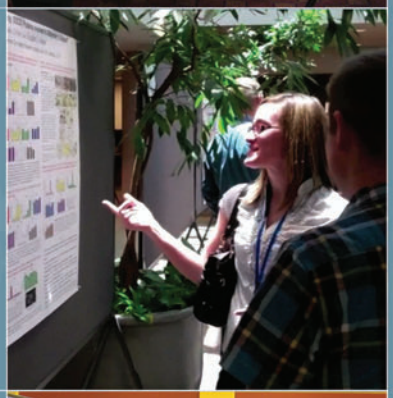

2013 Arizona Alzheimer's Consortium Annual Scientific Conference

Annual Report

May 3, 2013
University of Arizona College of Medicine
Phoenix, Arizona

ARIZONA ALZHEIMER'S CONSORTIUM

ANNUAL REPORT

July 1, 2012 to June 30, 2013

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In memory of our dear colleagues Drs. Marwan Maalouf and Ben Seltzer,
who passed away in October 2012.

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 Arizonaand from several affiliated organizations in the state. 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 has been 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. It receives critical support from the state of Arizona (through the Arizona Department of Health Services [ADHS] and its Arizona Biomedical Research Commission [ABRC]), the seven principal institutions, a competitive Arizona AD Center (ADCC) grant from the National Institute on Aging (NIA), and numerous other research grants and contracts.

Dr. Eric Reiman serves as Director of the Consortium, as well as its state and federally funded components. 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. Our external advisors include Drs. Marilyn Albert, Zaven Khachaturian, Bruce Miller, and Allen Roses, who are recognized for their pioneering contributions and leadership roles in AD research. They attend the Consortium's Annual Scientific Conference, review its progress and productivity, and provide formal feedback and recommendations to its researchers, the NIA and the state each year.

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, therapeutics, and neuropathology research. It has made critical contributions to the scientific understanding, unusually early detection and tracking of AD, and the accelerated evaluation of promising prevention therapies. It has also served as a model for multi-institutional research collaborations in other states.

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 and the "rocket fuel" needed launch new research initiatives, and the framework needed to reach the Consortium's over-arching goals. Funds are used to support about 40 research projects each

year, almost all of which involve researchers from different scientific disciplines, and about half of which include researchers from different institutions.

Funds from the NIA-sponsored Arizona ADCC grant are used to support the Consortium's Administrative, Clinical, Data Management and Statistics, Neuropathology, and Education and Information Transfer Cores, shared resources for researchers inside and outside our state. This year marks the second year of the Arizona ADCC's third consecutive five-year funding period. The ADCC's progress and productivity are detailed in its non-competing progress report to the NIA and will be reviewed by the external scientific advisors at its annual site visit on Saturday, May 4.

Productivity and Impact

Since the Consortium's inception, its researchers have generated more than 3,000 publications and 800 research grants and contracts. They have generated more than 500 million dollars in grants, contracts, philanthropy, new research programs and facilities, and numerous jobs. It is the leading statewide AD Center in the nation and among the most impactful AD research programs in the world.

Consortium researchers continue to make pioneering contributions to the scientific understanding, early detection and tracking of AD and related disorders, the discovery of promising new treatments, and the evaluation of promising disease-slowing and prevention therapies.

- They have made major contributions to the understanding of genetic and non-genetic risk factors and disease mechanisms, providing targets at which to aim new AD treatments. They have discovered promising ways to treat and prevent the disorder.

- They have used powerful brain imaging techniques in the unusually early detection and tracking of AD, characterize some of the progressive biomarker changes associated with preclinical AD, and set the stage for the accelerated evaluation of prevention therapies. They have discovered even earlier brain changes in individuals at genetic risk for AD, some of which may be apparent at the time of birth.

- They have shown how these techniques can be used to evaluate promising disease-slowing and prevention therapies in the shortest possible time.

- 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, test and apply powerful tools to survey the entire human genome, discover inherited genes that account for individual variations in normal human memory and/or the predisposition to AD, and provide targets for the discovery of AD-modifying, AD risk-reducing and memory-enhancing treatments.

- They have helped set the stage for the use of amyloid imaging techniques in the clinical setting.

- They have developed groundbreaking research methods and strategies in support for and the successful development of each of these endeavors.

- They have established an "Alzheimer's Prevention Initiative (API)" to help launch a new era in AD prevention research. API's first funded trial is supported by the NIA, philanthropic funds, and Genentech. It is intended to evaluate an amyloid immunization therapy in cognitively normal persons at certain risk for autosomal dominant early-onset AD, provide the best test yet 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 an unprecedented public resource of therapeutic trial data and biological samples to the research community after the trial is over. A complementary prevention trial has been proposed in cognitively normal persons at highest genetic risk for developing AD at older ages. National Alzheimer's Prevention Registries in Colombia and in North America (www.endalznow.org) have been launched to support enrollment in prevention trials. The first funded trial, which will begin later this year, was described by the director of NIH as "a cornerstone in the national plan to address AD" and by Scientific American as one of the "ten world-changing ideas in 2012." It is a testament to the Consortium's longstanding efforts and its over-riding goal of finding treatments to prevent AD without losing another generation.

We remain grateful to the state of Arizona, the NIA, our participating institutions, and all of our partners, supporters, and valued research participants. 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

15th Annual Conference – Friday May 3, 2012

University of Arizona College of Medicine

600 East Van Buren Street

Phoenix, Arizona

POSTER PRESENTATION SET-UP	7:00 – 8:30AM
CONTINENTAL BREAKFAST	7:30 – 8:30AM
WELCOMING REMARKS Leslie Tolbert, PhD Senior Vice President of Research, University of Arizona	8:30 – 8:45AM
INTRODUCTION Eric Reiman, M.D. Director, Arizona Alzheimer's Consortium	8:45 – 9:00AM
LEON THAL MEMORIAL LECTURE **"Spread of AD pathology in vivo: neuroanatomical considerations, mechanistic insights, functional outcomes and therapeutic potential"** Karen Duff, Ph.D. Professor, Columbia University Taub Institute New York State Psychiatric Institute	9:00 – 10:00AM
POSTER SESSION I	10:00 – 11:00PM
LUNCH	11:00 – 11:45PM
POSTER SESSION II	11:45 – 12:45PM
ORAL RESEARCH PRESENTATIONS	12:45 – 3:15PM
CLOSING REMARKS Eric M. Reiman, MD Director, Arizona Alzheimer's Consortium	3:15 – 3:30PM

Arizona Alzheimer's Consortium

Oral Research Presentations

SESSION I (Moderator: Dr. Allen Roses, M.D.)

12:45 – 12:57 **Pituitary adenylate cyclase activating polypeptide protects against beta-amyloid toxicity by enhancing mitochondrial function.** Jiong Shi. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

12:58 – 1:10 **Changing characteristics of neural stem cells across the lifespan during aging.** Kate Smith, University of Arizona; Arizona Alzheimer's Consortium.

1:11 – 1:23 **Extracellular miRNAs isolated from CSF and blood serum are potential biomarkers for Alzheimer's and Parkinson's diseases**. Kendall Van Keuren-Jensen. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

1:24 – 1:36 **Comprehensive profiling of DNA methylation differences in patients with Alzheimer's and Parkinson's disease.** Travis Dunckley. Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

1:37 – 1:49 **Impact of alpha7 nicotinic acetylcholine receptors in amyloid toxicity.** Jie Wu. St. Joseph's Hospital and Medical Center; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

SESSION II (Moderator: Dr. Zaven Khachaturian, Ph.D.)

1:50 – 2:02 **A methodical evaluation of androstenedione's cognitive effects in young surgically menopausal rats.** Heather Bimonte-Nelson. Arizona State University; Arizona Alzheimer's Consortium; Pennsylvania State University.

2:03 – 2:15 **Enhanced delivery and imaging of neurotherapeutics via US, MRI, SPECT.** Ted Trouard. University of Arizona; University of Notre Dame; Arizona Alzheimer's Consortium.

