 9-cis retinoic acid shared several DEGs with bexarotene. Differentially expressed genes following treatment with bexarotene and 9-cis retinoic acid were significantly enriched for AD genes.

Conclusions: Bexarotene specifically activates RXRs (and 9-cis retinoic acid activates RARs which form heterodimers with RXRs). Nuclear receptors can exhibit and wide array of communication processes according to variation in ligand structures. APOE expression has been enhanced by LXR agonists, along with other molecules related to cholesterol transport. However, expression patterns may significantly vary with alternative compounds. We propose that the mechanism of action of bexarotene on amyloid plaque clearance observed in the transgenic mouse model is due to a different molecular pathway, not initiated by increased expression of APOE. Further characterization of the global transcriptional changes elicited by bexarotene will shed light on these processes.

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SUBJECTIVE COGNITIVE IMPAIRMENT, APOE E4 STATUS, AND COGNITIVE AGING: THE ARIZONA APOE COHORT STUDY. Ruider H, Krell-Roesch J, Hentz J, Woodruff B, Nagle C, Stonnington CM, Locke DEC, Acosta JI, Stokin GB, Caselli RJ, Geda YE. Mayo Clinic Arizona; International Clinical Research Center and St. Anne's University Hospital Brno; Paracelsus Medical University; Arizona Alzheimer's Consortium.

Background: Subjective cognitive impairment (SCI) may constitute a high-risk state for dementia. We examined the association between SCI and APOE ε4, which is a well-known risk factor for Alzheimer's dementia.

Methods: We conducted a case-control study derived from the Arizona APOE cohort study in Maricopa County, Arizona. Cases and controls were not aware of their APOE ε4 status. There were 114 cognitively normal persons (47 APOE ε4 carriers and 67 non-carriers) that completed a self-reported Memory Frequency Questionnaire (MFQ). The subjects ranged in age from 24 to 91 years, with a mean of 69.1 years (SD 9.5). Eighty-three subjects (73%) were women. The mean (SD) education level was 16.4 years (SD 2.4). The MFQ has 64 items with ordinal responses ranging from 1 (extreme difficulty with a memory item) to 7 (no difficulty at all with a memory item). A score of less than 7 was classified as the presence of SCI.

Results: We conducted a multi-variable logistic regression analysis in order to calculate odds ratios (OR) and 95% confidence intervals (95% CI) after adjusting for age, sex, education, and marital status. We then used OR (95% CI) to compare the "risk" of SCI between the two groups (subjects that are APOE ε4 carriers vs. non-carriers). There were no group differences in age, sex, education, and marital status. SCI was common among both cases and controls, i.e., 23/23 (100%) of APOE ε4 carriers above age 70 years and 23/30 (77%) of non-carriers above age 70 years reported SCI. When comparing the two groups, the odds of having SCI among carriers were significantly higher than non-carriers (OR approaches ∞; p = 0.02) only among subjects aged >70 years; whereas no significant difference was observed in the frequency of SCI between carriers (20/23; 87%) and non-carriers (29/35; 83%) aged ≤70 years (OR = 1.38, 95% CI = 0.31-6.2).

Conclusions: The odds of having SCI are higher in cognitively normal individuals who are APOE ε4 carriers and who are also above age 70 years. Our finding should be considered preliminary until confirmed in a prospective cohort study with a larger sample size.

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FLORBETAPIR PET, FDG PET, AND MRI IN DOWN SYNDROME INDIVIDUALS WITH AND WITHOUT ALZHEIMER'S DEMENTIA. Sabbagh MN, Chen K, Rogers J, Fleisher AS, Liebsack C, Bandy D, Belden C, Thiyyagura P, Liu X, Roontiva A, Jacobson S, Malek-Ahmadi M, Parks S, Powell J, Reiman EM. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium; Banner Alzheimer's Institute; Arizona State University; SRI International; Translational Genomics Research Institute; University of Arizona.

Importance: Down syndrome (DS) is associated with a virtually certain risk of amyloid β (Aβ) plaque deposition and an increased risk of dementia due to Alzheimer's disease (AD).

Objectives: To characterize and compare brain imaging measurements of fibrillar Ab burden, regional cerebral metabolic rate for glucose (rCMRgl), hippocampal and regional gray matter volumes (rGMVs), and their associations with age in DS study participants with AD dementia (DS/AD+), DS participants without AD dementia (DS/AD-), and normal controls (NCs).

Design, Setting, and Participants: Florbetapir positron emission tomography (PET), fluorodeoxyglucose (FDG) PET, and volumetric magnetic resonance imaging (MRI) were used to assess fibrillar Ab burden, rCMRgl, and regional brain volumes in 5 DS/AD+ , 12 DS/AD-, and 9 NC participants.

Main Outcomes and Measures: Mean cortical-to-pontine florbetapir standard uptake value ratios (SUVRs), posterior cingulate-to-whole brain CMRgl, and hippocampal GMVs were characterized using pre-selected regions of interest and compared for group- and age-related differences. In post-hoc analyses, statistical brain maps were used for between-group comparisons and associations with age.

Results: There were significant group differences in mean cortical-to-pontine SUVRs for florbetapir with DS/AD+ having the highest, followed by DS/AD-, followed by NC). For FDG PET, posterior cingulate CMRgl in DS/AD+ was significantly reduced compared to DS/AD- and NC. For vMRI, hippocampal GMVs were significantly reduced for the DS/AD+ compared to DS/AD- and NC. Age-related SUVR increases and CMRgl reductions were greater in all DS participants than in NCs. The DS groups also had medial frontal CMRgl and GMV reductions.

Conclusions and Relevance: DS is associated with characteristic fibrillar Ab, regional CMRgl, and regional GMV alterations in the symptomatic dementia stage and prior to the presence of demonstrable clinical decline. This study provides a foundation for the longitudinal studies needed to inform AD treatment and prevention trials in this vulnerable population.

BANKING FIBROBLAST CELLS FROM AUTOPSY SKIN TISSUE TO ESTABLISH APOE GENOTYPE-SPECIFIC IPSC LINES. Schmitz CT, Serrano G, Sue L, Beach TG, Walker DG, Lue L. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Establishing better disease models for Alzheimer's disease (AD) is still a priority among researchers today. Induced pluripotent stem cells (iPSC) are emerging as potential new models for disease and cell therapy. Derived cells and iPSC have been shown to be greatly useful by their successful differentiation into a variety of somatic cells with specific phenotypes and functions. Our goal is to make fibroblast-derived iPSC lines specific to apolipoprotein E (ApoE) genotype from characterized autopsy cases, which have potential to serve as a model for molecular mechanisms in AD and aid in drug discovery.

Methods: To create a bank of fibroblast cells, scalp samples were collected from autopsy donors of the Brain and Body Donation Program at BSHRI. These skin tissues were processed by washing and trimming off the hair and fatty tissue, then finely chopped into small pieces for plating. Cells were grown from these skin pieces by feeding every two to three days with medium containing serum and antibiotic. The cells were passaged three times then cryoprotected and stored in liquid nitrogen, ultimately collecting 15-20 tubes of cells per autopsy case. At the time of freezing, a cell pellet of 100,000 cells was collected for each case to use for ApoE genotyping. For skin cell characterization, one tube of frozen cells was thawed to passage once then plated onto coverslips. These plated cells underwent standard immunocytochemical procedures to detect proteins found in fibroblasts—vimentin and fibroblast surface protein. A database of the autopsy cases was recorded that included demographical, clinical and pathological information, as well as cell processing and maintenance notes.

Results: We have collected 20 cases thus far, which consists of 15 males and 5 females with a mean age of 83.2 ± 1.6 years ($\pm$ standard error). Based on their clinical diagnoses, the clinical diagnosis of the cases is as follows: 5 AD; 5 probable/possible AD; 3 Parkinson's disease (PD); 1 PD with dementia; 2 dementia with Lewy bodies; 4 non-demented normal controls. Out of the 20 total cases that have been genotyped, 6 cases are ApoE4 carriers (3/4 or 4/4), and 9 are non-ApoE4 carriers (2/3 or 3/3). All of the cells which are stored under cyroprotected conditions have been characterized with positive immunoreactivity for both vimentin and fibroblast surface protein.

Conclusions: From these banked fibroblasts, we will establish and characterize iPSC lines from one ApoE4/4 and one ApoE3/3 case. The progress of the induction of pluripotency will be presented in the meeting. The long-term goal is to use these iPSC differentiated neural and vascular cells to model molecular mechanisms of ApoE in AD and to facilitate genotype-specific cell-based drug discovery.

CHANGES OF TREM2 PROTEIN EXPRESSION WITH NEUROPATHOLOGICAL FEATURES OF ALZHEIMER'S DISEASE. Schmitz CT, Serrano G, Sue L, Beach TG, Walker DG, Lue L. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: TREM2 is a member of an immunoglobulin superfamily that requires physically docking to the co-receptor, DNAX-activation protein 12 (DAP12), to induce signaling for their functions. Recently, GWAS identified the gene variant rs75932628-T of triggering receptor expressed by myeloid cells 2 (TREM2) to significantly increase the risk of Alzheimer's disease (AD). Because TREM2 is originally discovered and studied in the peripheral cells of myeloid lineage, there is a lack of characterization in human brains. We performed a biochemical and morphological analysis of TREM2 in the human postmortem temporal cortical tissues of neuropathologically-defined AD, possible AD, and normal control subjects.

Methods: The protein levels of TREM2, co-receptor DAP12, ionic calcium-binding adaptor molecule-1(IBA1), microglial alternative activation marker CD206, active caspase 3 as apoptotic marker, synaptosomal associated protein 25 (SNAP25), post-synaptic density protein 95 (PSD95), and phosphorylated paired-helical filament tau (phosphor-tau, pSer202/Thr205) in brain tissue samples were evaluated to determine how TREM2 protein expression is related to neurodegenerative pathologies of AD.

Results: Increased expression of TREM2 protein was found to significantly associate with increases in PHF-tau, tangle scores and active caspase 3, but with a decrease of presynaptic protein SNAP25. By immunohistochemistry, we demonstrated that TREM2 protein was detectable in the activated microglia, with increased expression in the microglia occupying amyloid plaques and in the areas enriched with PHF-tau-immunoreactive neurites.

Conclusions: We demonstrated that TREM2 protein expression has significant association with PHF-tau formation, microglial activation, and pre-synaptic loss. This study elevates the significance of evaluating the role of microglial TREM2 in neuronal interaction during AD pathological development.

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WEB-BASED PAIRED ASSOCIATES TESTING OF OVER 25,000 INDIVIDUALS DEMONSTRATES SIGNIFICANT MAIN EFFECTS OF CHRONOLOGICAL AGE, GENDER, EDUCATION, AND ALZHEIMER'S DISEASE FAMILY HISTORY ON PERFORMANCE. Schrauwen I, Corneveaux J, Siniard A, Peden J, Turk M, De Both M, Richholt R, Mueller M, Langbaum J, Reiman EM, Caselli RJ, Coleman P, Barnes C, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University of Arizona; LeaseHawk; Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute.

Background: Variation in cognitive function across individuals is well documented and is known to be due to a combination of heritable and non-heritable factors. Most studies performed to date have been largely underpowered to detect the changes that significantly influence cognitive performance, especially when such changes exert a subtle effect. To address this, we created a web-based paired associate learning task (PAL) in an attempt to interrogate the largest cohort to date that has been tested on any one cognitive task. Since April 1st 2013, we have had over 66,000 unique visitors on our website and over 25,000 test takers who have completed our entire PAL paradigm and answered our 20 demographic and health / disease risk factor questions. Our large dataset expands most studies involving cognitive testing, and has high power to reveal discrete effects important in human PAL performance.

Methods: Paired associate visual memory and learning test (PAL): Subjects were presented with a list of 12 word pairs sequentially with each pair shown on screen for two seconds. During the recall period, the subject is shown one half of the word pair and must enter the other paired word. This cycle repeats an additional two times for a total of three trials. Data-analysis: Strict filtering criteria were used to clean the data prior to analysis, which lead to a total of 19,202 unique entries. A multiple regression model was fitted with the memory test results as the dependent value and all of the demographic main effects as independent values. Significance of a demographic was tested by comparing the model with and without that demographic by analysis of variance. This allows us to test the main and interaction effects of the demographic of interest, while controlling for the effects of the other demographics. To account for bias during analysis of education level, all analyses regarding education were done on a subset excluding <25 year old participants (N= 15,111). Regression diagnostics and the fit of the models were carried out by visual inspection of several residual plots, testing the presence of high influential data points and/or outliers, and by testing autocorrelation of the residuals and the presence of multicollinearity. Effect sizes (r) were calculated by the regression coefficients and their standard errors.