2:16 – 2:28 **Florbetapir PET, FDG PET and MRI in Down Syndrome (DS) subjects with and without symptomatic Alzheimer's disease (AD).** Marwan N Sabbagh. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

2:29 – 2:41 **Enrollment and retention data from a multi-site randomized rehabilitation intervention trial for individuals with amnestic Mild Cognitive Impairment.** Dona EC Locke. Mayo Clinic Arizona; Mayo Clinic Rochester; Mayo Clinic Florida; Arizona Alzheimer's Consortium.

2:42 – 2:54 **EPIC (Early-stage Partners in Care): a successful pilot intervention for early-stage dyads.** David W Coon. Arizona State University; Benjamin Rose Institute; Desert Southwest Chapter of the Alzheimer's Association; Arizona Department of Economic Security; Arizona Alzheimer's Consortium.

2:55 – 3:07 **Brain imaging differences in infants at differential genetic risk for Alzheimer's disease**. Kewei Chen. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

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Poster Presentations

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1. **Evaluation of oligomeric alpha-synuclein aggregates in rotenone and MPP+ treated cell models and in mouse models of Parkinson's disease.** Alam N, Emadi S, Sierks M, Chesselet M, Yacoubian T. Arizona State University; Brain Research Institute UCLA; University of Alabama; Arizona Alzheimer's Consortium.

2. **TDP-43 deposition in prospectively followed, cognitively normal elderly individuals: correlation with concomitant pathologies.** Arnold SJ, Dugger BN, Beach TG. University of Arizona College of Medicine, Phoenix, Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

3. **Validation of the Alzheimer's Prevention Initiative composite cognitive test score.** Ayutyanont N, Langbaum JBS, Hendrix SB, Fleisher AS, Caselli RJ, Monsell SE, Chen K, Kukull WA, Bennett DA, Tariot PN, Reiman EM. Banner Alzheimer's Institute; Pentara Corp; Mayo Clinic; U Washington; NACC; Arizona State U; Rush U Medical Center; U Arizona; TGen; Arizona Alzheimer's Consortium.

4. **Natural redistribution of end-protection proteins in aging cells as telomeres shorten**. Baribault ME, Swanson MJ, Bae NS. Midwestern University; Mercer University School of Medicine.

5. **Association between higher fasting serum glucose levels and the pattern of lower regional gray matter volumes in cognitively normal adults.** Bartell J, Burns C, Thiyyagura P, Li A, Parks S, Protas H, Lee W, Fleisher A, Kaszniak A, Chen K, Reiman EM. Banner Alzheimer's Institute; University of Arizona College of Medicine; University of Arizona; Arizona Alzheimer's Consortium.

6. **Autopsy-based feasibility study of submandibular gland biopsy for the diagnosis of dementia with Lewy bodies.** Beach TG, Adler CH, Shill HA, Sue LI, Serrano G, Dugger BN, Mariner M, Hidalgo J, Henry-Watson J, Chiarolanza G, Intorcia A, Saxon-LaBelle M, Carew J, Carter N, Jacobson S, Davis K, Akiyama H, Sabbagh MN. Banner Sun Health Research Institute; Mayo Clinic, Scottsdale; Tokyo Institute of Psychiatry; Arizona Alzheimer's Consortium.

7. **Hippocampal volumes and age-related memory decline of post-menopausal women are modulated by hormone therapy status.** Braden BB, Dassel KB, Connor DJ, O'Rourke HP, Sabbagh MN, Caselli RJ, Bimonte-Nelson HA, Baxter LC. Barrow Neurological Institute; Sun Health Research Institute; Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

8. **The effects of caffeine and exercise on implicit and explicit memory performance in younger adults: An investigation of physiological arousal.** Buckley T, Sherman S, Baena E, Ryan L. University of Arizona; University of Texas at Austin; Arizona Alzheimer's Consortium.

9. **Extracellular miRNAs isolated from CSF and blood serum are potential biomarkers for Alzheimer's and Parkinson's diseases**. Burgos K, Courtright A, Malenica I, Ghaffari L, Aldrich J, Rakela B, Metpally R, Tembe W, Beach T, Van Keuren-Jensen K. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

10. **Elevated fasting serum glucose levels and brain function: an FDG PET study of younger adults**. Burns CM, Kaszniak A, Chen K, Lee W, Caselli RC, Reiman EM. University of Arizona; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

11. **A methodical evaluation of androstenedione's cognitive effects in young surgically menopausal rats.** Camp BW, Acosta JI, Mousa A, Alderete T, Mennenga SE, Koebele S, Demers L, Bimonte-Nelson HA. Department of Psychology, Arizona State University; Arizona Alzheimer's Consortium; Pennsylvania State University.

12. **Alzheimer's disease biomarkers as outcome measures for clinical trials.** Caroli A, Prestia A, Wade S, Chen K, Ayutyanont N, Landau SM, Madison CM, Haense C, Herholz K, Reiman EM, Jagust WJ, Frisoni GB, the Alzheimer's Disease Neuroimaging Initiative. Laboratory of Epidemiology and Neuroimaging - IRCCS S. Giovanni di Dio-FBF, Brescia, Italy; Mario Negri Institute for Pharmacological Research, Bergamo, Italy; Bocconi University, Milan, Italy; Banner Alzheimer's Institute; Helen Wills Neuroscience Institute, University of California, Berkeley; Hannover Medical School, Clinic for Nuclear Medicine, Hannover, Germany; University of Manchester; Arizona Alzheimer's Consortium.

13. **Phosphorylated α–synuclein histopathology in the esophagus of a subject with dementia with Lewy bodies and severe dysphagia.** Carter N, Serrano G, Sue L, Mariner M, Hidalgo J, Intorcia A, Saxon-LaBelle M, Adler C, Akiyama H, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Tokyo Institute of Psychiatry; Arizona Alzheimer's Consortium.

14. **Amyloid PET imaging using AZD2184 and unusually brief radiotracer uptake and scanning periods.** Chen K, Langbaum JB, Bandy D, Roontiva A, Liu X, Thiyyagura P, Luo J, Protas H, Ayutyanont N, Lee W, Richter NK, Goodwin S, Jakimovich L, Prouty A, Fleisher AS, Reiman EM. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of California San Diego, San Diego; Translational Genomics Research Institute; Univeristy of Arizona.

15. **Baseline FDG PET and volumetric MRI predicts Alzheimer's disease conversion from mild cognitive impairment: An ADNI study.** 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. Banner Alzheimer's Institute; Banner Good Samaritan PET Center; Arizona State University; University of Arizona; University of California, San Diego; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

16. **Neither Alzheimer's disease nor the apolipoprotein E allele is associated with a lower glomerular filtration rate.** Chiarolanza G, Sue L, Mariner M, Hidalgo J, Henry-Watson J, Davis K, Jacobson S, Sabbagh M, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

17. **EPIC (Early-stage Partners in Care): a successful pilot intervention for early-stage dyads.** Coon DW, Whitlatch C, Felix V, Walker T, Contreras V, Allen A, Schaus D, Besst D. Arizona State University; Benjamin Rose Institute; Desert Southwest Chapter of the Alzheimer's Association; Arizona Department of Economic Security; Arizona Alzheimer's Consortium.

18. **Lenalidomide as anti-neuroinflammatory and BACE1 inhibitor: pilot study on APP23 mice**. Decourt B, Walker A, Macias MP, Gonzales A, Sabbagh MN. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

19. **ApoE and quality of life in the Arizona ApoE cohort.** Dueck AC, Locke DEC, Caselli RJ. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

20. **Neuropathological outcome of prospectively followed normal elderly brain bank volunteers.** Dugger BN, Hentz J, Adler C, Sabbagh M, Shill H, Jacobson S, Caviness J, Belden C, Driver-Dunckley E, Davis K, Sue L, Beach TG, APDC. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

21. **The distribution of phosphorylated tau in spinal cords of Alzheimer's disease and non-demented individuals.** Dugger BN, Hidalgo JA, Chiarolanza G, Mariner M, Henry-Watson J, Sue LI, Beach TG. Civin Laboratory for Neuropathology, Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

22. **Examination of body mass index, organ weights, and diagnosed medical conditions in an autopsy series of Alzheimer's disease and non-demented individuals.** Dugger BN, Saxon-LaBelle M, Chiarolanza G, Hidalgo JA, Maarouf C, Malek-Ahmadi MH, Wilson J, Roher AE, Beach TG. Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

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

24. **Mapping the spatial navigation network of young and aged rhesus macaque monkeys: A positron emission tomography study.** Engle JR, Machado CJ, Maurer AP, Permenter M, Vogt J, Barnes CA. Evelyn F. McKnight Brain Institute; University of Arizona; California National Primate Research Center, Davis CA; ARL Div Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

25. **Regional brain network of MRI gray matter with gradual induction of hypertension in the Cyp1a1-Ren2 transgenic rat.** Fitzhugh MC, Totenhagen JW, Yoshimaru ES, Richards A, Hoang LT, Allen AN, Turk M, Krate J, Biwer LA, Hale TM, Chen K, Moeller JR, Coleman PD, Mitchell KD, Huentelman MJ, Barnes CA,Trouard TP, Alexander GE. University of Arizona and McKnight Brain Institute; TGen; Banner Alzheimer's Institute; Columbia University; Banner SHRI; Tulane University; Arizona Alzheimer's Consortium.

26. **Pre-symptomatic functional brain changes in PS1 E280A mutation carriers compared to other biomarkers: pilot data from the Alzheimer's Prevention Initiative Biomarker project.** Fleisher AS, Chen K, Quiroz YT, Jakimovich LJ, Gomez MG, Langbaum JBS, Roontiva A, Thiyyagura P, Liu X, Lee W, Ayutyanont N, Parks SA, Ruiz A, Tariot PN, Lopera F, Reiman EM. Banner Alzheimer's Institute; Banner Good Samaritan PET Center; Arizona State University; University of Arizona; University of California, San Diego; Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Boston University; Universidad de Antioquia.

27. **A study of the community-based ElderVention® suicide prevention program on the risk factor of social isolation in older adults**. Flint M, Virden T, McDermott B. Midwestern University, Area Agency on Aging, Region One.

28. **Pituitary adenylate cyclase activating polypeptide protects against beta-amyloid toxicity by enhancing mitochondrial function.** Han P, Tang Z, Yin J, Maalouf M, Beach TG, Reiman EM, Shi J. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

29. **The effects of conjugated equine estrogen on cognition and anxiety-like behavior.** Hiroi R, Mennenga S, Koebele S, Hewitt L, Mendoza P, Lavery C, Weyrich G, Kolodziej A, Karber L, Atchison H, Patel S, Poisson M, Bimonte-Nelson H. Department of Psychology, Arizona State University; Arizona Alzheimer's Consortium.

30. **Investigating KIBRA/WWC1 DNA-binding activity (ChIP-Seq) during in vitro neural development**. Hjelm BE, Corneveaux JJ, Nguyen C, Beach TG, Huentelman MJ, Craig DW. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

31. **Glial fibrillary acidic protein interacts with a human telomeric protein that stabilizes genome integrity**. Israel JN, Swanson MJ, Bae NS. Midwestern University; Mercer University School of Medicine.

32. **Changes in dendritic branching, brain cell packing density, and gene expression in a mouse model of neurodevelopmental disease**. Jentarra G, Olfers S, Rice G, Naidu SB, Narayanan V. Midwestern University; Barrow Neurological Institute; Kennedy Krieger Institute.

33. **The effects of KIBRA, APOE, and hypertension status on a composite measure of memory functioning in older adults.** Kawa K, Ryan L, Stickel A, Walther K, Glisky E, Hackett N, Huentelman MJ. Evelyn F. McKnight Brain Institute, University of Arizona; Ludwig Maximilians University, Munich, Germany; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

34. **Effects of cytoprotective multifunctional radical quenchers on lymphocytes from representative mitochondrial and neurodegenerative diseases.** Khdour OM, Arce PM, Goldschmidt R, Dey S, Jaruvangsanti J, Hecht SM. Arizona State University; Arizona Alzheimer's Consortium.

35. **Comparison of two estrogens that circulate endogenously and are given as components of hormone therapy on place versus visual object recognition in middle-aged surgically menopausal rats.** Koebele S, Engler-Chiurazzi E, Jordan A, Hiroi R, Bimonte-Nelson H. Department of Psychology, Arizona State University; Arizona Alzheimer's Consortium.

36. **Biochemical consequences of traumatic brain injury in dementia pugilistica.** Kokjohn TA, Daugs ID, Maarouf CL, McKee AC, Sabbagh MN, Beach TG, Roher AE. Banner Sun Health Research Institute; Midwestern University; Boston University School of Medicine; Arizona Alzheimer's Consortium.

37. **Methylation and expression profiling of medial temporal gyrus in Alzheimer's disease patients reveals an enrichment in neurotransmission signaling pathways**. Krate J*, Piras IS*, Delvaux ER, Nolz JD, Persico AM, Beach TG, Huentelman MJ, Coleman PD. TGen; Univ. Campus Bio-Medico; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

38. **Behavior of the statistical distribution and diffusion kurtosis models in human ischemic stroke**. Lee C, Bennett KM, Debbins JP. Barrow Neurological Institute; Arizona State University.

39. **Aging does not affect the proportion of dorsal medial entorhinal cortex cells active during track running behavior.** Liang J, Lister JP, Barnes CA. Evelyn F. McKnight Brain Institute and ARL Division of Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

40. **Impact of alpha7 nicotinic acetylcholine receptors in amyloid toxicity.** Liu Q, Gao M, Lukas RJ, Wu J. St. Joseph's Hospital and Medical Center; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

41. **Depressive symptoms in healthy APOE e4 carriers and noncarriers: a longitudinal study**. Locke DEC, Dueck A, Stonnington CM, Caselli RJ. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

42. **Enrollment and retention data from a multi-site randomized rehabilitation intervention trial for individuals with amnestic mild cognitive impairment.** Locke DEC, Hoffman Snyder C, Cuc AV, Fields JA, Smith GE, Chandler Greenaway M. Mayo Clinic Arizona; Mayo Clinic Rochester; Mayo Clinic Florida; Arizona Alzheimer's Consortium.

43. **Neurodegenerative-related proteins in the evolution of the aging brain.** Maarouf CL, Walker DG, Kokjohn TA, Daugs ID, Hunter JM, Sabbagh MN, Reiman EM, Beach TG, Roher AE. Banner Sun Health Research Institute; Midwestern University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

44. **Development of a cellular model Of amyloidogenesis to identify BACE1 modulators.** Macias MP, Decourt B, Gonzales AM, Walker A, Sabbagh MN. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

45. **KIF6 719Arg carrier status association with homocysteine and c-reactive protein and mild cognitive impairment and Alzheimer's disease.** Malek-Ahmadi M, Sabbagh MN. Banner Sun Health Research Institute, Cleo Roberts Center for Clinical Research; Arizona Alzheimer's Consortium.

46. **Determining the tissue basis of nicotine rescue in the Drosophila Parkinson's Disease model**. Meyer DO, Buhlman LM, Call GB. Midwestern University; Arizona Alzheimer's Consortium.

47. **Dose and delivery method impact cognitive outcome of ethinyl estradiol administration in the surgically menopausal rat**. Mennenga SE, Gerson JE, Kingston ML, Koebele SV, Acosta JI, Camp BW, Engler-Chiurazzi EB, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

48. **Interactive effects of self-reported memory complaints and hypertension status on cognitive performance in the elderly.** Nguyen LA, Haws KA, Totenhagen JW, Torre GA, Gillespie WL, Fitzhugh MC, Hishaw GA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

49. **Grey matter volume in the orbital prefrontal cortex correlates with reinforcer devaluation but not reversal learning performance in bonnet macaques.** Plange K, Burke SN, Thome A, Engle JR, Trouard TP, Gothard KM, Barnes CA. Evelyn F. McKnight Brain Institute; ARL Div Neural Systems Memory and Aging; Dept Physics & Dept Physiology and College of Medicine, University of Arizona; Arizona Alzheimer's Consortium.

50. **Muscarinic receptor dysfunction in Alzheimer's disease**. Potter PE, Jones D, Monzon N, Slater K, Killpack L, Beach TG. Arizona College of Osteopathic Medicine, Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.

51. **Advancing a functional assay for mitochondrial cytochrome c oxidase: diagnostic potential in Alzheimer's disease**. Procopio C, Lowry A, Nowak L, Perkins M, Valla J. Midwestern University; WP Carey School of Business Fulton School of Engineering, Arizona State University; Arizona Alzheimer's Consortium.