Results: Our results indicate that Age, Gender, and Education have the highest effect on memory performance ($p < 2.2 \times 10^{-16}$ for each comparison). In addition, we found that having a first-degree relative with Alzheimer's disease also significantly impairs memory performance ($p = 0.002$). Per year, on average we decline 0.16 word pairs (+/- SE 0.005; 0.44%) per year, which equates to a full word pair in performance loss every 6 years (2.8%). Females have an overall better PAL performance than males and the decline in performance with age is significantly pronounced in males (Age:Gender interaction $p < 2.2 \times 10^{-16}$). The difference between men and women is highest during the 50s and 60s, suggesting a performance enhancing effect of the menopause in females. Secondly, we found that individuals with higher education have a better PAL performance, however, the decline in memory performance with increasing age is the same in all education groups (Age:Education interaction $p = 0.902$). Therefore education level doesn't alter the noted age-related PAL performance decline rate. The influence of education on PAL performance is different between males and females (Gender:Education interaction $p = 0.0008$) which means that women with a higher PAL performance are more likely to have a higher education background than men. Lastly, having a first-degree relative diagnosed with Alzheimer's disease

significantly influences PAL performance. Interestingly, the effect is most obvious in participants less than 43 years old (Alzheimer's:Age interaction p = 0.0003; under 43 years: p = 4.30x 10-5; r = -4.11% +/- 1.00%). In addition, the effect of having an AD first degree relative is different between males and females (Alzheimer's:Gender interaction p = 0.001), although it is significant in both sexes.

Conclusions: In conclusion, we found that age, gender and education level significantly influence PAL performance. Having a first degree relative with Alzheimer's disease significantly impairs PAL performance, an effect that is most significant in the younger age groups. Our results demonstrate the effectiveness of web-based recruitment for the study of cognition across a diverse cohort. We plan to further investigate the gender and first degree relative findings through the use of on-line questionnaire follow ups with the study participants as well as APOE genotyping.

Poster 67

MTOR REGULATES TAU PHOSPHORYLATION AND DEGRADATION: IMPLICATIONS FOR ALZHEIMER'S DISEASE AND OTHER TAUOPATHIES. Shaw DM, Branca C, Hartman LK, Farrell EK, Caccamo A, Oddo S. Banner Sun Health Research Institute; University of Brescia; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Accumulation of tau is a critical event in several neurodegenerative disorders, collectively known as tauopathies, which include Alzheimer's disease and frontotemporal dementia. Pathological tau is hyperphosphorylated and aggregates to form neurofibrillary tangles. The molecular mechanisms leading to tau accumulation remain unclear and more needs to be done to elucidate them. Age is a major risk factor for all tauopathies, suggesting that molecular changes contributing to the aging process may facilitate tau accumulation and represent common mechanisms across different tauopathies. Here, we use multiple animal models and complementary genetic and pharmacological approaches to show that the mammalian target of rapamycin (mTOR) regulates tau phosphorylation and degradation. Specifically, we show that genetically increasing mTOR activity elevates endogenous mouse tau levels and phosphorylation. Complementary to it, we further demonstrate that pharmacologically reducing mTOR signaling with rapamycin ameliorates tau pathology and the associated behavioral deficits in a mouse model overexpressing mutant human tau. Mechanistically, we provide compelling evidence that the association between mTOR and tau is linked to GSK3β and autophagy function. In summary, we show that increasing mTOR signaling facilitates tau pathology while reducing mTOR signaling ameliorates tau pathology. Given the overwhelming evidence showing that reducing mTOR signaling increases lifespan and health span, the data presented here have profound clinical implications for aging and tauopathies and provide the molecular basis for how aging may contribute to tau pathology. Additionally, these results provide pre-clinical data indicating that reducing mTOR signaling may be a valid therapeutic approach for tauopathies.

NOVEL FTO INHIBITOR MODULATES MICRORNA AND MRNA. <u>Shen L, Iacoban P, Rowles J, Olsen M.</u> Midwestern University; Arizona Alzheimer's Consortium.

<u>Background</u>: Genetic variation in FTO has been linked with Alzheimer's Disease (AD) in human studies, and patients with variant FTO are also associated with decreased brain volume. FTO is a highly expressed 2-oxoglutarate utilizing enzyme in the brain involved in the demethylation of RNA N6-methyladenosine (m6A) residues. m6A residues are the most common mRNA modification in humans, and are associated with microRNA binding sites in the 3'UTR of mRNA transcripts. We have synthesized a novel blood-brain barrier penetrating FTO inhibitor, demonstrated a significant increase in cellular mRNA m6A residues, and investigated the modulation of microRNA by microarray analysis.

<u>Methods</u>: Neuroblastoma cells were cultured and treated with vehicle or a novel FTO inhibitor. Following vehicle or drug treatment, mRNA was isolated, degraded, and A,G,C,T and m6A were quantified by HPLC. Neuroblastoma cells were also cultured and treated with vehicle or FTO inhibitor, total mRNA was isolated, labeled with Cy5, and analyzed by microarray and by Digital Gene Expression.

<u>Results</u>: Numerous microRNAs were either up-regulated or down-regulated by the novel FTO inhibitor. Analysis of modulated mRNA includes protein folding chaperones, energy associated mitochondrial proteins, and SNORDs.

<u>Conclusions</u>: FTO variation has been identified as a risk factor for AD. A novel blood-brain barrier penetrating FTO inhibitor has demonstrated the ability to increase cellular m6A residues, and subsequent modulation of microRNA. The pattern of microRNA modulation suggests that mitochondrial transport may be altered in treated cells relative to control. Future studies investigating the modulation of microRNA in CNS cell types may be useful in evaluating the potential of a FTO inhibitor in CNS disease states, including AD.

GENETIC INFLUENCE OF APOLIPOPROTEIN E4 GENOTYPE ON HIPPOCAMPAL SURFACE MORPHOMETRY. Shi J, Baxter LC, Caselli RJ, Thompson PM, Wang Y. Arizona State University; Barrow Neurological Institute; Mayo Clinic Arizona; University of California, Los Angeles, School of Medicine; Alzheimer's Disease Neuroimaging Initiative; Arizona Alzheimer's Consortium.

Background: The apolipoprotein E (ApoE) e4 allele is the most prevalent genetic risk factor for Alzheimer's disease (AD), and is present in roughly 20-25% of North Americans and Europeans. It has been found that the presence of this allele is more frequent in AD patients than age-matching normal persons and is associated with a younger age of disease onset. As an important MRI biomarker for AD, hippocampal volumes are generally smaller in AD patients carrying the e4 allele compared to e4 non-carriers. Here we carry out a study of genetic influence of the ApoE e4 genotype on hippocampal surface morphometry with a novel surface fluid registration method in a large cohort of MR images from the Alzheimer's Disease Neuroimaging Initiative (ADNI) baseline dataset.

Methods: First, T1-weighted MR images from ADNI baseline dataset were segmented by FSL/FIRST and binary images representing hippocampal volumes were obtained. Hippocampal surfaces were reconstructed from the binary segmentations and refined in order for generating conformal grid. Then all surfaces were registered to an MNI standard space. Second, a conformal grid on each hippocampal surface was generated by the holomorphic 1-forms and was used as the canonical parameter space for surface registration. Third, we computed the conformal representation of each surface, i.e., the summation of local conformal factor and mean curvature, and linearly scaled the dynamic range of the conformal representation to [0, 255] to form the feature image of the surface. With the conformal representation, we essentially converted the 3D surface registration problem to a 2D image registration problem. The Navier-Stokes equation, which we have extended to a general form, was used to introduce a matching of feature images. Due to the correction term we introduced to the traditional fluid registration method, the correspondence field obtained in the feature image domain also induces a surface registration in 3D. We also extended the new method to maintain the inverse consistency of the registration. We call the algorithm the inverse consistent surface fluid registration method. Finally, multivariate statistics consisting of multivariate tensor-based morphometry (mTBM) and radial distance were computed as a measure of local shape deformation. Hotelling's T2 test was used to analyze the differences between groups of subjects with different genotypes.

Results: In our experiments, 725 ADNI baseline subjects with known ApoE information were studied, including 167 AD, 354 mild cognitive impairment (MCI), and 204 controls. We pooled both the subjects who are heterozygous ApoE e4 carriers (e3/e4) and homozygous ApoE e4 carriers (e4/e4) together to form the ApoE e4 carriers group. We studied the differences in hippocampal shape between ApoE e4 carriers and non-carriers (e3/e3) (1) in the entire sample (343 carriers vs. 322 non-carriers) and (2) in non-demented subjects (236 carriers vs. 270 non-carriers). The experiments aimed to determine if the APOE e4 allele was associated with hippocampal atrophy in all subjects or in subjects who have not yet developed AD. With permutation test, we detected significant differences in the first experiment and the local regions with significant differences are consistent with prior studies. More importantly, our method found significant differences between ApoE e4 carriers and ApoE e4 non-carriers in the non-demented cohort, which have not been detected by prior studies.

Conclusions: We studied the genetic influence of the ApoE e4 allele on hippocampal surface morphometry in one of the largest publically available AD database with our inverse consistent surface fluid registration method. Our method achieved results that are consistent with prior studies with more

detection power. Our findings suggest that the new algorithm may provide an alternative way for hippocampal shape analysis.

VENTRICULAR MORPHOMETRY ANALYSIS IN MILD COGNITIVE IMPAIRMENT WITH HYPERBOLIC RICCI FLOW. Shi J, Stonnington CM, Thompson PM, Chen K, Gutman B, Reschke C, Baxter LC, Reiman EM, Caselli RJ, Wang Y, the Alzheimer's Disease Neuroimaging Initiative. Arizona State University; Mayo Clinic Arizona; UCLA School of Medicine; Banner Alzheimer's Institute and Banner Good Samaritan PET Center; University of Southern California; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Lateral ventricle, the fluid-filled subcortical structure deep in human brain, usually expand in Alzheimer's disease (AD). The enlargement of lateral ventricle suppresses its surrounding structures and makes its neighboring substructures atrophy. Furthermore, due to the high contrast between the cerebrospinal fluid (CSF) and the surrounding brain tissues in T1-weighted images, ventricular enlargement is a highly reproducible measure of disease progression. On the other hand, surface based ventricular morphometry analyses are limited due to the complex and branchy structure of ventricular surfaces. In human brain mapping, surface registration is usually done by first mapping each 3D surface to a canonical parameter space such as a unit sphere or a planar domain and then registering the surfaces by the corresponding fields induced in the simpler parameter domains. However, an integrated parameter domain for ventricular surfaces without segmentation and singularities does not exist, making the registration problem more challenging for lateral ventricle. Here we introduce such a canonical parameter domain with the hyperbolic Ricci flow method and define meaningful geodesics to constrain ventricular surface registration. We have tested our algorithm on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to study the ventricular difference between mild cognitive impairment (MCI) patients who converted to AD during subsequent few months and MCI patients who did not during the same period.

Methods: First, we introduce a conformal parameterization to a lateral ventricular surface with the hyperbolic Ricci flow method and isometrically embed the surface onto the hyperbolic Poincaré disk. Second, in the parameter domain, with the deck transformation group generators, we tile a portion of the universal covering space, i.e., the entire Poincaré disk. Third, we compute consistent geodesic curves across subjects in the parameter domain. A canonical parameter domain, constrained by the geodesic curves is then converted from hyperbolic Poincaré disk to a Euclidean polygon with the Klein model. Finally, the constrained harmonic map is computed with the Klein polygon to match different ventricular surfaces. To study ventricular surface abnormality, the tensor-based morphometry (TBM), i.e., the determinant of Jacobian matrix of the deformation is computed and applied in group difference analysis.

Results: We tested the algorithm on 133 MCI patients from the ADNI baseline dataset, including 71 patients who converted to AD during the subsequent 36 months, which we call the MCI converter group, and 62 patients who did not convert to AD during the same period, which we call the MCI stable group. The ventricular surfaces were from a prior work. With permutation test, our method detected significant difference between the two groups. Given 0.05 as the significance value, the permutation test correct p-value is 0.0172. We also compared with two global measures of surface morphometry, the total volume and total surface area. Neither of them detected significant difference between the groups. The significant p-values are 0.0803 for the volume and 0.2922 for the area.

Discussion and Conclusion: We introduced an integrated conformal parameter domain for lateral ventricular surface registration with the hyperbolic Ricci flow method. The parameter domain is integrated and introduces no singularity. Our algorithm may provide a new solution to the ventricular surface

registration problem. Our future work will be to apply this method on different large-scale datasets and study ventricular abnormalities along with different diseases such as AD, HIV/AIDS, or prematurity.

ALTERATIONS IN MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION PROTEINS IN YOUNG-ADULT CARRIERS OF THE ALZHEIMER'S RISK FACTOR APOE4. Shonebarger D, Pangle P, Perkins M, Valla J. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common cause of dementia and a leading cause of death in the elderly. Despite its prevalence, there remains ample debate regarding its etiology and the role of various risk factors. The epsilon 4 allele of apolipoprotein E (APOE4) provides the strongest established genetic risk for developing late-onset, sporadic AD. Additionally, specific regions of the AD brain, those commonly associated with high level cognition, demonstrate decreased energy metabolism. These regional decreases in energy metabolism have also been shown to occur in asymptomatic middle-aged and young-adult carriers of APOE4. We previously showed that postmortem tissue from young-adult APOE4+ individuals exhibited reduced electron transport chain Complex IV activity in the posterior cingulate cortex (PCC), an area of the brain which appears to be particularly vulnerable to the bioenergetic declines seen in AD.

Methods: To investigate this finding further, we have evaluated the expression level of oxidative phosphorylation (OXPHOS) protein subunits in postmortem young-adult PCC samples from 12 APOE4+ and 12 APOE4- individuals (mean age=29.2 years; mean postmortem interval (PMI) = 14.8 hours).