52. **The pattern of cerebral hypometabolism and its association with clinical ratings in cognitively normal older adults with and without significant fibrillar amyloid burden: Findings from the Alzheimer's Disease Neuroimaging Initiative.** Protas HD, Chen K, Reschke C, Roontiva A, Liu X, Parks S, Lee W, Bauer III R, Ayutyanont N, Thiyyagura P, Koeppe RA, Jagust W, Foster NL, Weiner M, Fleisher AS, Reiman EM, ADNI. Banner Alzheimer's Institute; U Michigan; UC Berkeley; U Utah; UC San Francisco; Arizona Alzheimer's Consortium.

53. **Effects of self-reported sleep quality on cognitive functioning in healthy older adults**. Reid BA, Haws KA, Totenhagen JW, Torre GA, Gillespie WL, Fitzhugh MC, Bergfield KL, Hishaw GA, Alexander GE. University of Arizona; Evelyn F. McKnight Brain Institute; Arizona Alzheimer's Consortium.

54. **Association between the Alzheimer's disease-related hypometabolic convergence index and clinical ratings in cognitively normal older adults with and without significant fibrillar amyloid burden: Findings from the Alzheimer's Disease Neuroimaging Initiative.** Roontiva A*, Chen K*, Ayutyanont N, Protas H, Liu X, Thiyyagura P, Lee W, Reschke C, Parks S, Bauer III R, Koeppe RA, Jagust W, Foster NL, Weiner M, Fleisher A, Reiman EM, ADNI. Banner Alzheimer's Institute; U Michigan; UC Berkeley; U Utah; UC San Francisco; Arizona Alzheimer's Consortium.

55. **Florbetapir PET, FDG PET and MRI in Down Syndrome (DS) subjects with and without symptomatic Alzheimer's disease (AD).** Sabbagh MN, Chen K, Rogers J, Liebsack C, Bandy D, Belden C, Fleisher AS, Thiyyagura P, Liu X, Parks S, Jacobson S, Malek-Ahmadi M, Reiman EM. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

56. **Diminished place field density and direction-dependent learning in the aged rat.** Schimanski LA, Lipa P, Barnes CA. Evelyn F. McKnight Brain Institute and ARL Division of Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

57. **Inflammatory cytokines IL-1 beta and TNF-alpha caused disturbance in insulin signaling regulation in human astrocytes.** Schmitz CT, Serrano G, Walker DG, Lue L-F. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

58. **Feasibility study of needle core biopsy of the frontal lobe for tau staging in Alzheimer's disease.** Serrano GE, Carew J, Carter N, Chiarolanza G, Dugger BN, Hidalgo J, Intorcia A, Mariner M, Saxon-LaBelle M, Watson-Henry J, Sue LI, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

59. **Hyperbolic Ricci flow for lateral ventricular surface registration**. Shi J, Thompson PM, Wang Y. Arizona State University; UCLA; Arizona Alzheimer's Consortium.

60. **Activity regulated transcript identification in the hippocampus and the genetic association with AD risk**. Siniard AL, Corneveaux JJ, Turk M, Allen A, Chawla M, Reiman R, Rose H, Barnes CA, Huentelman MJ. TGen; Arizona Alzheimer's Consortium; University of Arizona.

61. **Changing characteristics of neural stem cells across the lifespan during aging.** Smith K, Barnes CA, Corenblum M, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

62. **Sleep spindle activity in Down Syndrome: effects of obstructive sleep apnea and cognitive correlates.** Spanò G, Werchan D, Nyhuis C, Edgin JO. University of Arizona; Arizona Alzheimer's Consortium.

63. **Coalition against major diseases: advancement of CSF and neuroimaging biomarkers as drug development tools to enable clinical trials in MCI.** Stephenson D, Hill D, Beckett L, Boccardi M, Carrillo M, Cole PE, Dean R, Fox N, Frisoni G, Gordon M, Isaac M, Jeromin A, Kelleher T, Meibach R, Novak G, Romano G, Schwarz A, Shaw L, Simon A, Raunig D, Soares H, Suhy J, Vanderstichele H, Yu P, Wang H, Hill D. Critical Path Institute; IXICO Ltd; University of California at Davis; Fatebenefratelli; Alliance for Aging Research; Bristol-Myers Squibb; Alzheimer's Association; Eli Lilly and Company; University of Antwerp; University College London; Boehringer-Ingelheim; European Medicines Agency; NextGenSciences; Novartis; Janssen; AstraZeneca; University of Pennsylvania; CeroraInc; ICON Medical Imaging; Synarc; ADxNeuroSciences; US Food and Drug Administration; Arizona Alzheimer's Consortium.

64. **BMI and BDNF are associated with memory tasks in older adult females.** Stickel A, Kawa K, Ryan L, Huentelman MJ. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

65. **The Effect of Zumba on cognition in healthy APOE ε4 carriers and noncarriers.** Stonnington CM, Locke DEC, Hentz JG, Dueck AC, Geda YE, Tariot P, Caselli RJ. Mayo Clinic in Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

66. **Regulation of APP processing using antibody fragments reduces stress induced toxicity in cell models of Alzheimer's Disease.** Suryadi V, Emadi S, Boddapati S, Sierks M. Arizona State University; Arizona Alzheimer's Consortium.

67. **Localization of the corticosterone-sensitive organic cation transporter 3 (OCT3/Slc22a3) mRNA and protein in the male rat brain via in situ hybridization and immunohistochemistry.** Talboom JS, Molinaro J, Tompkins HC, Mumaw L, Lowry CA, Renner KJ, Orchinik M. Arizona State University; University of Colorado; University of South Dakota; Arizona Alzheimer's Consortium.

68. **Exploring the mechanism of nicotine-mediated rescue of a Drosophila model of Parkinson's disease**. Techau JA, Call GB, Buhlman LM. Midwestern University; Arizona Alzheimer's Consortium.

69. **Senescence modifies the structure of information encoding in the medial temporal lobe.** Thome A, Lipa P, Erickson CA, Barnes CA. Evelyn F. McKnight Brain Institute; ARL Division of Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

70. **Single chain variable fragment specific for trimeric tau as a tool to study Alzheimer's disease.** Tian H, Davidowitz E, Moe J, Sierks M. Department of Chemical Engineering, Arizona State University; Oligomerix Inc; Arizona Alzheimer's Consortium.

71. **Magnetic resonance morphometry in a mouse model of Niemann Pick Type C Disease**. Totenhagen J, Yoshimaru E, Erickson R, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

72. **ROCK inhibitor development for cognitive enhancement and blockade of tau phosphorylation.** Turk MN, Adams MD, Wang T, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Arizona State University; Midwestern University; Evelyn F. McKnight Brain Institute at the University of Arizona.

73. **Enhanced delivery and imaging of neurotherapeutics via US, MRI, SPECT.** Valdez M, Yoshimaru E, Ingram P, Totenhagen J, Forbes A, Moore S, Helquist P, Matsunaga T, Witte R, Furenlid L, Liu Z, Erickson R, Trouard T. University of Arizona; University of Notre Dame; Arizona Alzheimer's Consortium.

74. **Identification and neuropathology of an Alzheimer's disease case with the TREM-2 rs75932628 variant polymorphism.** Walker DG, Whetzel A, Lue L-F. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

75. **Studies of CD33, a new risk factor for Alzheimer's disease, in human brains and human microglia.** Walker DG, Whetzel A, Lue L-F. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

76. **Mitochondria-targeted pharmaceutical nanocarriers for antioxidant delivery**. Weissig V, Gaudenti D, Boger B. Midwestern University; Arizona College of Osteopathic Medicine; Arizona Alzheimer's Consortium.

77. **Ketone bodies improve learning, memory and mitochondrial complex I activity in APP transgenic mice.** Yin J, Han P, Tang Z, Schweizer F, Reiman EM, Maalouf M, Shi J. Barrow Neurological Institute; University of California, Los Angeles; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

78. **Novel FTO inhibitor modulates microRNA**. Zheng G, Shen L, Zaidi A, Iacoban P, Rowles J, He C, Olsen M. University of Chicago; Midwestern University.

2013 Oral Research Presentation

Abstracts

Pituitary adenylate cyclase activating polypeptide protects against beta-amyloid toxicity by enhancing mitochondrial function. Han P, Tang Z, Yin J, Maalouf M, Beach TG, Reiman EM, Shi J. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: The prevention and treatment of Alzheimer's disease and other neurodegenerative conditions remain a challenge for medical research. One of the primary goals is to find a highly efficient neuroprotective agent with insignificant adverse effects. Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) is intrinsically expressed in mammals and is considered to be a potent neurotrophic and neuroprotective peptide.

Methods: Post mortem human brain samples from AD and Non-AD patients were provided by Sun Health Research Institute Body and Brain Donation program. Cortical neurons from P0-P3 pups were obtained to establish primary neuronal cell culture. A short sequence of 19 nucleotides targeting Sirtuin3 location 764 was constructed into OmicsLink shRNA expression clone to knock down the expression of Sirt3. This vector and control vector were packaged in Lentiviruses to transfect the cultured neurons. Mitochondrial respiratory function was measured by metal-porphyrin based oxygen probe. Western blot and immunochemistry were used to detect and quantify PACAP and Sirt3 protein expression.

Results: PACAP level was reduced in both human AD brain and the 3×Tg-AD mouse brain. This reduction of PACAP correlated with the lower expression of SIRT3, a modulator for mitochondrial respiratory chain. PACAP protected neurons from beta-amyloid induced toxicity in vitro by potentiating mitochondrial respiratory function, as knocking down intrinsic SIRT3 expression abolished this protective effect.

Conclusions: PACAP is neuroprotective in Alzheimer's disease by enhancing mitochondrial respiratory function.

Changing characteristics of neural stem cells across the lifespan during aging. Smith K, Barnes CA, Corenblum M, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Our present study is directed at understanding how the brain changes during the normal aging process. It has been shown that active stem cells, which continually generate new nerve cells, are in fact present in the aging brain. These cells, termed neural stem cells when present in the brain, can both self-renew and become the more mature cells of the nervous system such as neurons, astrocytes, and oligodendrocytes. In rodents, primates, and humans, the largest population of these cells exists in the Subventricular Zone. Although neural stem cells exist in this region throughout life, they are also depleted over a lifetime, making them an intriguing target for study with respect to aging. While other studies have compared these cells at the young and old endpoints of the aging spectrum, a comprehensive characterization that fully illustrates the details of how and why the population changes with age has not been conducted.

Methods: Neural stem cells (NSCs) were obtained from the subventricular zones of Fisher 344 rats spanning an aging continuum of 0 (post natal), 2 (adolescent), 9 (mature), 15 (middle-aged), and 24 (old) months. The cells were characterized in vitro, focusing on proliferative capacity (by measuring the incorporation of Bromodeoxyuridine and a serial dilution assay), survival (using a Live/Dead cell assay), and ability to differentiate (quantification of neurons, astrocytes, and oligodendrocytes with immunocytochemistry).

Results: The dilution assay indicated that adolescent and mature cells formed significantly greater numbers of neurospheres than the middle aged and old cells at every dilution level. Concurrent with this, a significant decline in the fraction of BrdU labeled cells was observed with increasing age. Interestingly, in both the dilution and BrdU assays, NSCs isolated from the middle-aged animals showed greater impairment in proliferative ability compared to the cells from old animals. In support of this proliferation data, the survival of NSCs did not show any significant differences between adolescent, mature, and old age groups, but the middle-aged cells displayed a considerably greater fraction of dead cells. With respect to differentiation, the number of oligodendrocytes remained fairly constant, neuronal differentiation declined, and astrocytic differentiation increased with age.

Conclusions: The overall results indicate (1) increased senescence, (2) reduced survival, proliferation, and neuronal differentiation of NSCs as aging progresses, and (3) suggests a particular vulnerability of cells during middle-age which will merit further analysis.

Extracellular miRNAs isolated from CSF and blood serum are potential biomarkers for Alzheimer's and Parkinson's diseases. Burgos K, Courtright A, Malenica I, Ghaffari L, Aldrich J, Rakela B, Metpally R, Tembe W, Beach T, Van Keuren-Jensen K. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Because of their small size, tissue specificity, and stability, miRNAs have the potential to be sensitive biomarkers for neurodegenerative diseases, including Alzheimer's disease. We profiled the miRNAs in cerebrospinal fluid (CSF) and serum of subjects with Alzheimer's disease (AD), Parkinson's disease (PD) and normal controls.

Methods: We used next generation sequencing to profile the full compliment of miRNAs in CSF and serum samples. This method allowed us to examine all miRNAs associated with disease as well as to identify novel miRNAs.

Results: We identified several miRNA markers that are differentially expressed between AD or PD subjects and control subjects, as well as between AD and PD. We also assessed miRNAs associated with Braak stage, tangle, and plaque density.

Conclusions: miRNAs show promise as diagnostic markers of Alzheimer's disease. CSF may have a stronger signal-to-noise ratio than serum.

Comprehensive profiling of DNA methylation differences in patients with Alzheimer's and Parkinson's disease. Dunckley T, Meechoovet B, Caselli RJ, 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.

Impact of alpha7 nicotinic acetylcholine receptors in amyloid toxicity. Liu Q, Gao M, Lukas RJ, Wu J.
St. Joseph's Hospital and Medical Center; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) pathogenesis and to find an effective strategy to treat AD. AD is a neuron-degenerative dementia characterized by increased accumulation of Aβ, degeneration of neurons of basal forebrain, hippocampus and neocortex, and a gradually-developing learning and memory deficit. It has been postulated that an aberrant high-level of Aβ may contribute to the pathogenesis in AD, but the mechanism of Aβ-induced neurodegeneration remains unclear. Nicotinic acetylcholine receptors (nAChRs) are important mediators of cholinergic signaling in basal forebrain, hippocampus and neocortex. One of the earliest events in the pathogenesis in AD patients or AD model animals is a significant increase of mRNA and protein expressions of α7 nAChRs. However, a consensus is yet to emerge as to how these enhanced α7 nAChRs play a role in the mediation of Aβ-induced neuronal degeneration and death.

Methods: Relevant nAChR function and structure were characterized using electrophysiological, cell and molecular biological approaches in primary cultured hippocampal neurons prepared from wide-type and nAChR α7 knockout mice. Neurotoxicity will be evaluated by measuring lactate dehydrogenase (LDH) release.

Results: 1. Chronic exposure with 100 nM Aβ1-42 fibrils for 7-10 days significantly increased LDH release, suggesting a neurotoxicity. 2. Similar treatment of Aβ1-42 fibrils up-regulated α7 nAChR expression and function, but this up-regulation occurred (at day 4) early than the increased LDH level (after 7 days). 3. Pharmacological block or genetic deletion of α7 nAChR significantly prevented Aβ toxicity. 4) Pharmacological block or genetic deletion of β2 nAChR did not prevent Aβ toxicity.

Conclusions: Chronic exposure of nanomolar concentrations of Aβ1-42 fibrils up-regulates α7 nAChR and then, results in neurotoxicity in primary hippocampal cultured neurons. Pharmacological block or genetic deletion of α7, but not β2 nAChR significantly prevented Aβ toxicity. These results suggest an important role played by α7 nAChRs in the mediation of Aβ toxicity.

A methodical evaluation of androstenedione's cognitive effects in young surgically menopausal rats.
Camp BW, Acosta JI, Mousa A, Alderete T, Mennenga SE, Koebele S, Demers L, Bimonte-Nelson HA. Department of Psychology, Arizona State University; Arizona Alzheimer's Consortium; Pennsylvania State University.

Background: It has been recently shown that androstenedione, the main circulating hormone present after menopause and follicle depletion, is positively correlated with poor spatial memory in chemically-induced follicular depleted rats (Acosta 2009a), and impairs spatial memory when administered as an exogenous treatment (Camp 2012). Androstenedione can be converted to either an estrogen (e.g., estrone) or to another androgen (e.g., testosterone).

Methods: We hypothesize that the impairment of spatial memory found previously after androstenedione administration is due to its conversion to either estrone or testosterone. The current study was conducted with the goal of elucidating the hormonal mechanism of the observed androstenedione effects on cognition by methodically blocking the conversion of androstenedione to estrone, or blocking androgen receptor activity, and evaluating changes in cognition.