Results: Despite showing a functional decline in Complex IV activity, the APOE4+ subjects demonstrated significantly higher OXPHOS protein subunit levels. We are currently assessing these results in conjunction with glucose and ketone catabolism pathways, and our collective results suggest a possible energy compensatory mechanism, which appears to associate with APOE4.

Conclusions: These results indicate a significant dysregulation of energy metabolism in the APOE4+ neocortex which may relate to later vulnerability to AD in this population.

THE INFLUENCE OF DEMOGRAPHIC AND DISEASE RISK FACTORS ON PAIRED ASSOCIATES LEARNING IN AN INTERNET RECRUITED COHORT OF OVER 25,000 INDIVIDUALS. Siniard A, Schrauwen I, Corneveaux J, Peden J, Turk M, De Both M, Richholt R, Mueller M, Langbaum J, Reiman EM, Caselli RJ, Coleman P, Barnes C, Glisky E, Ryan L, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; University of Arizona; LeaseHawk; Banner Alzheimer's Institute; Mayo Clinic Arizona;Banner Sun Health Research Institute.

Background: The demographic and health/disease risk factors associated with differential cognitive performance in humans are poorly understood. Most studies have utilized cohorts that are only moderately powered to detect differences in task performance and in many cases the study cohort wasn't purposefully recruited to cover a wide range of demographics and general health and disease risk factors. To address this, we developed a web-based task that examines paired associates learning (PAL, Mary Whiton Calkins, 1894) and combined this with 20 basic demographic and health questions. Through our site at www.mindcrowd.org we have recruited over 25,000 individuals to complete the entire test. This large data set and the nature of the recruited cohort, which spans the age spectrum from 18 to 85 years of age, uniquely powers us to identify even subtle factors that may influence paired associates learning across the lifespan.

Methods: Paired associate visual memory and learning test (PAL): Subjects were presented with a list of 12 word pairs sequentially with each pair shown on screen for two seconds. During the recall period, the subject is shown one half of the word pair and must enter the other paired word. This cycle repeats an additional two times for a total of three trials. Data-analysis: Strict filtering criteria were used to clean the data prior to analysis, which lead to a total of 19,202 unique entries. A multiple regression model was fitted with the memory test results as the dependent value and all of the demographic main effects as independent values. Significance of a demographic was tested by comparing the model with and without that demographic by analysis of variance. This allows us to test the main and interaction effects of the demographic of interest, while controlling for the effects of the other demographics. Regression diagnostics and the fit of the models were carried out by visual inspection of several residual plots, testing the presence of high influential data points and/or outliers, and by testing autocorrelation of the residuals and the presence of multicollinearity. Effect sizes (r) were calculated by the regression coefficients and their standard errors.

Results: Of all the demographics tested, we found that Handedness (p = 5.9 x 10-4, Right Handedness; r = 1.66% +/- 0.48%), Marital Status (p = 1.71 x 10-4, Single vs Married r = 1.32% +/- 0.37%) and Race (2.71 x 10-9) significantly influence PAL performance. In addition, we found that High Blood Pressure and Smoking significantly affect PAL performance but only at specific ages or within specific gender groups. High Blood Pressure significantly affects PAL performance when present in individuals under the age of 35 (Age:HighBloodPressure interaction p = 0.003; in test takers under 35 years of age, p = 0.002, r =-4.37% +/- 1.41%). Smoking affects PAL performance in females only (Smoking:Gender p = 0.004; Females p = 0.01; r = -2.00% +/- 0.77%; Males p = 0.626). The difference in PAL performance between female smokers and non-smokers was greatest during the 40s and 50s when smoking was observed to negate the positive effect of menopause on PAL performance. There was no effect of Drug/Alcohol abuse, Diabetes, Dizziness, Heart Disease, Hispanic ethnicity, Loss of Consciousness, Seizures and Stroke on PAL performance after correcting for all other demographics.

Conclusions: We identified novel demographic and health risk factors associated with PAL performance in humans using a large web-recruited cohort. The most influential lifestyle factor influencing PAL

performance is smoking, which abolishes the performance enhancing effect of menopause in females. Also interestingly, test takers under 35 years of age with high blood pressure have a significantly lower PAL performance. Previous studies examining hypertension status and cognitive task performance have mainly focused on older age groups and our data demonstrates that the largest effect is found in young adults. Limitations of our study include the fact that it is a cross sectional study and the potential for biased recruiting and/or PAL test taking through the use of the internet. Web-based recruitment and testing of a large and demographically diverse sample is both feasible and can uncover novel associations with cognitive task performance. Future work will include the expansion of the cognitive test battery to examine multiple other aspects of cognitive performance.

APPROXIMATE ENTROPY AS A METRIC FOR QUANTIFYING FMRI CHANGES ACROSS TIME. Steinke K, Braden BB, Frakes D, Baxter LC. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Functional MRI (fMRI) lacks a stable baseline and therefore is of limited use in longitudinal studies that examine changes over time. To overcome this shortcoming, we applied a time signal processing technique that can facilitate comparisons among two or more fMRI tasks to create a quantitative fMRI (qfMRI) method. A fMRI is expressed as a correlation between signal fluctuations and the expected model.Unfortunately this quantitative technique is relative, as areas of "activation" are expressed as significant correlations rather than with a "normalized" numerical value that can be used across time. This study hypothesized that quantitative fMRI could be established if the responsivity during an fMRI task of interest (e.g., finger motor movement) could be "normalized" through comparison to a task that would likely be unchanged by commonly studied neurological diseases, including aging and Alzheimer's disease. For the stable task, we chose a very simple vision task because a) it produces robust and reproducible results, b) it has minimal cognitive load, and c) the occipital lobe is generally spared in many neurological conditions. We chose the method of approximate entropy (ApEn) to develop a quantitative measure because it produces an inherently normalized value. ApEn is a calculation that quantifies the regularity or unpredictability of time series data via statistical methods. ApEn can be utilized to determine the complexity or randomness of measurements, including fMRI time series data. ApEn is robust to noise and produces a value that corresponds to the complexity of the signal being studied, with higher values indicating greater unpredictability and complexity. Since patterns do not generally arise from random noise, a signal wherein they are detected must, theoretically, contain some structured information. ApEn is used to quantify the complexity of this information. A fundamental alteration of a signal changes the "information" it contains (which is reflected in ApEn) and indicates a shift in functionality of the system producing the signal. We hypothesized that ApEn could be used to reflect the stability of the signal for a target task (e.g., a motor task) relative to a "control" task (e.g., a visual task) independent of a static baseline.

Subject Data and Task Design: All subjects performed motor and vision tasks. Motor tasks consisted of on-off blocks of movement and rest. Visual tasks consisted of on-off blocks of pictures and blank crosshair images. ApEn values for the motor tasks were then compared to ApEn values for the vision tasks (for each subject). Our subjects were members of two different groups: one group designed to theoretically demonstrate stable ApEn ratios ("Caffeine Group"), and one group that we expected to show changes in ApEn ratios over time ("Surgical Group"). The Caffeine Group consisted of 4 healthy normal controls scanned twice, a week apart, with and without having been administered a 100mg caffeine pill. Caffeine was used as an intervention because it increases blood flow uniformly throughout the brain; and therefore would be expected to affect the BOLD signal, but not the ratio between vision and motor task ApEn values, as both ApEn values should be amplified similarly. The Surgical Group consisted of two patients who underwent fMRI assessment prior to surgery for tumor removal and then had repeated fMRI assessments after surgical treatment (and before a second treatment in one case). These two patients were chosen for examination because they were scanned more than once, and demonstrated altered behavioral function. This group was expected to show changes in ApEn ratios based on changes in their behavioral function.

Imaging Parameters: All participants were scanned on the same 3.0 Tesla GE Signa HDX system with an 8-channel head coil. Scan parameters for echo planar imaging (EPI) were: TR = 3000 ms, TE = 25 ms, flip angle = 80°, FOV 24mm, in-plane resolution 64x64, 4 mm slice thickness (covering the entire brain).

Each scan varied between 40 and 80 volumes. A high-resolution, 3D T1 SPGR image was obtained for all subjects to facilitate registration. Parameters for those scans were: TR = minimum, TE = 2.5 ms, flip angle = 8°, FOV = 26mm, 1.2 mm slice thickness.

Task Analysis: Data analysis was conducted using SPM5. The collected data were smoothed, coregistered, and resliced to the standard MNI template in order for the dimensions of the data to be consistent between all subjects. The processed data were analyzed using the ApEn technique. A 3-voxel radius sphere centered on the area of greatest activation for each subject was used as the region of interest for study. Time series signals were extracted from this ROI, each corresponding to an individual voxel within the ROI. Errant signals that fell below 70.7% of the maximum signal contained in the ROI were removed, and the average ApEn of the remaining time signals was calculated. The motor ApEn was divided by the vision ApEn to form a ratio that could be used to quantify differences between the longitudinal scans.

All individuals showed significant activation within the motor cortex and occipital lobe via standard SPM analysis. Initial analysis of the time series signals in the activated areas indicated that the signals showed the sinusoidal pattern associated with on-off tasks. The control subjects demonstrated small changes in the ApEn ratio with and without caffeine, while the surgical patients demonstrated much larger changes in the ApEn ratio. The maximum percent change in the control subjects was 12.4% between caffeinated and non-caffeinated states. In contrast, the changes for the surgical patients ranged from 27.0% to 72.3%.

Conclusions: Based on our preliminary results, ApEn may be a useful method to provide quantitative information describing fMRI activation. As expected, the ApEn ratios were not altered due to amplification of the BOLD signal caused by caffeine intake. Conversely, they were markedly different between scans for the clinical patients, mirroring the patients' behavioral changes. This strategy of using a "baseline" task, combined with ApEn analysis, showed alterations in a signficant manner when it could be expected to (in this case in surgical patients) but was relatively unaffected merely due to other biological processes or longitudinal drift.

THE COALITION AGAINST MAJOR DISEASES: REGULATORY PATH TO ENABLE TARGETING THE RIGHT PATIENTS IN CLINICAL TRIALS OF EARLY STAGES OF PARKINSON'S DISEASE. Stephenson D, Cole PE, Comery TA, Gordon M, Grachev I, Hewitt D, Babcock D, Lindstedt K, Meibach R, Matthews D, Romero K, Breen K, Kelly M, Russell D, Stark Y, Imam S, Harbron C, Jimenez T, Marek K. Critical Path Institute/ Coalition Against Major Diseases**;** Takeda Pharmaceuticals International, Inc; Pfizer**;** Boehringer Ingelheim**;** GE**;** Merck & Co.**;** NIH/NINDS**;** Orion**;** Novartis**;** ADM Diagnostics, LLC**;** GlaxoSmithKline**;** Institute for Neurodegenerative Disorders**;** Teva**;** FDA**;** AstraZeneca.

Background and Objective: The Coalition Against Major Diseases (CAMD) is a precompetitive consortium aimed at accelerating drug development for Neurodegenerative Diseases through formal regulatory qualification. As therapeutic trials aim to intervene in earlier stages of Alzheimer's and Parkinson's diseases, diagnostic accuracy based purely on clinical criteria is a significant challenge. CAMD's Parkinson's disease (PD) imaging biomarker team seeks to qualify reductions in dopamine transporter (DAT) density measured by SPECT imaging as a prognostic biomarker for PD clinical trials.

Methods: A literature review was conducted to identify observational and clinical studies that utilized DAT imaging per defined criteria. The rate of SWEDD (scans without evidence of dopamine deficit) cases in clinical trials to date was reviewed. The team developed a comprehensive research plan including longitudinal analysis of the PRECEPT clinical trial and the PPMI study to estimate the degree of enrichment and impact on future trials in patients with early PD.

Results: In PD clinical trials enrolling recently diagnosed patients, approximately 10-15% of research subjects are classified as SWEDD. The rate of SWEDD is related to the time interval between the subjects' diagnosis and trial enrollment. Approximately 11% of the imaged subjects enrolled in PRECEPT had a SWEDD at baseline. SWEDD subjects (91) compared to DAT deficit subjects (708) showed reduced UPDRS at baseline and minimal change in UPDRS at follow-up assessments. Recent results of baseline measures in the Parkinson's Progression Markers Initiative longitudinal biomarkers study (PPMI) demonstrate that approximately 20% of subjects clinically diagnosed with PD are classified as SWEDD.

Conclusion: Exclusion of SWEDD cases in future trials aims to enrich clinical trial populations with idiopathic PD patients, improve statistical power, and spare subjects who do not have PD from being exposed to novel therapeutic agents. This precompetitive consortium initiative promises to increase the probability of success in future PD therapeutic trials.

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RESOLVING THE TRANSPORT KINETICS OF THE CORTICOSTERONE-SENSITIVE ORGANIC CATION TRANSPORTER 3 (OCT3/SLC22A3) IN THE MALE RAT BRAIN. Talboom JS, Molinaro J, Lowry CA, Renner KJ, Orchinik M. Arizona State University; University of Colorado Boulder; University of South Dakota; Arizona Alzheimer's Consortium.

Background: Monoamines (e.g., serotonin, norepinephrine, & dopamine) are a class of small molecule neurotransmitters whose signaling, after release and uptake, is in part terminated by monoamine oxidase (MAO)-mediated degradation. Monoamine degradation via MAO produces many metabolites including hydrogen peroxide, a reactive oxygen species (ROS). The organic cation transporter 3 (OCT3/Slc22a3) is a low affinity and high capacity polyspecific monoamine transporter. OCT3 is found throughout the human and rodent brain, including the rodent MAO expressing ciliated ependymal cells lining the ventral third cerebral ventricle (V3V). OCT3 may complement other specific (e.g., serotonin, norepinephrine, and dopamine transporters) or polyspecific (e.g., plasma membrane monoamine transporter, OCT1, & OCT2) monoamine transporters. OCT3 is thought to clear monoamines from the extracellular fluid in the brain, thereby helping to terminate their signal after release, via uptake and in part subsequent MAO-mediated degradation. This suggests that OCT3 may contribute to ROS generation, oxidative damage, aging, and Alzheimer's disease (AD). In rats, OCT3 appears to be a unique transporter. Corticosterone (CORT) has been found to be a potent and relatively selective OCT3 inhibitor. In this study, capitalizing on the specificity of CORT as an OCT3 inhibitor, we tested the hypothesis that uptake of organic cations in ependymal cells is in part mediated by OCT3. This study is unique because it was able to measure ependymal cell uptake, with high resolution, using an acute V3V slice preparation. Previous studies measuring OCT3-mediated uptake have used either brain minces or cell culture only.

Methods: We quantified the uptake of 4-(4-dimethylaminostyryl)-N-methylpyridinium (ASP+), a fluorescent organic cation, in live ciliated ependymal cells lining the ventral third cerebral ventricle (V3V). Three hundred μm acute V3V slices from male Sprague Dawley® rats (~250 g) were collected in artificial cerebrospinal fluid (aCSF) equilibrated with O_2 and CO_2. Slices were individual placed in a perfusion chamber filled with one of three ASP+ solutions (see below), and placed under a confocal microscope equipped with a 40x water immersion objective. ASP+ was excited using a 488 nm Argon laser during which images of the V3V ependymal cells were acquired. Our dependent measure was relative fluorescent intensity across time. Separate acute V3V slices from several rats were treated with: 1) ASP+ alone in equilibrated aCSF, 2) ASP+ in equilibrated aCSF containing a cocktail of specific transporter inhibitors, or 3) or ASP+ in equilibrated aCSF containing a cocktail of specific transporter inhibitors with CORT. These conditions were used to determine 1) OCT3-mediated ASP+ uptake and 2) CORT-mediated ASP+ uptake inhibition in an acute rat V3V slice preparation.

Results: We found that CORT inhibited both the cumulative amount and rate (slope) of ASP+ uptake in the presence of specific inhibitors of the serotonin, norepinephrine, and dopamine transporter. These data suggest that a portion of the uptake of organic cations, which include monoamines, is mediated via OCT3 in the rat V3V ependyma.

Conclusions: Since monoamine degradation leads to the generation of ROS, a better understanding of OCT3-mediated monoamine transport in the brain may aid in the development novel therapies to treat AD. Specifically, therapies that decrease OCT3-mediated monoamine transport, in cells also expressing MAO, may attenuate oxidative and neuronal damage.

PROTEIN AGGREGATES AS BIOMARKERS FOR NEURODEGENERATIVE DISEASES. <u>Tian H, Davidowitz E, Moe J, Sierks M</u>. Arizona State University; Oligomerix. Inc; Arizona Alzheimer's Consortium.

<u>Background</u>: Aggregation of proteins such as amyloid-beta (Abeta), alpha-synuclein and tau are thought to play a role in the neurodegenerative diseases including Alzheimer's and Parkinson's. During the aggregation process various oligomeric protein species are formed and increasing evidence implicates these oligomeric aggregates in disease onset and progression. Early detection of specific oligomer protein species could facilitate earlier and more accurate diagnoses and targeting these oligomers may also alter the disease manifestations. Our lab focuses on targeting specific oligomeric protein species and identifying their role in different neurodegenerative diseases.

<u>Methods</u>: Using novel technology, our lab isolated single chain antibody fragments (scFvs) that bind to monomeric and different oligomeric forms of Abeta, alpha-synuclein and taufrom a phage display library. We utilized these scFvs in a novel sandwich ELISA to characterize post-mortem human brain tissue representing different neurodegenerative diseases.

<u>Results</u>: The morphology specific scFvs can detect the presence of different oligomeric protein aggregate species in homogenized brain tissue. The presence of different oligomeric aggregates correlates with different neurodegenerative diseases.

<u>Conclusion</u>: Since our scFvs recognizes oligomeric forms of aggregated proteins that occur in Alzheimer's and Parkinson diseases these scFvs may be useful in facilitating early and accurate diagnoses in these diseases. Because the targeted oligomeric proteins are neurotoxic, these scFvs may also be useful as therapies since they could target and remove the oligomers before further damage could occur. Further research is necessary though to establish the role these scFvs can play in managing neurodegenerative diseases.

RESTING STATE MRI FUNCTIONAL CONNECTIVITY DIFFERENCES IN HEALTHY MIDDLE-AGED TO ELDERLY ADULTS. Totenhagen JT, Lines JW, Bergfield KL, Fitzhugh MC, Torre GA, Gillespie WL, Haws KA, Reid BA, Nguyen LA, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; Evelyn F. McKnight Brain Institute; Arizona Alzheimer's Consortium.

Background: Healthy aging has been associated with differences in brain structure and function as measured by noninvasive medical imaging. Resting functional connectivity MRI (fcMRI) provides a method to investigate age-related functional connections between brain regions and associated functional networks. In this study, we sought to investigate differences in resting state functional connectivity of the default-mode network in a sample of healthy middle-aged to elderly adults.

Methods: We studied 60 neurologically healthy adults ages 53-91 (mean±sd age 74±9 yr, 26F/34M, mean±sd Mini-Mental State Exam = 28.5±1.6). Subjects were medically screened to exclude neurological and psychiatric illness. Resting state MRI scans were processed to determine functional connections between brain regions. Temporal band pass filtering of the fcMRI data retained signal between 0.01 and 0.08 Hz., images were spatially smoothed, and covariates were included to control for non-gray matter signal and motion effects. A seed point in the posterior cingulate cortex was used to examine age-related differences in connectivity in the default mode network between healthy young-old (n = 30, 53-74) and old-old (n = 30, 75-91) groups. Additionally, residual motion effects were calculated as the mean framewise displacement (FD; Power et al., 2012) for each subject.

Results: FD values did not differ between the two groups (p = 0.56). The young-old and old-old groups differed in medial prefrontal cortical regions (z = 3.75-4.11), with the older group showing greater reductions in default mode network connectivity. After adding the FD as an additional covariate in the analysis, the regional group differences remained significant.

Conclusions: The results indicate reductions in resting functional connectivity in older elderly compared to middle-aged to younger elderly adults. These findings suggest that healthy aging may be associated with reductions in posterior to anterior functional connectivity of the default mode network, further supporting the potential of fcMRI in the evaluation of cognitive aging.

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ROCK INHIBITOR DEVELOPMENT FOR COGNITIVE ENHANCEMENT AND BLOCKADE OF TAU PHOSPHORYLATION. Turk MN, Adams MD, Wang T, Dunckley T, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Arizona State University; Midwestern University; University of Arizona.

Background: Rho-associated protein kinase (ROCK) is an enzyme that plays an important role in mediating actin organization. The ROCK inhibitor Fasudil has been shown to increase learning and working memory in normal rats, but a different inhibitor, Y27632, has been shown to impair learning and memory in control rats. These observations suggest potential different mechanisms of action for these two structurally different ROCK inhibitors.

Methods: 13 different ROCK inhibitors, 5 of which are commercially available and 8 of which are newly designed, were used to treat H4-tau cells across a 96-hour time course. The IC-10 dosage, at which 10% of H4-tau cells are no longer viable after 120 hours, was used with fresh drug-containing media added every 24 hours for 96 hours. The ratio of Serine 396 phosphorylated tau (p-tau) to total tau was measured using ELISA at each of 8 time points. All drug treatments were compared against the corresponding time point for vehicle (either water or DMSO) treated cells.
Fasudil, Y87632, and two novel ROCK inhibitors (T343 and T299) were validated using the IC-50 dosage across the 10 time points over 96 hours. New time points were at 0 hour and 6 hours.

Results: IC-10 dosage: Fasudil was the only commercial drug to decrease the p-tau to total tau ratio ($p=0.0004$). Of note, Y27632 did not decrease this ratio ($p=0.218$). Several novel ROCK inhibitors developed at Translational Drug Development decreased the p-tau to total tau ratio. Of these drugs, T343 had the greatest difference ($p=0.003$).
IC-50 dosage: Fasudil displayed significant decrease in the p-tau to total tau ratio beginning at 24 hours after treatment began ($p=0.01$) and no difference until then ($p=0.08$). T343 displayed a significant decrease ($p=0.003$). Y27632 showed no change at any point ($p=0.08$) and T299 displayed a significant increase in the ratio ($p=0.0009$).

Conclusions: Phosphorylation of tau at Serine 396 decreases tau mobility and ability of tau to bind to microtubules, contributing to the tauopathy of Alzheimer's disease. The differential effects of ROCK inhibitors on the p-tau to total ratio as well as on learning and memory in healthy animals are compelling. Further research is ongoing to parse out whether the effects of Fasudil on learning and memory are mediated through changes in p-tau to total tau expression or through other on- or off-target effects.

DEFICITS OF SYNAPTIC FUNCTIONS IN HIPPOCAMPAL SLICES PREPARED FROM AGED MICE NULL A7 NICOTINIC ACETYLCHOLINE RECEPTORS. Turner D, Gao M, Wu J. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Alpha 7 (α7) nicotinic acetylcholine receptor (α7-nAChR) is one of most high expressed nAChR subtypes in the brain. The activation of nAChRs enhances animal cognitive, learning and memory abilities. However, the role of genetic knockout (KO) of α7-nAChRs in animal cognition-associated behaviors is still obscure. An early report showed that α7-nAChR KO mice did not exhibit behavioral phenotypes, concerning the roles of α7-nAChRs in normal, cognition-associated behaviors. Later, α7-nAChR KO mice were found a deficit in animal spatial discrimination. The roles of α7-nAChRs in the alterations of hippocampal synaptic function during aging process are largely unknown.

Methods: Here, we address this question by examining synaptic function using field potential recording in hippocampal slice preparations from adult (12-14 months old) and aged (22-24 months old) α7-nAChR KO and age-matched wild-type (WT) mice.

Results: We found that compared to aged WT mice, aged α7-nAChR KO mice exhibited significantly reduced size of evoked field synaptic potential and impaired long-term potentiation (LTP) in hippocampal CA3-CA1 synapses. However, adult α7-nAChR KO mice did not show a clear deficit in LTP although the basic synaptic transmission was also reduced compared to adult WT mice. In both age groups, there was no significant difference of paired-pulse facilitation between α7-nAChR KO and WT mice.

Conclusions: Collectively, this study provides direct evidence, for the first time, that the impaired synaptic function occurs in aged α7-nAChR KO mice, suggesting an importance of α7-nAChRs in maintaining cognitive function during aging process.

INTERLEUKIN-34, A NEW PLAYER IN INFLAMMATORY PROCESSES OF ALZHEIMER'S DISEASE AND PARKINSON DISEASE. Walker DG, Whetzel AM, Huentelman MJ, Lue L. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Interleukin (IL)-34 is a recently identified cytokine that has identified properties indicating it may have critical and unique roles in regulating the health of microglia and controlling inflammatory processes in pathology affected brains. Although lacking similarities in protein structure features, IL-34 shares functional properties with macrophage colony stimulating factor (CSF)-1. Both cytokines bind to the CSF-1 receptor (CSF-1R) and activate signaling processes that can lead to cell proliferation. IL-34 has a molecular weight of 27 kD compared to 60 kD for CSF-1. Studies have shown that the cell signaling pathways activated by IL-34 binding to CSF-1R have some differences with those activated by CSF-1. Considering the results of several studies, it appears that IL-34 has a normal function of maintaining the homeostasis of macrophages/microglia and controlling inflammation by activating anti-inflammatory signaling, while CSF-1 is involved in microglia activation and proliferation under pathological conditions. It has been suggested that IL-34 is primarily produced by neurons in brain suggesting it controls microglia-neuronal interactions. Studies on the properties of IL-34 in brain have primarily been in rodent models. We sought to understand whether IL-34 levels could be altered in human brains from cases with Alzheimer's disease (AD) and Parkinson's disease (PD) and how human microglia derived from such cases respond to IL-34

Methods: This study utilized RNA and protein extracts from human brain tissue samples from control, AD and PD cases, and also human microglia derived from human autopsy brains that had been stimulated in vitro with IL-34. The techniques included quantitative polymerase chain reaction (qPCR) to measure expression of IL-34 messenger RNA (mRNA) and related molecules, western blots and ELISA to measure IL-34 protein levels and immunohistochemistry to identify the cellular localization of IL-34.

Results: The most significant finding to date was the demonstration that there was a decrease in IL-34 mRNA and IL-34 protein levels in samples of inferior temporal gyrus from AD cases compared to matching samples from normal samples. This is a brain region significantly affected by AD pathology. Analysis of samples from the substantia nigra from normal and PD cases showed significant correlation between tyrosine hydroxylase (TH) levels and IL-34. As this disease also has a significant inflammatory component, this result showed that higher IL-34 levels associated with reduced inflammation and thus reduced loss of TH positive neurons. By immunohistochemistry, we have only been able to localize IL-34 to neuronal cells in human brain sections.