Results: Measures of spatial working and reference memory performance were evaluated via the Water Radial Arm Maze and the Morris Water Maze. The previously found effects of androstenedione were supported. However, when decreasing the conversion of androstenedione to estrone, the impairing effects of andro were alleviated. When androgen receptor activity is blocked, there is negligible difference in comparison with the cognitive profile of andro given alone. The implications of this study are important in understanding andro's effects on cognition, especially in post-menopausal women.

Conclusions: Androstenedione's impairment seen on several spatial memory tasks in female rats appears to be mediated by its conversion to estrone. The implications of this study are important in understanding androstenedione's effects on cognition, especially in post-menopausal women.

Enhanced delivery and imaging of neurotherapeutics via US, MRI, SPECT. Valdez M, Yoshimaru E, Ingram P, Totenhagen J, Forbes A, Moore S, Helquist P, Matsunaga T, Witte R, Furenlid L, Liu Z, Erickson R, Trouard T. University of Arizona; University of Notre Dame; Arizona Alzheimer's Consortium.

Background: Treatment of neurological disorders is hampered by the inability of drugs to cross the blood-brain barrier (BBB). Over the last several years, novel techniques that use focused ultrasound (FUS) energy in combination with microbubble (uB) contrast agents have been developed that reversibly open up the BBB. Foundational studies have been carried out in several animal models, including mice. BBB opening is readily verified with MRI using gadolinium contrast agents. This does not give specific information about the delivery of actual drugs to the brain. To address this point, we have initiated studies combining FUS-mediated BBB opening with high-resolution single photon computed tomography (SPECT) of radiolabeled I-123-beta-cyclodextrin (I-123-BCD) in mice. BCD is a promising treatment for Niemann-Pick type C (NPC) disease, a childhood affliction that involves errors in cholesterol trafficking and results in neurodegeneration and death in the early teen years. BCD has shown promising results in animal models of NPC disease when delivered directly into the brain. Although this work focuses on NPC disease, it is adaptable to other neurological diseases such as Alzheimer's disease.

Methods: Mice were imaged prior to BBB opening in a 7T Bruker Biospec MRI system. A 72 mm ID birdcage coil was used for excitation and a 4-channel phased array coil was used for reception. The mice were secured in an MRI cradle with ear bars and a bite bar. Rapid whole-brain 3D T1-weighted GRE images (5 minute acquisition) were obtained prior to and after IP injection of Gd-DTPA. BBB opening utilized a 40 uL bolus of custom gas filled uBs that were injected into the tail vein, followed by a 120 uL saline flush. Immediately after the injection, 3.3 MHz FUS was transcranially administered to the mouse brain. Thirty 2-second sonications were delivered with a 5 second pause between sonications (37% duty cycle, 6 ms pulse width, 0.80 MPa peak negative pressure). A custom built positioning apparatus was used to position the FUS transducer (30 mm diameter, 49.4 mm focal length) such that its focal spot was within the brain of the mouse. After FUS, the mice were returned to their original position in the MRI magnet and identical T1-weighted imaging was carried out for 30 minutes. T1-weighted 2D spin-echo images were also obtained. Other mice underwent the same procedure, except that no FUS was applied. Mice were allowed to recover and showed no obvious deficits in neurologic function. Within 3 hours of the MRI procedure, pairs of mice were injected with I-123-BCD and imaged simultaneously using a custom-built y-ray scintigraphy system to verify the injection of I-123-BCD. Following this, mice were individually imaged on a custom built SPECT/CT imaging system to determine the distribution of I-123-BCD in the brain. Finally, mice were sacrificed and 1 mm excised brain slices underwent autoradiography to verify in vivo measurements.

Results: MRI image enhancement maps after the administration of Gd-DTPA, uBs and FUS showed a strong increase in signal in the brain parenchyma in the mouse after receiving FUS. Diffusion of Gd-DTPA through the tissue was apparent 90 minutes post FUS. y-ray scintigraphy images of the two mice showed greater signal intensity in the brain region of the animal that received FUS compared to the control animal. The SPECT/CT imaging system showed increased signal in the brain of the experimental mouse. This increase was confirmed by a 4.8 times increase in signal in autoradiographic images of brain slices.

Conclusions: This demonstrated that focal BBB opening procedures allow passage of I-123-BCD into the brains of mice. While these experiments are directed towards NPC disease, they could have a significant impact on other common neurological disorders (e.g. Alzheimer's and Parkinson's).

Florbetapir PET, FDG PET and MRI in Down Syndrome (DS) subjects with and without symptomatic Alzheimer's disease (AD). Sabbagh MN, Chen K, Rogers J, Liebsack C, Bandy D, Belden C, Fleisher AS, Thiyyagura P, Liu X, Parks S, Jacobson S, Malek-Ahmadi M, Reiman EM. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: A link between Down's syndrome (DS) and Alzheimer disease (AD) is widely recognized. Most individuals with DS will manifest AD by the age of 50. Trisomy 21 results in a 4 to 5-fold increase in expression of the APP gene and accelerated deposition of β-amyloid. Compared to normal controls (NCs), brain imaging studies in late-onset AD (LOAD) have demonstrated increased fibrillar β-amyloid binding and a characteristic and progressive pattern of regional reductions in glucose metabolism and gray matter volume. This study aimed to assess the difference of the measures based on these 3 neuroimaging modalities among young/old DS, DS-with dementia (DSWD), and NC subjects.

Methods: There were 9 NC (3F, 6M) participants, 12 DS (7F, 5M) participants without dementia, and 5 DSWD (3F, 2M) participants, all consented or assented depending on established capacity. Of the 26 participants enrolled, two received cognitive testing but did not tolerate imaging procedures. 24 participants underwent cognitive testing, volumetric MRI, florbetapir PET (n=24) and FDG-PET. SPM8 was used for voxel-wise data analysis (FDG, MRI and florbetapir) using predefined regions of interest (ROI). Mean cortical-to-pontine florbetapir SUVRs (standard uptake value ratios) were calculated cortical and pontine reference regions-of-interest (ROIs).

Results: Mean cortical-to-pontne florbetapir SUVRs were significantly higher in DSWD subjects than in DS or NCs (ANOVA with pair-wise comparisons, $p<0.001$) and associated with progressively higher SUVRs in the NC, DS and DSWD groups (1.15 ± 0.06, 1.27 ± 0.09 and 1.54 ± 0.21, respectively, linear trend, $p=0.00002$). Regional-to-whole brain glucose metabolism and gray matter volumes were lower in DSWD patients than in DS patients in XX, XX, and XX regions known to be preferentially affected by AD ($P<0.001$, uncorrected for multiple comparisons).DS (DS-AD) patients than both older compared to young DS (older or young DS) in the regions known to be affected by LOAD.

Conclusions: In comparison with DS patients and NCs, DSWD subjects have significantly greater fibrillar Aβ burden, as well as significantly lower glucose metabolism and gray matter volume in AD-affected regions, similar to that observed in LOAD. The differences occur between 36 and 50 years of age. Additional studies are needed to expand our samples, track these changes over time, and provide sample size estimates for clinical and preclinical AD trials in patients with DS.

Enrollment and retention data from a multi-site randomized rehabilitation intervention trial for individuals with amnestic mild cognitive impairment. Locke DEC, Hoffman Snyder C, Cuc AV, Fields JA, Smith GE, Chandler Greenaway M. Mayo Clinic Arizona; Mayo Clinic Rochester; Mayo Clinic Florida; Arizona Alzheimer's Consortium.

Background: To date, there are no FDA approved medications options for MCI. Moreover, patients with MCI want to engage active strategies to improve or maintain their memory functioning and prevent or delay further neurodegeneration. This is why non-pharmacologic or behavioral interventions are growing in popularity with patients with MCI. Memory compensation techniques and cognitive activity are two such activities and were studied here.