Conclusions: Examining the effects of IL-34 on human microglia has demonstrated that it has a significant mitogenic effect on these cells that normally do not divide in culture. 1.□Contrary to a published finding using rodent microglia, we have demonstrated that human microglia do not respond to IL-34 by increased expression of transforming growth factor- This had been suggested as a mechanism for IL-34 anti-inflammatory action. Neuronal expression of IL-34 was demonstrated in vitro but this was not affected by treatment of these cells with different inflammatory agents. Further studies using RNA sequencing of IL-34 and CSF-1 microglia are underway to define the different consequences of CSF-R1 activation.
We have demonstrated that there are roles for IL-34 in human neurodegenerative diseases. A deficit of IL-34 is strongly suggested in AD and PD, which could lead to a dysregulation in inflammatory activation. As this is a relatively unexplored field in the human brain, this study has pointed to additional needed investigations.

THE INSTITUTE FOR HEALTHCARE INNOVATION-THE HEART OF ONE HEALTH INNOVATION. Weingand K, Sidaway B, Fossum T. Midwestern University; Arizona Alzheimer's Consortium.

The Institute for Healthcare Innovation™ (IHI) is a new One Health initiative that expands clinical research capabilities for all professional disciplines at Midwestern University (MWU). The clinical research focus areas will include oncology and neuroscience/behavior with emphasis on neurodegenerative diseases (Alzheimer's) and the human-animal bond. The IHI will be located in a new facility on the MWU-Glendale campus and will contain Centers of Excellence (CoE) in Clinical Research, Qualitative Research, and Advanced Imaging. The Clinical Research (CR) CoE will consist of a clinical research organization including personnel in Clinical Operations, Clinical Coordination, Biostatistics, Data Management, Regulatory/Quality Assurance, Recruiting, and Veterinary Technology. The CRC will be able to conduct clinical research studies with humans, domestic animals, and humans interacting with animals. To enhance enrollment of companion animals into clinical trials, the CRC will partner with approximately 15 high volume veterinary clinics and/or hospitals across the U.S. to form a National Veterinary Clinical Trial Network™ for conduct of multi-site clinical trials. The Qualitative Research (QR) CoE will contain a focus group room for interviewing volunteer subjects and pet owners that participate in the clinical trials and focus on subjective likes, dislikes, and feelings of the clinical research participants. The QR-CoE will also contain a Creative Ideation room for brainstorming next steps with study sponsors and will be able to conduct in-home, on-farm, and in-store qualitative research. The QR focus area will be patient-provider habits and practices. The Advance Imaging CoE will contain magnetic resonance imaging (MRI) and positron emission tomography/computerized tomography (PET/CT) scanners for studying cancer and central nervous system diseases. The IHI will be the "Heart of One Health Innovation".

USING MORPHOLOGY SPECIFIC REAGENTS TO DISTINGUISH BETWEEN DIFFERENT NEURO-DEGENERATIVE DISEASES. Williams SM, Sierks MR. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aggregation of proteins such as amyloid-beta (Abeta) and alpha-synuclein are thought to play major roles in the neurodegenerative diseases Alzheimer's and Parkinson's, respectively. During the aggregation process various oligomeric protein species are formed and increasing evidence implicates these oligomeric aggregates in disease onset and progression. Early detection of specific oligomer protein species could facilitate earlier and more accurate diagnoses and targeting these oligomers may also alter the disease manifestations. Our lab focuses on targeting specific oligomeric protein species and identifying their role in different neurodegenerative diseases.

Methods: Using novel technology, our lab isolated single chain antibody fragments (scFvs) that bind to monomeric and different oligomeric forms of Abeta and alpha-synuclein from a phage display library. These scFvs were previously characterized in our lab. We then used these scFvs in a novel immunological assay we developed to characterize brain tissue from various animal models and from post-mortem human cases representing different neurodegenerative diseases.

Results: The morphology specific scFvs can detect the presence of different oligomeric protein aggregate species in homogenized brain tissue. The presence of different oligomeric aggregates correlates with different neurodegenerative diseases.

Conclusions: Since our scFvs recognize specific oligomeric forms of aggregated proteins that occur in Alzheimer's and Parkinson diseases these scFvs may be useful in facilitating early and accurate diagnoses in these diseases. Because the targeted oligomeric proteins are neurotoxic, these scFvs may also be useful as therapies since they could target and remove the oligomers before further damage could occur. Further research is necessary to establish the role these scFvs can play in managing neurodegenerative diseases.

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WHAT ROLE DOES THE ANTERIOR TEMPORAL LOBE PLAY IN SENTENCE-LEVEL PROCESSING? NEURAL CORRELATES OF SYNTACTIC PROCESSING IN SEMANTIC PPA.
Wilson SM, DeMarco AT, Henry ML, Gesierich B, Babiak M, Miller BL, Gorno-Tempini ML. University of Arizona; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: Neuroimaging and neuropsychological studies have implicated the anterior temporal lobe (ATL) in sentence-level processing, with syntactic structure-building and/or combinatorial semantic processing suggested as possible roles. A potential challenge to the view that the ATL is involved in syntactic aspects of sentence processing comes from the clinical syndrome of semantic variant primary progressive aphasia (semantic PPA, also known as semantic dementia). In semantic PPA, bilateral neurodegeneration of the anterior temporal lobes is associated with profound lexical semantic deficits, yet syntax is strikingly spared. The goal of this study was to investigate the neural correlates of syntactic processing in semantic PPA, in order to determine which regions normally involved in syntactic processing are damaged in semantic PPA, and whether spared syntactic processing depends on preserved functionality of intact regions, preserved functionality of atrophic regions, or compensatory functional reorganization.

Methods: We scanned 20 individuals with semantic PPA and 24 age-matched controls using structural and functional MRI. Participants performed a sentence comprehension task that emphasized syntactic processing and minimized lexical semantic demands.

Results: We found that in controls, left inferior frontal and left posterior temporal regions were modulated by syntactic processing, while anterior temporal regions were not significantly modulated. In the semantic PPA group, atrophy was most severe in the anterior temporal lobes, but extended to the posterior temporal regions involved in syntactic processing. Functional activity for syntactic processing was broadly similar in patients and controls; in particular, whole-brain analyses revealed no significant differences between patients and controls in the regions modulated by syntactic processing. The atrophic left anterior temporal lobe did show abnormal functionality in semantic PPA patients, however this took the unexpected form of a failure to deactivate.

Conclusions: Taken together, our findings indicate that spared syntactic processing in semantic PPA depends on preserved functionality of structurally intact left frontal regions and moderately atrophic left posterior temporal regions, but no functional reorganization was apparent as a consequence of anterior temporal atrophy and dysfunction. These results suggest that the role of the anterior temporal lobe in sentence processing is less likely to relate to syntactic structure-building, and more likely to relate to higher level processes such as combinatorial semantic processing.

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ABSENCE OF A "WIDOWHOOD EFFECT" ON INCIDENCE OF DEMENTIA IN COGNITIVELY NORMAL RESEARCH SUBJECTS. Woodruff B, Stonnington C, Locke DEC, Hentz J, Dueck AC, Wojtulewicz L, Caselli RJ, Geda YE. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Spousal death is associated with negative health outcomes such as the "broken heart syndrome". The impact of spousal death on the risk of developing dementia is unknown. We hypothesized that spousal demise would accelerate the incidence of dementia in surviving spouses with normal cognition.

Methods: Subjects enrolled in an NIA-Alzheimer's Disease Center who were married and cognitively normal at entry were identified from the National Alzheimer's Coordinating Center (NACC) database for Uniform Data Set visits conducted between September 2005 and September 2013. Those who became divorced or separated during followup were excluded. The primary outcome was age of dementia diagnosis. Cox regression was used to compare the incidence of dementia among subjects who became widowed with that of subjects who remained married.

Results: 6,088 subjects were married and cognitively normal at entry. 59 subjects subsequently divorced or separated and were excluded. 1583 who had no follow-up were excluded. Of those remaining, 398 became widowed and 4048 remained married. Number of visits ranged from 2 to 9 (mean 4.3, SD 1.9), with study duration up to 7.8 years (mean 3.8, SD 2.0). 218 subjects became demented. The median age of dementia onset in the widowed group was not younger than in the married group (96 vs 96 y, HR 0.92, 95% CI 0.66 to 1.29, P .64). Adjustment for sex, presence of an ε4 allele, or age at first visit did not increase the HR for loss of a spouse.

Conclusions: Loss of a spouse does not predict earlier development of dementia in this group of subjects enrolled in NIA-Alzheimer's Disease Centers. The absence of a "widowhood effect" may reflect increased resilience in individuals who elect to participate in such research studies, or could be a result of selection bias if subjects excluded on the basis of being widowed at entry developed dementia at a younger age. Replication of this analysis in a longitudinal community-based cohort could clarify such potential biases.

The NACC database is funded by NIA Grant U01 AG016976.

*This data is to be presented at the Alzheimer's Association International Conference in Copenhagen, Denmark on July 14, 2014.

PARADOXICAL IMPACT OF WIDOWHOOD ON INCIDENCE OF DEMENTIA IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT. Woodruff B, Stonnington C, Locke DEC, Hentz J, Dueck AC, Wojtulewicz L, Geda YE, Caselli RJ. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Spousal death is associated with negative health outcomes such as the "broken heart syndrome". The impact of spousal death on the risk of developing dementia is unknown. We hypothesized that spousal demise would accelerate the incidence of dementia in surviving spouses with Mild Cognitive Impairment (MCI).

Methods: Subjects enrolled in an NIA-Alzheimer's Disease Center who were married and diagnosed with MCI at entry were identified from the National Alzheimer's Coordinating Center (NACC) database for Uniform Data Set visits conducted between September 2005 and September 2013. Those who became divorced or separated during followup were excluded. The primary outcome was age of dementia diagnosis instead of time from study entry to control for the difference in age at first visit. Cox regression was used to compare the incidence of dementia among subjects who became widowed with that of subjects who remained married.

Results: 3,783 subjects were married and had MCI at entry. 15 subjects subsequently divorced or separated and were excluded. An additional 1177 with no follow-up were excluded. Of those remaining, 134 became widowed and 2457 remained married. Number of visits ranged from 2 to 9 (mean 3.7, SD 1.7), with study duration up to 7.5 years (mean 3.1, SD 1.8). 1078 subjects became demented. The median age of dementia onset in the widowed group was older than in the married group (92 vs 83 years, HR 0.36, 95% CI 0.26 to 0.48, P <.001). Adjustment for sex, presence of an ε4 allele, or age at first visit did not substantially increase the HR for loss of a spouse.

Conclusions: Loss of a spouse is associated with later age of dementia onset in this group of MCI subjects enrolled in NIA-Alzheimer's Disease Centers. This might reflect implementation of more robust support for widowed MCI subjects compared to married subjects, or could be a result of selection bias if subjects with MCI at entry who were excluded on the basis of being widowed developed dementia at a younger age. Replication of this analysis in a longitudinal community-based longitudinal cohort could clarify such relationships.

*This data is to be presented at the Alzheimer's Association International Conference in Copenhagen, Denmark on July 14, 2014.

DYNAMIC BRAIN CHANGES ASSOCIATED WITH NEW LEARNING. Yang S, Nie Z, Braden BB, Morrone-Strupinski J, Steinke K, Ye J, Baxter LC. Arizona State University; Barrow Neurological Institute; Private Practice, Chandler, Arizona; Arizona Alzheimer's Consortium.

We utilized a novel functional MRI analysis procedure to investigate differences in brain connectivity associated with new learning in patients with Mild Cognitive Impairment (MCI) compared to controls. We developed a task to investigate new learning associated with repetition of information, which in MCI is affected early in the disease (Albert et al 2001). The task involves repeated exposure to a small group of faces in order to determine how brain connectivity dynamically alters as individuals passively learn the faces. We aim to infer the brain connectivity networks from this task to investigate how neural activity in specific brain regions change during learning of new faces, and to determine how this pattern is altered in patients with Mild Cognitive Impairment.

The successive volumes of fMRI scan are temporally correlated and reflect a certain form of brain connectivity patterns that can be used to study the difference of brain changes between normal people and MCI. One single brain connectivity network cannot represent the changes of brain connectivity pattern over time. Therefore, we used a sparse network analysis approach to examine multiple brain connectivity networks to determine the variance of brain connectivity patterns over time.

We recruited MCI patients (n = 9; 6M/3F) through a clinical practice and cognitively normal (C) participants (n = 14 7M/7F) through the community. There were no group demographic differences (MCI/C Mean) in age (70.6 years/69.4 years) or education (15.3/16.6). All were right-handed. MCI patients performed significantly worse on both new learning and delayed recall on the Auditory Verbal Learning Test (p's < .01); MMSE scores were slightly lower in MCI group (26.8/29.8). All participants underwent fMRI scanning on the same 3Tesla GE scanner. The paradigm repeated a block of 10 faces 6 times, with a gray circle "control" condition alternating each repetition. In order to monitor participation and new learning (reaction time), participants used a button press to indicate whether faces were happy or sad. Realignment and normalization were performed using SPM8. Regions of interest (ROI) from the frontal lobe (32 regions), amygdala (L/R), hippocampus (L/R), fusiform gyrus (L/R) and occipital lobe were segmented based on the automated anatomical labeling method. We jointly estimated multiple connectivity networks from the ROIs to study the dynamic brain change during new learning. The estimated connectivity networks share some common structures based on the assumption that the brain connectivity pattern changes smoothly due to temporal smoothness of fMRI. However, they are not identical because of the brain connectivity variations between regions. The multiple brain connectivity networks can be jointly estimated using fused multiple graphical lasso. More specifically, we estimated the networks by maximizing a penalized log likelihood with fused lasso regularization. The l-1 regularization yields sparse networks while the fused regularization encourages the connectivity networks to be similar to their adjacencies.

We found connectivity among the frontal lobe ROIs and the hippocampus for both MCI and control groups; however, a larger number of frontal lobe ROI connectivity was observed for the MCI patients compared to controls. Controls showed a more regular pattern of frontal connectivity that reached a plateau after several repetitions while the MCI patients did not show a diminishment of recruitment, with more frontal lobe regions participating, especially by the 4th repetition of the stimuli.

The preliminary results demonstrated that the proposed method of dynamically measuring brain connectivity in fMRI is a promising in studying brain changes during new learning in MCI patients. The MCI group showed a greater degree of frontal lobe utilization while maintaining performance (71 vs 76% accuracy) during this simple learning task. This suggests that the MCI group likely compensates for disrupted fronto-temporal connectivity by recruiting greater frontal lobe regions to perform the task.

Additional Abstracts

OVERVIEW OF HISPANIC RECRUITMENT TO THE ARIZONA ALZHEIMER'S DISEASE CORE CENTER STUDY. <u>Baxter LC, Mar L</u>. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

<u>Introduction and Background</u>: Hispanics represent 30% of the Arizona's population. Given that the rate of Alzheimer's Disease and other dementias in Hispanics is one and one-half times the rate of non-Hispanic whites (Alzheimer's Association, 2013), the importance of including Hispanics on longitudinal studies of aging and dementia is critical for Arizona. We have examined the enrollment of Hispanics in the Arizona Alzheimer's Disease Core Center (AzADCC) in order to characterize our current recruitment trends. We compare and contrast characteristics of AzADCC Hispanics (Hisp) to both the non-Hispanic whites (NH) in the study and the Hispanic population in Arizona and the US. Our goals include a) describing current recruitment trends in order to determine possible strategies to increase recruitment and better serve the Hispanic community and b) determine the relationship between cognitive performance and factors that may influence cognitive health that may be over-represented in the Hispanic community.
<u>Methods</u>: The AzADCC recruits cognitively impaired patients from neurology clinics as well as cognitively normal participants through community efforts. All participants undergo extensive neurocognitive assessment as well as neurological exam. For most participants, APOE genotyping is performed. All data reported are generated from the AzADCC database and were analyzed using the variables available within the database. Participants self-report as Hispanic. Data can be separately examined based on community vs. clinical recruitment. There are three sites that recruit participants from the community; the Sun Health Research Institute via their large brain donation program, Barrow Neurological Institute, which recruits participants through community events, and Mayo Clinic Arizona, which recruits cognitively normal individuals to be part of a parallel study examining longitudinal cognitive functioning. They have several methods for recruiting participants including media and community groups. In the current analyses, participation is categorized as community or clinical sources only. Current analyses focus on the first epoch of study only.

<u>Results</u>: To date, 13% of all participants completing at least one epoch are Hispanic. The majority of Hisp (65%) have been recruited through neurology clinics rather than through the community. Most successful community recruitment efforts include community events, such as social groups or health fairs. Most Hisp spoke English as their primary language (80.7%). Recruitment did not differ relative to participant diagnoses between NH and Hisp individuals (NH vs Hisp) AD: 13% vs 17%; MCI: 12% vs 8%; other dementia: 6% vs 4.4%; Cognitively intact: 68% vs 69%. Among impaired patients, the two groups had similar distribution of CDR scores: CDR 0: 28% vs 22%; CDR 1: 17% vs 16%, CDR 1: 8% vs 9%; CDR 2: 4% vs 7%; CDR 3: 1.2% vs 0.6%. Age of diagnosis was also similar: 71.7 vs 74.8.
Overall, Hisp have a lower mean education level than NH (mean: 15.25 vs 12.88). However, distinguishing clinical patients from community volunteers revealed that while Hisp patients have a lower education level (11 yrs vs 15 yrs), there were no group differences for community volunteers, who tended to be well-educated (15 years, both groups). Interestingly, approximately 75% of both clinical and community NH participants had 12 years of education or better. This was also true for the community Hisp group; however, only about 40% of the Hisp clinical patients had a high school level education or better. Rates of hypertension, hypercholesterolemia, and cardiovascular disease were not significantly different (Chi-square > 0.05); however, the Hisp group had higher mean BMI scores (27.6 vs. 25.4; p = .001) and self reported Diabetes mellitus (p < .001). In the cognitively normal, Hisp had lower education (p < .001) and lower CDR scores (p< .02), and long term memory scores tended to be lower (p = .07). Among AD patients, Hisp were less educated, (p < .001), but showed no other differences in MMSE, Mattis DRS, memory, or CDR levels. Among MCI patients, Hisp patients were less educated (p < .001) but had higher long term memory scores (p = .012).

Conclusions: Many similarities were observed regarding recruitment of Hispanic and Non-Hispanic participants in this study. The Hispanic group of patients tended to be represented similarly in diagnosis and level of impairment. The largest difference in patient populations was the level of education. Recruiting from the community shows a bias towards higher educated individuals in both the Hispanic and Non –Hispanic groups. Regardless of group, Hispanics have higher rates of Diabetes mellitus and higher BMI scores. In these preliminary analyses, we find that education level may be a barrier in recruiting cognitively normal Hispanics, as it is with Non-Hispanics, but that Hispanic patients with lower educational attainment are willing to participate through their doctors. Best recruitment for Hispanics in the community appears to be through community outreach during events such as health fairs. We plan to further study the relationship between health disparities in the groups and cognitive functioning and also examine factors affecting attrition.

SEX-BASED MEMORY ADVANTAGES DO NOT MITIGATE PRECLINICAL MEMORY DECLINE IN APOE E4 CARRIERS. Caselli RJ, Dueck AC, Locke DEC, Baxter LC, Woodruff B, Geda Y. Mayo Clinic Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Either in isolation or in various combinations years of education (most frequently), linguistic skill, intellectually stimulating leisure activity, social engagement, socioeconomic status , occupational complexity, measures of crystallized intelligence, literacy, bilingualism, and musical background, have all been utilized as proxies for CR , yet all are associated with other environmental factors such as housing, nutrition, access to healthcare, educational opportunities, and cultural resources possibly explaining discrepancies between studies examining their relationships to cognitive aging, incident MCI, incident dementia, rate of decline, mortality, and neuropathology. A more ideal proxy for CR should have a minimum of potential confounds, should directly reflect cognition, and should be sensitive to the earliest stages of AD. A potential category of proxies meeting these criteria are sex-related memory differences. To determine whether superior performance confers neuroprotection, we examined whether the rate of APOE e4 mediated memory decline was reduced in the advantaged sex.

Methods: Within the context of a previously described comprehensive neuropsychological battery, members of the Arizona APOE Cohort, a genetically enriched longitudinal study of cognitive aging, completed the following two verbal memory and two visuospatial memory tests: Rey Auditory Verbal Learning Test (AVLT), Buschke Selective Reminding Test (SRT), Rey-Osterrieth Complex Figure Test (CFT), and Benton Visual Retention Test (VRT). The acceleration of the rate of decline for each of the predetermined measures for women (collectively and also separately for each of the subgroups of e4 carrier and noncarrier) was compared to those of men using a mixed model approach for modeling cross-sectional and longitudinal data. A quadratic model was selected to allow for comparison of the acceleration in the rate of decline between groups, as well as linear effects (velocity of decline).

Results: Age-related memory decline was accelerated in APOE e4 carriers on both verbal memory measures (AVLT-LTM, p=.03; SRT-free recall $P < .001$), as well as on one visuospatial memory measure (VRT p=.006), but not on the CFT-recall (p=.39). No sex differences in rate of decline were found for any measure: AVLT-LTM p=.89, SRT-free recall p=.84, CFT-recall p=.17, VRT p=.49.

Conclusions: Sex-associated intellectual advantage on a memory test was retained throughout adulthood, and while we cannot exclude the possibility of an effect during the ninth and tenth decades of life, there was otherwise no evident effect on the rate of decline associated with age in either APOE e4 noncarriers or carriers.

PUBLIC PERCEPTIONS OF PRESYMPTOMATIC TESTING FOR ALZHEIMER'S DISEASE.

Caselli RJ, Langbaum J, Marchant GE, Lindor RA, Hunt KS, Henslin BR, Dueck AC, Robert JS. Mayo Clinic Arizona**;** Banner Alzheimer Institute**;** Arizona State University; Arizona Alzheimer's Consortium.

Background: To explore, among online visitors to an Alzheimer's disease (AD) website, the self-expressed desire for, envisioned reaction to, and basic understanding of presymptomatic AD-related genetic and biomarker tests.

Methods: Information about presymptomatic testing, and an online multiple choice format survey were posted from November 1, 2012 through June 20, 2013 on the AD Prevention Registry website (www.endALZnow.org).

Results: Of 4036 respondents, 80.8% wanted genetic testing if paid by insurance; 58.7% if it would cost them at least $100. 80.2% wanted biomarker testing. If found to be at high risk for AD, 90.5% endorsed that they would "pursue a healthier lifestyle," but 11.6% endorsed "seriously consider suicide." The implication of a positive genetic test was incorrectly understood by 13.1%, and 32.6% failed to view a positive biomarker test as evidence of either increased risk for or the presence of AD.

Conclusions: Despite efforts to increase public awareness of AD, our survey results suggest that greater education of the public is needed. Interested patients should probably undergo psychological screening to identify those at high risk of adverse psychological outcomes, and disclosure of presymptomatic test results should be anchored to tangible constructive action plans such as healthy lifestyle changes, long term care planning, and when available and appropriate, participation in research trials.

HANDLING RATHER THAN ROUTE OF ADMINISTRATION IS ASSOCIATED WITH MEMORY IMPAIRMENTS OF CONJUGATED EQUINE ESTROGEN TREATMENT: A CAUTIONARY TALE REGARDING THE IMPACT OF EXPERIMENTAL MANIPULATIONS ON COGNITIVE OUTCOMES. Engler-Chiurazzi EB, Scheldrup M, Ciciolla L, Bowman BL, Schaeffer KR, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Conjugated equine estrogen (CEE; trade-named Premarin) is the most widely used estrogen component of menopausal hormone therapy in North America. CEE effectively relieves urogenital and vasomotor menopausal symptoms, but cognitive performance findings of clinical and basic science studies are mixed. Studies testing the cognitive effects of subcutaneous CEE treatment in middle-aged, Ovx rats have generally revealed favorable results for memory performance. Of note, CEE is prescribed to women in the form of a daily oral pill; there is disagreement as to its effectiveness when given orally for cognitive outcomes in women. To date, no study has methodically evaluated the cognitive impact of orally administered CEE in the rodent model. In Study 1, we conducted a dose-response study to evaluate the impact of oral CEE on memory in middle-aged Ovx rats. Results showed impairments induced by oral CEE administration. We performed a follow-up study to determine whether memory effects were induced by the estrogen treatment, or were imparted by the handling procedures necessary to administer the hormone. Study 2 assessed the mnemonic impact of oral handling procedures independent of hormone treatment. Therefore, in summary, oral CEE impaired spatial working memory performance (Study 1), and the handling used to administer the treatments impaired spatial working memory performance on the same task (Study 2). These findings suggest that some experimental manipulations necessary to administer hormones could account for the conflicting literature regarding the memory effects of estrogen treatments. The effects of these experimental manipulations should be considered carefully when interpreting the cognitive impacts of estrogen treatments.

THE EFFECTS OF HORMONE THERAPY ESTROGENS ON THE MIDBRAIN SEROTONERGIC SYSTEM: ASSOCIATION BETWEEN SUBREGION-SPECIFIC CHANGES OF THE TRYPTOPHAN HYDROXYLASE-2 MRNA LEVELS IN THE DORSAL RAPHE NUCLEUS AND COGNITIVE, ANXIETY-LIKE, AND DEPRESSIVE-LIKE BEHAVIORS. Hiroi R, Weyrich G, Talboom JS, Jordan A, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Accumulating evidence indicates that decreased serotonin (5-HT) function is associated with a wide range of cognitive disorders, severity of Alzheimer's disease (AD), and affective disorders. Notably, women are more vulnerable to both cognitive and affective disorders than men, and postmenopausal women exhibit decreased serotonergic activity. The serotonergic neurons in the dorsal raphe nucleus (DRN) are a major source of 5-HT in the forebrain. In particular, polymorphisms of tryptophan hydroxylase-2 (TpH2, the brain specific, rate limiting enzyme for 5-HT biosynthesis) that result in loss of function are implicated in affective disorders and a wide spectrum of cognitive disorders, suggesting that TpH2 plays an important role in both affect and cognition.