Methods: Two hundred and one people with MCI were approached to participate in a four-armed (2 by 2) trial of Memory Support System (MSS) versus Posit Brain fitness (Posit) training delivered in either a 6-week or 10-day format. Ultimately 64 participants with MCI were randomized. Individuals in the Posit group were given the MSS materials and encouraged to use them, but given no formal training. Primary aims of this pilot trial were (1) to generate a reliable estimation of expected enrollment in this type of time-intensive training program, (2) to assess retention rates for this type of behavioral program, and (3) to assess adherence with the MSS program with and without training. Secondary aims included comparing delivery of the MSS training in a condensed 2 week program to an extended 6 week program. Finally, an exploratory aim focused on preliminary efficacy comparison data for the MSS and Posit. Because follow-up data collection is ongoing, those efficacy data receive only cursory presentation here.

Results: Enrollment data show that 37% of those approached about the study expressed interest and completed an eligibility visit (75/201). In Arizona, specifically, 41% of those approached for the study completed an eligibility visit. Eleven individuals across sites were ineligible after the screening visit. The remaining 63% (126/201) were not interested in the program with the primary reasons for decline being (1) time commitment and (2) distance to travel. Only 4 individuals declined to participate because they did not think such an intervention would be helpful and 11 declined due to concerns about the randomization process and which group they would be assigned. Retention was high with 86% (55/64) of those enrolling in the study completing their training program. End of program MSS adherence was greater in the MSS-trained participants compared to Posit participants despite the later group also being encouraged to use the materials ($p < 0.001$; Cohen's $d = 3.64$, CI 2.82-4.30). With the MSS training group, there was no difference in adherence for MSS participants who received extended training over 6 weeks compared to training 10 days over 2 weeks format ($p = .56$; Cohen's $d = .23$, CI = -1.14 to +1.14). As mentioned above, follow-up visits continue such that secondary outcome measures are not presented in detail here. However, we did see that overall self-efficacy increased slightly in the MSS group ($p=.03$) but remained unchanged in the Posit group. The Posit group showed a small reduction in anxiety ($p=.05$) while the MSS group remained stable.

Conclusions: The enrollment and retention data suggest that though perhaps only a minority of eligible patients would be interested in a comprehensive program with this time demand, it is a sizable minority in Arizona and those who enroll do not drop out of the program once they've begun. In addition, these data suggest in-person training sessions are necessary to help patients with MCI implement a memory support system, but that those who receive the training CAN learn to implement such a system. Finally, preliminary efficacy data suggest that these two rehabilitation strategies may impact individual functioning in different ways with increased self-efficacy with the memory support system and reduced anxiety with a computerized brain fitness task.

EPIC (Early-stage Partners in Care): a successful pilot intervention for early-stage dyads. Coon DW, Whitlatch C, Felix V, Walker T, Contreras V, Allen A, Schaus D, Besst D. Arizona State University; Benjamin Rose Institute; Desert Southwest Chapter of the Alzheimer's Association; Arizona Department of Economic Security; Arizona Alzheimer's Consortium.

Background: Roughly 5.4 million Americans live with Alzheimer's disease and related disorders (AD), and this number is expected to grow 30% by 2025. Identification of AD in the early stages creates advantages for early-stage people (EPs) and their care partners (CPs). For example, earlier intervention affords EPs the opportunity to more fully participate in care decision-making; it permits EPs and CPs to work together to more effectively mobilize support and develop future plans; and, as a result, it helps to enhance positive EP/CP outcomes. While the emphasis on early detection and treatment is growing, there has not been a corresponding emphasis on psychosocial interventions that would address the CP's or EP's mental health and well-being at the early stage of the disease. Although evidence-based, nonpharmacological multimodal treatment protocols for EPs have produced some positive outcomes, these interventions have usually focused solely on EPs, ignoring CPs and the opportunity for the EPs' voices to be heard by CPs regarding future treatment decisions and care options.

Methods: Funded by a U.S. Administration on Aging grant, 42 dyads of EPs and their current or future CPs (N=84) across the state of Arizona participated in EPIC, a seven session group dyadic intervention. EPIC was embedded into the community through the local Alzheimer's Association from its inception. Trained and supervised chapter staff delivered EPIC which focuses on EP care preference and values clarification, skill building, and social support. This pilot project used a basic pre-post quasi-experimental design. Key outcomes included measures of positive and negative affect and care preparedness for both EPs and CPs; EP self-esteem and quality of life; and, CP self-efficacy, and knowledge of EP future care preferences.

Results: EPIC yielded a variety of significant outcomes (*ps*<.05) including improved care preparedness and partner interactions, and reductions in depressive symptoms for both EPs and CPs. EPs also reported increased quality of life, self-esteem, and positive affect, and reduced anger/hostility. Additional outcomes for CPs included increased problem solving self-efficacy, and knowledge of EP's daily care preferences and long-term care wishes. Over 94% of participants said EPIC improved their understanding of memory loss, increased their confidence in dealing with memory problems, made their lives easier, and enhanced their ability to care for each other. Effect sizes ranged from .28 to 1.49.

Conclusions: EPIC is a feasible and acceptable intervention for early-stage individuals and their care partners, and it is the first of its kind embedded into a community based organization from its inception that yielded significant outcomes for both EPs and CPs. In addition, its group based, manualized format holds promise for delivery in a cost effective manner when compared to more intensive individualized treatments. Findings warrant a future EPIC RCT with longitudinal follow-up.

Brain imaging differences in infants at differential genetic risk for late-onset Alzheimer's disease. Dean III DC*, Jerskey BA*, Chen K*, Protas H, Thiyyagura P, Roontiva A, O'Muircheartaigh J, Dirks H, Waskiewicz N, Lehman K, Siniard AL, Turk MN, Hua X, Madsen SK, Thompson PM, Fleisher AS, Huentelman MJ, Deoni SCL[#], Reiman EM[#]. Brown University; Alpert Medical School of Brown University; Banner Alzheimer's Institute; Arizona State University; University of Arizona School of Medicine; Arizona Alzheimer's Consortium; King's College London, Institute of Psychiatry; University of California, Los Angeles School of Medicine; University of California, San Diego, School of Medicine; Translational Genomics Research Institute.

Background: What are the earliest brain alterations associated with a predisposition to Alzheimer's disease (AD)? While AD may begin with amyloid-β_{42} accumulations, starting 1-2 decades before cognitive impairment, studies in healthy persons at differential genetic risk imply even earlier brain alterations.

Objective: To compare magnetic resonance imaging (MRI) measurements of white matter myelin content and gray matter volume in infant carriers and non-carriers of the *apolipoprotein E (APOE)* ε4 allele, the major late-onset AD susceptibility gene.

Design/Methods: MRI measurements of myelin water fraction (MWF), a quantitative measure of myelin content, were acquired in 162 healthy 2-25 month-old infants, including 60 *ε4* carriers and 102 non-carriers using the mcDESPOT processing technique. T_1-weighted volumetric MRIs, which provide information about regional gray matter, were acquired in 59 of the infants, 6-24 months of age, including 23 *ε4* carriers and 36 non-carriers. Buccal swab samples were used for *APOE* genotyping. Automated brain mapping algorithms were used to characterize between-group differences in regional MWF and gray matter volume and to characterize and compare age-related trajectories in the *ε4* carrier and non-carrier groups.

Results: In comparison with non-carriers, infant *ε4* carriers had significantly lower gray matter volume and MWF measurements than non-carriers in posterior brain regions, several of which are preferentially affected in AD ($p<0.001$, uncorrected for multiple comparisons); significantly greater gray matter and MWF measurements in frontal regions; and an attenuated relationship between MWF and age in several major white matter regions.

Conclusions: Infant *APOE ε4* carriers and non-carriers have regional differences in white matter myelin and gray matter. This study raises new questions about the role of APOE in normal human brain development and the earliest processes involved in the predisposition to AD, how they relate to subsequent AD pathology, and the extent to which they can be targeted by AD prevention therapies.

Institutional Information

Research Summaries and Key Personnel
from Each Participating Institution

ARIZONA STATE UNIVERSITY
Institutional Abstract

Arizona State University has four ongoing projects, each the responsibility of different investigators with different areas of expertise. We briefly describe here the main interests and research objectives of each of the principal investigators leading AAC projects at ASU.