Benefits of 17β-estradiol (E2), the most potent naturally circulating estrogen in women and rats, on cognitive, anxiety-like, and depressive-like behaviors have been shown. Moreover, E2 also has been shown to increase TpH2 mRNA in the DRN and this increase plays a critical role in regulation of anxiety-like and depressive-like behaviors. Although conjugated equine estrogen (CEE) is the most commonly prescribed estrogen component of hormone therapy in menopausal women, there is a marked gap in knowledge regarding whether CEE affects cognition, anxiety-like, and depressive-like behaviors, and the 5-HT system. Therefore, we evaluated and compared the effects of CEE and E2 treatment on TpH2 mRNA in the DRN, and examined correlations with cognitive, anxiety-like, and depressive-like behaviors. Female rats were ovariectomized, administered vehicle, CEE, or E2, and tested on a battery of cognitive, anxiety-like, and depressive-like behaviors. Brains of these animals were then analyzed for TpH2 mRNA in subregions of the DRN. Results showed that E2 increased TpH2 mRNA in the caudal and mid subdivisions of the DRN, corroborating previous findings. On the other hand, CEE increased TpH2 mRNA in the caudal and rostral, but not the mid, DRN. Collectively, the findings suggest that different types of estrogens can have subregion-specific effects on DRN TpH2 gene expression. We also found differential correlations between some behaviors and level TpH2 mRNA, depending on the type of behavior and the specific subdivisions of DRN. These distinct associations imply that regulation of cognition vs anxiety-like vs depressive-like behaviors are modulated by unique serotonergic neurocircuitry, opening a possibility of novel avenues of targeted treatment for different types of cognitive and affective disorders.

THE SEX-SPECIFIC EFFECTS OF CHRONIC ANTIDEPRESSANT ADMINISTRATION ON SPATIAL COGNITION, ANXIETY-LIKE, AND DEPRESSIVE-LIKE BEHAVIOR IN MIDDLE-AGED RATS. <u>Hiroi R, Quihuis A, Lavery C, Granger S, Weyrich G, Bimonte-Nelson HA</u>. Arizona State University; Arizona Alzheimer's Consortium.

Aging and the menopausal transition are each associated with affective disorders such as depression and anxiety, which is often co-morbid with cognitive impairment amongst elderly patients. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are commonly prescribed to alleviate symptoms of depression and anxiety. Although preclinical studies have investigated the antidepressant effects of SSRIs in adults, antidepressant and cognitive effects of SSRIs in aged populations are not well characterized, especially regarding sex differences. As women are more vulnerable to both cognitive and affective disorders than men and aged, post- and peri- menopausal women are at higher risk for cognitive and affective disorders, we investigated the sex-specific effects of chronic SSRI citalopram administration on cognitive, anxiety-like, and depressive-like behaviors in middle-aged rats, using the water radial arm maze (WRAM), open field test (OFT), and forced swim test (FST), respectively. We found a robust sex difference in WRAM performance; in middle-aged rats, females outperformed males in working memory tasks, extending a previous finding in young rats. Citalopram improved memory retention, despite the slower rate of learning during acquisition of the task for working memory. We also found that chronic citalopram had sex-specific effects on depressive-like behaviors in the FST. These results suggest that age, sex, and the type of behavior may play an important role in predicting the outcome of SSRIs on cognitive and affective behaviors. This study raises important considerations and warrants further investigations to decipher the distinct parameters in which mood- and cognitive- enhancing effects of antidepressants can be realized.

NEUROCHEMICAL PROFILE OF DEMENTIA PUGILISTICA. Kokjohn TA, Maarouf CL, Daugs ID, Hunter JM, Whiteside CM, Malek-Ahmadi M, Rodriguez E, Kalback W, Jacobson SA, Sabbagh MN, Beach TG, Roher AE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Dementia pugilistica (DP) is a suite of neuropathological and cognitive function declines following chronic traumatic brain injury (TBI) present in approximately 20% of retired boxers. Epidemiological studies indicate TBI is a risk factor for neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson's disease (PD). Some biochemical alterations observed in AD and PD may be recapitulated in DP and other TBI subjects. In this report we investigate long-term biochemical changes in the brains of former boxers with neuropathogically confirmed DP. Our experiments revealed biochemical and cellular alterations in DP that are complementary to and extend information already provided by histological methods. ELISA and 1D- and 2D-Western blot techniques revealed differential expression of select molecules between 3 DP cases and 3 age-matched non-demented control (NDC) cases without a history of TBI. Structural changes such as disturbances in the expression and processing of glial fibrillary acidic protein, tau and alpha-synuclein were evident. The levels of the Abeta-degrading enzyme neprilysin were reduced in the DP cases. Amyloid-beta levels were elevated in the DP subject with the concomitant diagnosis of AD. In addition, the levels of brain-derived neurotrophic factor and the axonal transport proteins kinesin and dynein were substantially decreased in DP relative to NDC subjects. Traumatic brain injury is a risk factor for dementia development and our findings are consistent with permanent structural and functional damage in the cerebral cortex and white matter of boxers. Understanding the precise threshold of damage required for the induction of pathology in DP and TBI is vital.

DEVELOPMENT AND IMPLEMENTATION OF THE NATIONAL ALZHEIMER'S PREVENTION REGISTRY. Langbaum JB, High N, Aisen PS, Albert MS, Comer M, Cummings JL, Manly JJ, Petersen RC, Sperling RA, Strobel G, Weiner MW, Tariot PN, Reiman EM. Banner Alzheimer's Institute; University of California San Diego, Alzheimer's Disease Cooperative Study; Johns Hopkins University; Geoffrey Beene Foundation; Lou Ruvo Cleveland Clinic; Columbia University; Mayo Clinic; Harvard University; Alzforum; University of California San Francisco; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: To help advance the evaluation of Alzheimer's disease (AD) prevention therapies, we launched a web-based Alzheimer's Prevention Registry ("Registry"). This Registry is intended to provide a shared resource to facilitate enrollment in prevention studies and to complement and enhance local efforts. The Registry will inform enrollees about the latest news in AD prevention research and about opportunities to participate in research in their community.

Methods: Interested adults of all ages, with and without memory and thinking problems, are eligible to join at www.endALZnow.org. Modeled after other disease registries, this Registry was purposefully designed to have a low threshold of commitment at entry. Individuals are asked to provide their email address at enrollment. Additional contact and demographic information can be completed after joining through surveys at their convenience and discretion. Enrollees receive regular email communication to keep them apprised of the latest news in Alzheimer's prevention research. Individuals receive email notifications when study opportunities are available in their communities, and whom to contact to explore the possibility of their participation.

Results: To date 28,735 have joined. 95% of enrollees have provided some additional contact and demographic information, with 85% of enrollees answering all questions. Registrants are predominantly women (78%), report a family history of dementia (72%) and have no diagnosis of cognitive impairment (95%). 36% of enrollees are between the ages of 46-60; 37% are between the ages of 61-75.The most successful outreach mechanisms include news articles, TV and radio interviews, and paid online advertising.

Conclusion: The Registry, which intends to create an interactive community of individuals who are passionate about fighting the disease and accelerate enrollment in prevention studies, has been well-received. In preparation for a pipeline of prevention-focused studies, including the ADCS "A4" trial and the planned API trial in apolipoprotein E (APOE) ε4 homozygotes, efforts are underway to develop a robust Researcher portal. We continue to explore new approaches for increasing enrollment and engagement of enrollees, as well as work with a large number of researchers to help increase enrollment within their catchment areas.

QUANTITATIVE APPRAISAL OF VENTRICULAR CEREBROSPINAL FLUID BIOMARKERS IN NEUROPATHOLOGICALLY DIAGNOSED PARKINSON'S DISEASE CASES LACKING ALZHEIMER'S DISEASE PATHOLOGY. Maarouf CL, Beach TG, Adler CH, Malek-Ahmadi M, Kokjohn TA, Dugger BN, Walker DG, Shill HA, Jacobson SA, Sabbagh MN, Roher AE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Identifying biomarkers that distinguish Parkinson's disease (PD) from normal control (NC) individuals has the potential to increase diagnostic sensitivity for the detection of early-stage PD. A previous proteomic study identified potential biomarkers in postmortem ventricular cerebrospinal fluid (V-CSF) from neuropathologically diagnosed PD subjects lacking Alzheimer's disease (AD) neuropathology. In the present study, we assessed these biomarkers as well as p-tau(181), Abeta42, and S100B by ELISA in PD (n = 43) and NC (n = 49) cases. The p-tau(181)/Abeta42 ratio and ApoA-1 showed statistically significant differences between groups. Multiple regression analysis demonstrated that p-tau(181)/Abeta42 had a significant odds ratio: OR = 1.42 (95% confidence interval [CI], 1.12-1.84), P = 0.006. Among the molecules investigated, intriguing correlations were observed that require further investigation. Our results suggest coexistent AD CSF biomarkers within the PD group notwithstanding that it was selected to minimize AD neuropathological lesions.

MOLECULAR DIFFERENCES AND SIMILARITIES BETWEEN ALZHEIMER'S DISEASE AND THE 5XFAD TRANSGENIC MOUSE MODEL OF AMYLOIDOSIS. Maarouf CL, Kokjohn TA, Whiteside CM, Macias MP, Kalback WM, Sabbagh MN, Beach TG, Vassar R, Roher AE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Transgenic (Tg) mouse models of Alzheimer's disease (AD) have been extensively used to study the pathophysiology of this dementia and to test the efficacy of drugs to treat AD. The 5XFAD Tg mouse, which contains two presenilin-1 and three amyloid precursor protein (APP) mutations, was designed to rapidly recapitulate a portion of the pathologic alterations present in human AD. APP and its proteolytic peptides, as well as apolipoprotein E and endogenous mouse tau, were investigated in the 5XFAD mice at 3 months, 6 months, and 9 months. AD and nondemented subjects were used as a frame of reference. APP, amyloid-beta (Abeta) peptides, APP C-terminal fragments (CT99, CT83, AICD), beta-site APP-cleaving enzyme, and APLP1 substantially increased with age in the brains of 5XFAD mice. Endogenous mouse tau did not show age-related differences. The rapid synthesis of Abeta and its impact on neuronal loss and neuroinflammation make the 5XFAD mice a desirable paradigm to model AD.

NAVIGATING TO NEW FRONTIERS IN BEHAVIORAL NEUROSCIENCE: TRADITIONAL NEUROPSYCHOLOGICAL TESTS PREDICT HUMAN PERFORMANCE ON A RODENT-INSPIRED RADIAL-ARM MAZE. Mennenga SE, Baxter LC, Grunfeld IS, Brewer GA, Engler-Chiurazzi EB, Camp BW, Acosta JI, Braden BB, Schaefer KR, Gerson JE, Lavery CN, Tsang CWS, Hewitt LT, Kingston ML, Koebele SV, Patten KJ, Ball BH, McBeath MK*, Bimonte-Nelson HA*. Arizona State University; Arizona Alzheimer's Consortium; Barrow Neurological Institute.

*equal contribution to this project

We constructed an 11-arm, walk-through, human radial-arm maze (HRAM) as a translational instrument to compare existing methodology in the areas of rodent and human learning and memory research. The HRAM, utilized here, serves as an intermediary test between the classic rat radial-arm maze (RAM) and standard human neuropsychological and cognitive tests. We show that the HRAM is a useful instrument to examine working memory ability, explore the relationships between rodent and human memory and cognition models, and evaluate factors that contribute to human navigational ability. One-hundred-and-fifty-six participants were tested on the HRAM, and scores were compared to performance on a standard cognitive battery focused on verbal memory, working memory capacity, and visuospatial ability. We found that errors on the HRAM increased as working memory demand became elevated, similar to the pattern typically seen in rodents, and that performance corroborated Miller's classic description of human working memory capacity as 7±2 items. Regression analysis revealed that working memory capacity tasks, visuospatial ability tasks, and a test of short-term episodic memory accounted for a large proportion of variance in HRAM scores, while measures of long-term episodic memory and general intelligence did not serve as valuable predictors of HRAM performance. We present the HRAM as a novel instrument for measuring navigational behavior in humans, thus providing a useful tool to help connect and translate between human and rodent models of cognitive functioning.

HARMINE TREATMENT ENHANCES MEMORY IN OLD RATS: CAUTIOUS INTERPRETATIONS WHEN TESTING THE COGNITIVE EFFECTS OF A DRUG THAT ALSO INDUCES TEMPORARY MOTOR DEFICITS AT HIGH DOSES. Mennenga SE, Gerson JE, Bimonte-Nelson HA*, Dunckley T*. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

*equal contribution to this project

Harmine is a naturally occurring monoamine oxidase inhibitor that has recently been shown to selectively inhibit the dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A (DYRK1A). We investigated the cognitive effects of 1mg (low dose) Harmine and 5mg (high dose) Harmine using the delayed-match-to-sample (DMS) asymmetrical 3-choice water maze task to evaluate spatial short term memory, and the Morris water maze task (MM) to test spatial reference memory. Animals were also tested on the visible platform task, a water-escape task with the same motor, motivational, and reinforcement components as the other tasks used to test cognition, but differing in that the platform was visible above the surface of the water. Harmine treatment enhanced performance on DMS, but had no effect on MM. These results are in agreement with previous findings that Harmine treatment enhances short-term, but not long-term, memory on the non-spatial object recognition task in mice, and extends these findings to spatial tasks, and to rats. A subset of the Harmine-high treated animals showed clear motor impairments on all behavioral tasks, and the visible platform task confirmed a lack of competence to perform the procedural components of the task in these animals. Thus, this study also demonstrates the importance of confirming motor and visual competence when studying animal cognition, and verifies the one-day visible platform task as a reliable measure of ability to perform the procedural components necessary for completion of a swim task.

EXERCISE, APOE GENOTYPE, AND THE EVOLUTION OF THE HUMAN LIFESPAN.

Raichlen DA, Alexander GE. University of Arizona; University of Arizona; Arizona Alzheimer's Consortium.

Background: Humans have exceptionally long lifespans compared with other mammals. However, our longevity evolved when our ancestors had two copies of the apolipoprotein E (APOE) ε4 allele, a genotype that leads to a high risk of Alzheimer's disease (AD), cardiovascular disease, and increased mortality.

Methods: We reviewed the neuroscience, anthropology, and brain-imaging literature to investigate how human aging evolved within this genetic constraint.

Results: We propose the hypothesis that the evolution of increased physical activity approximately 2 million years ago served to reduce the amyloid plaque and vascular burden of APOE ε4, relaxing genetic constraints on aging.

Conclusions: This multidisciplinary approach links human evolution with health and provides a complementary perspective on aging and neurodegenerative disease that may help identify key mechanisms and targets for intervention.

BAPINEUZUMAB ALTERS ABETA COMPOSITION: IMPLICATIONS FOR THE AMYLOID CASCADE HYPOTHESIS AND ANTI-AMYLOID IMMUNOTHERAPY. Roher AE, Cribbs DH, Kim RC, Maarouf CL, Whiteside CM, Kokjohn TA, Daugs ID, Head E, Liebsack C, Serrano G, Belden C, Sabbagh MN, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

The characteristic neuropathological changes associated with Alzheimer's disease (AD) and other lines of evidence support the amyloid cascade hypothesis. Viewing amyloid deposits as the prime instigator of dementia has now led to clinical trials of multiple strategies to remove or prevent their formation. We performed neuropathological and biochemical assessments of 3 subjects treated with bapineuzumab infusions. Histological analyses were conducted to quantify amyloid plaque densities, Braak stages and the extent of cerebral amyloid angiopathy (CAA). Amyloid-beta (Abeta) species in frontal and temporal lobe samples were quantified by ELISA. Western blots of amyloid-beta precursor protein (AbetaPP) and its C-terminal (CT) fragments as well as tau species were performed. Bapineuzumab-treated (Bapi-AD) subjects were compared to non-immunized age-matched subjects with AD (NI-AD) and non-demented control (NDC) cases. Our study revealed that Bapi-AD subjects exhibited overall amyloid plaque densities similar to those of NI-AD cases. In addition, CAA was moderate to severe in NI-AD and Bapi-AD patients. Although histologically-demonstrable leptomeningeal, cerebrovascular and neuroparenchymal-amyloid densities all appeared unaffected by treatment, Abeta peptide profiles were significantly altered in Bapi-AD subjects. There was a trend for reduction in total Abeta42 levels as well as an increase in Abeta40 which led to a corresponding significant decrease in Abeta42:Abeta40 ratio in comparison to NI-AD subjects. There were no differences in the levels of AbetaPP, CT99 and CT83 or tau species between Bapi-AD and NI-AD subjects. The remarkable alteration in Abeta profiles reveals a dynamic amyloid production in which removal and depositional processes were apparently perturbed by bapineuzumab therapy. Despite the alteration in biochemical composition, all 3 immunized subjects exhibited continued cognitive decline.

SUBJECTS HARBORING PRESENILIN FAMILIAL ALZHEIMER'S DISEASE MUTATIONS EXHIBIT DIVERSE WHITE MATTER BIOCHEMISTRY ALTERATIONS. Roher AE, Maarouf CL, Malek-Ahmadi M, Wilson J, Kokjohn TA, Daugs ID, Whiteside CM, Kalback WM, Macias MP, Jacobson SA, Sabbagh MN, Ghetti B, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Alzheimer's disease (AD) dementia impacts all facets of higher order cognitive function and is characterized by the presence of distinctive pathological lesions in the gray matter (GM). The profound alterations in GM structure and function have fostered the view that AD impacts are primarily a consequence of GM damage. However, the white matter (WM) represents about 50% of the cerebrum and this area of the brain is substantially atrophied and profoundly abnormal in both sporadic AD (SAD) and familial AD (FAD). We examined the WM biochemistry by ELISA and Western blot analyses of key proteins in 10 FAD cases harboring mutations in the presenilin genes PSEN1 and PSEN2 as well as in 4 non-demented control (NDC) individuals and 4 subjects with SAD. The molecules examined were direct substrates of PSEN1 such as Notch-1 and amyloid precursor protein (APP). In addition, apolipoproteins, axonal transport molecules, cytoskeletal and structural proteins, neurotrophic factors and synaptic proteins were examined. PSEN-FAD subjects had, on average, higher amounts of WM amyloid-beta (Abeta) peptides compared to SAD, which may play a role in the devastating dysfunction of the brain. However, the PSEN-FAD mutations we examined did not produce uniform increases in the relative proportions of Abeta42 and exhibited substantial variability in total Abeta levels. These observations suggest that neurodegeneration and dementia do not depend solely on enhanced Abeta42 levels. Our data revealed additional complexities in PSEN-FAD individuals. Some direct substrates of gamma-secretase, such as Notch, N-cadherin, Erb-B4 and APP, deviated substantially from the NDC group baseline for some, but not all, mutation types. Proteins that were not direct gamma-secretase substrates, but play key structural and functional roles in the WM, likewise exhibited varied concentrations in the distinct PSEN mutation backgrounds. Detailing the diverse biochemical pathology spectrum of PSEN mutations may offer valuable insights into dementia progression and the design of effective therapeutic interventions for both SAD and FAD.

SEPARATING LEXICAL-SEMANTIC ACCESS FROM OTHER MNEMONIC PROCESSES IN PICTURE-NAME VERIFICATION. Smith JF, Braun AR, Alexander GE, Chen K, Horwitz B. National Institutes of Health; University of Arizona and Evelyn F. McKnight Brain Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: We present a novel paradigm to identify shared and unique brain regions underlying non-semantic, non-phonological, abstract, audio-visual (AV) memory vs. naming using a longitudinal functional magnetic resonance imaging experiment.

Methods: Participants were trained to associate novel AV stimulus pairs containing hidden linguistic content. Half of the stimulus pairs were distorted images of animals and sine-wave speech versions of the animal's name. Images and sounds were distorted in such a way as to make their linguistic content easily recognizable only after being made aware of its existence. Memory for the pairings was tested by presenting an AV pair and asking participants to verify if the two stimuli formed a learned pairing. After memory testing, the hidden linguistic content was revealed and participants were tested again on their recollection of the pairings in this linguistically informed state. Once informed, the AV verification task could be performed by naming the picture.

Results: There was substantial overlap between the regions involved in recognition of non-linguistic sensory memory and naming, suggesting a strong relation between them. Contrasts between sessions identified left angular gyrus and middle temporal gyrus as key additional players in the naming network. Left inferior frontal regions participated in both naming and non-linguistic AV memory suggesting the region is responsible for AV memory independent of phonological content contrary to previous proposals. Functional connectivity between angular gyrus and left inferior frontal gyrus and left middle temporal gyrus increased when performing the AV task as naming.

Conclusions: The results are consistent with the hypothesis that, at the spatial resolution of fMRI, the regions that facilitate non-linguistic AV associations are a subset of those that facilitate naming though reorganized into distinct networks.

THE ALZHEIMER'S PREVENTION INITIATIVE. Tariot PN, Lopera F, Langbaum JB, Ho C, Suliman S, Cho W, Paul R, Rios SR, Thomas RG, Chen K, Ayutyanont N, Hendrix S, Jakimovich L, Langlois C, High N, Reiman EM. Banner Alzheimer's Institute; University of Arizona; University of Antioquia; Genentech; University of California, San Diego; Pentara Corporation; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The Alzheimer's Prevention Initiative (API) is a collaborative research program involving the Banner Alzheimer's Institute (BAI) and key partners that evaluates promising treatments with the ultimate goal to postpone, reduce the risk of, or prevent the clinical onset of Alzheimer's disease (AD). API's preclinical treatment studies focus on cognitively unimpaired people who, based on their age and genetic background, are at the highest imminent risk of developing AD symptoms. Aims include establishing whether cognitive decline can be slowed; relating a treatment's biomarker effects to clinical outcome; robustly testing the amyloid hypothesis; giving persons at highest risk access to investigational treatments; creating large prevention registries for these and other preclinical trials; and complementing other prevention initiatives.

Methods: API includes the following. a) The API Autosomal Dominant Alzheimer's Disease (ADAD) Trial, conducted in full partnership with Genentech and the University of Antioquia (UdeA), is evaluating crenezumab in unimpaired ADAD mutation carriers at certain risk for developing early onset AD. b) The API APOE4 Trial will evaluate a to-be-selected amyloid-modifying medication or immunization therapy in unimpaired 60-75 year-old apolipoprotein E4 (APOE4) homozygotes, who are at the highest genetic risk for developing AD at older ages. c) The Colombian API Registry, created by the UdeA in conjunction with BAI and Genentech, includes >3,300 members of an extremely large ADAD kindred, providing a resource for enrollment into the API ADAD Trial and for biomarker and cognitive studies of ADAD. d) The Alzheimer's Prevention Registry (www.endALZnow.org), is a web-based resource that aims to enroll > 250,000 individuals who are interested in Alzheimer's prevention research, facilitates enrollment into AD prevention studies, and provides regular communication to members.

Results: We launched the ADAD Trial in 2013 and continue to: characterize the preclinical trajectory of early-onset and late-onset AD in our ADAD and APOE cohorts; establish composite cognitive endpoints; estimate sample sizes using biomarker and cognitive endpoints; vet treatment options; engage academic, industry and regulatory stakeholders; expand the registries; and prepare for our APOE4 Trial.

Conclusion: We will review our progress and plans, and address our approach to genetic risk disclosure, cognitive endpoints, recruitment, and data and sample sharing plans.

DETECTION OF OLIGOMERIC A-SYNUCLEIN USING A NOVEL SANDWICH ELISA AS A POTENTIAL EARLY DIAGNOSIS OF PARKINSON'S DISEASE. Williams SM, Sierks MR. Arizona State University; Arizona Alzheimer's Consortium.

Background: Misfolding and aggregation of the protein alpha-synuclein is thought to play a role in the progression of PD. Alpha-synuclein can aggregate into a variety of different small oligomeric structures as well as the large fibrillar aggregates found in lewy bodies. Numerous studies indicate that various oligomeric forms are neurotoxic and may be involved in the spread of the disease. Detection of specific oligomeric alpha-synuclein species therefore has potential as a tool to facilitate early diagnosis of PD.

Methods: Detection of low levels of the different oligomeric aggregates requires reagents that can selectively target the different species and a sensitive detection method. We isolated morphology specific reagents to different alpha-synuclein species including two different oligomeric forms using a phage display single-chain variable domain fragment (scFv) library. We used these scFvs to develop a phage capture ELISA with enough sensitivity to detect oligomeric alpha-synuclein at the low concentrations found in brain tissue.

Results: Using this ELISA protocol, we could readily distinguish between PD, Alzheimer's disease and age matched cognitively normal samples using homogenized brain tissue, cerebrospinal fluid and sera.

Conclusions: Our new capture ELISA should therefore be a useful tool for the diagnosis of PD. These scFvs may also be useful as future therapeutics since they could bind to their target oligomers and remove them from the brain.

MULTI-MODAL SUPPORT VECTOR MACHINE ANALYSIS OF NEUROIMAGING DATA FOR THE CLASSIFICATION OF MILD COGNITIVE IMPAIRMENT. Zhan Y, Guo X, Wu X, Yao L, Chen K. Beijing Normal University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Mild cognitive impairment (MCI) is a transitional stage between AD and healthy controls (HCs). Thus, it is particularly important for early accurate diagnosis of MCI. Many neuroimaging technologies, such as structural and functional magnetic resonance imaging (MRI), positron emission tomography (PET), have been used in pattern classification in AD, MCI and HCs.□(AD) is one of the most serious neurodegenerative disease in the elderly.□□Alzheimer's disease

Methods: In this study, we applied the multi-modal support vector machine (SVM) method to classify MCI from HCs using multi-modal neuroimaging data from structural MRI (sMRI), 18F-fluorodeoxyglucose (FDG) PET and 18F-florbetapir (AV45) PET. All data were from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database including 130 subjects (72 MCI patients and 58 HCs). We extracted features from 90 regions of interest (ROIs) in gray matter (GM) and standardized uptake value ratios (SUVR) images of PET, separately. Then, a classifier was built using 270 features of each subject based on the multi-modal SVM method.

Results: Using multi-modal SVM method based on three modalities data, the accuracy, sensitivity and specificity were 70.1%, 74.5%, and 67.6%, respectively, for the classification of identification of MCI from HCs. Using a single modality, the best accuracy is 65.1% for AV45-PET, while the lowest accuracy is only 62.5% for sMRI.

Conclusions: Our study fused three complementary modalities with different weights to classify MCI from HCs based on the multi-modal SVM method with reasonable discriminability. The results of the multi-modal SVM method are markedly superior to that of each single modality. This multi-modal classifier makes a contribution to the diagnosis of MCI.