Dr. Heather Bimonte-Nelson, Associate Professor and Behavioral Neuroscience Program Director at the Department of Psychology (Behavioral Neuroscience) in the College of Liberal Arts and Sciences, leads a study to determine which factors influence whether hormone therapy acts as a protectant or risk factor for cognitive and brain aging. Specifically, the study seeks to determine the hormonal mechanism related to observed androstenedione-induced cognitive detriments in the surgically menopausal rat. The implications of this study are important in understanding androstenedione's effects on cognition in post-menopausal women.

Dr. David Coon, Associate Vice Provost for Research Collaborations and Professor in the College of Health Solutions, is interested in the design, evaluation, and translation of effective psychosocial interventions for midlife and older adults facing chronic illness (e.g., Alzheimer's disease, cancer, HIV/AIDS) and their family caregivers. He leads a study to investigate how caring for someone with ADRD and managing one's own health conditions might impact one another; and to begin to develop a new or refine an existing evidence based intervention to address self-care issues.

Dr. Graciela Gonzalez, Assistant Professor in Biomedical Informatics within the College of Health Solutions, focuses her research in biomedical informatics approaches for knowledge discovery. She leads a project 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.

Dr. Michael Sierks, Professor in the Department of Chemical Engineering, whose area of expertise is Neurodegenerative Disease Protein Engineering Enymology is interested in researching antibody based therapeutics for treating neurodegenerative diseases such as Alzheimer's and Parkinson's Diseases. His project focus on studying the correlation of concentrations of specific Aß and tau aggregate species with AD progression, which can lead to identification of promising biomarkers for early detection of AD and other neurodegenerative diseases.

ARIZONA STATE UNIVERSITY
Key Personnel

Name (last, first)	Degree	Role on Project
Bimonte-Nelson, Heather	PhD	Investigator
Coon, David	PhD	Investigator
Gonzalez, Graciela	PhD	Investigator
Sierks, Michael	PhD	Investigator
Mennenga, Sarah		Graduate student
Camp, Bryan		Graduate student
Engler-Chiurazzi, Elizabeth		Graduate student
Tian, Huilai		Graduate student
Venkataraman, Lalitha		Graduate student
Brownlee, Tayler		Graduate student
Suryadi, Vick		Graduate student
Felix, Vitae		Graduate student
Walker, Terrence		Graduate student
Tahsin, Tasnia		Graduate student
Furniss, Stephanie		Graduate student
Hewitt, Lauren		Undergraduate student
Mousa, Abeer		Undergraduate student
Alderete, Tanya		Undergraduate student
Lavery, Courtney		Undergraduate student
Mendoza, Perla		Undergraduate student
Torres, Laura		Undergraduate student
Jordan, Ambra		Undergraduate student
Karber, Lily		Undergraduate student
Atchison, Hailey		Undergraduate student
Weyrich, Giulia		Undergraduate student
Alam, Now Bahar		Undergraduate student
Sharma, Ankush		Undergraduate student
Dolberg, Taylor		Undergraduate student
Kim, Michael		Undergraduate student
Tao, Kevin		Undergraduate student
Macias, Nelly		Undergraduate student
Santos, Kelvin		Undergraduate student
Koebele, Stephanie		Laboratory manager
Schulz, Phillip		Laboratory manager
Wojtulewicz, Laura		Data manager
Bhalla, Amol		Data manager
Hiroi, Sheri	PhD	Postdoctoral fellow

Acosta, Jazmin	PhD	Postdoctoral fellow
Williams, Stephanie	PhD	Postdoctoral fellow
Yang, Patrick	PhD	Postdoctoral fellow
Xin, Wei	PhD	Postdoctoral fellow
Burleson, Mary H.	PhD	Collaborator
McClain, Darya		Collaborator
Huentelman, Matthew	PhD	Collaborator

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 Memory Disorders Center, a Family and Community Services Program, a Clinical Trials Program, a Brain Imaging Program, 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 presymptomatic treatment trials of promising experimental treatment trials in cognitively normal individuals at increased risk of developing symptomatic Alzheimer's disease, along with the registries that support the trials. The first prevention treatment trial will be a public-private partnership 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. Mutation carriers from the United States will be included to share both the benefits and risks with the Colombian participants. Similar presymptomatic treatment trials will be conducted in other genetic risk groups, such as adults who carry one or two copies of the apolipoprotein E (APOE) ε4 allele, the major AD susceptibility gene. In 2012, the API created the U.S.-based Alzheimer's Prevention Registry 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. The Registry aims to enroll 100,000 people by June 2013, and 250,000 by June 2015.

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
Barton, Rose Ann		Outreach Coordinator
Blanco, Regal	BS	Research Data Specialist
Boker, Connie	MPH	Finance Director
Brand, Helle	PA	Physician's Assistant, Memory Disorders Center
Burke, Anna	MD	Dementia Specialist
Chen, Kewei	PhD	Director, Computational Brain Imaging Director Biomathematician
Chen, Wei	MS	Research Data Specialist
Cooper, Lisa	BSN, CCRP	Research Nurse Coordinator
Dougherty, Jan	RN, MS	Director, Family & Community Services
Fleisher, Adam	MD	Director, Brain Imaging
Goodwin, Sandy	CNMT	Senior PET Technologist
Hall, Geri	PhD, ARNT, CS, FAAN	Clinical Nurse Specialist, Family & Community Services
High, Nellie	MS	Research Project Coordinator
Intorcia, Debbie	CRC	Regulatory Affairs Coordinator
Jakimovich, Laura	RN	Multi-Center Clinical Trials Manager
Langbaum, Jessica	PhD	Principal Scientist
Langlois, Carolyn	MA	Research Project Coordinator
Lee, Wendy	MS	Assistant Director, Computational Brain Imaging
Liu, Xiaofen	MS	Computer Specialist
Medina-Rodriguez, Sarah	MD	Clinical Trials Senior Manager
Pandya, Yoga	BS	Regulatory Affairs Coordinator
Protas, Hillary	PhD	Associate Scientist
Prouty, Anita	BS, CNMT	Director, Business Operations
Reeder, Stephanie	MS	Research Coordinator
Reschke, Cole	BS	Computer Specialist
Richter, Nicole	CNMT	PET Technologist
Seward, Jim	PhD	Neuropsychologist
Yaari, Roy	MD	Director, Memory Disorders Center

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 and recruitment of clinical subjects, 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 2012, 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 72 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 6868 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, BACE, genomics of tangle-bearing neurons, tau splicing, and neuroinflammation. Dr Walker received an NIH R21 investigating neuroinflammation (Toll-Like Receptor 3 Signaling in 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. IRB approval to collect 200 blood samples, in collaboration with UA and BNI, has been obtained and collection is in progress. This also includes collaboration with biotech industry partners including Scout, Satoris, Pfizer, ProVista, and Power3 medical products. This was also developed under the purview of ADNI. Many investigators at BSHRI including DeCourt, Coleman, Sparks, 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 approved and funded since 2010. 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. Another phase III trial of a amyloid imaging compound is being secured.
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.

7. Cardiovascular Stem Cell initiative: Dr Gaballa's lab has secured NIH grants and private funding from SHF to perform translational research of extracting CV stem cells, growing them in culture, and implanting autologously. His animal studies are nearly completed. The Clean Room for the Stem Cell cultures is built out. IRB approval has been sought for the harvesting procedure.

BANNER SUN HEALTH RESEARCH INSTITUTE
Key Personnel

Name (last, first)	Degree	Role on project
Sabbagh, Marwan	MD	Principal Investigator, Clinical Core Site PI
Beach, Thomas	MD, Ph.D.	Neuropathology Core Director, Principal Investigator
Belden, Christine	PsyD.	Neuropsychologist
Coleman, Paul	Ph.D.	Principal Investigator
Davis, Kathryn	B.A., CSP, CRC	BSHRI Site Clinical Core Coordinator
Boris Decourt	Ph.D.	Staff Scientist
Gaballa, Mohamed	Ph.D.	Principal Investigator
Grover, Andrew	Ph.D.	Staff Scientist
Jacobson, Sandra	MD	Geriatric Neuropsychiatrist
Lue, Lih-Fen	Ph.D.	Principal Investigator
Nieri, Walter	M.D.	Principal Investigator
Roher, Alex	MD, Ph.D.	Principal Investigator
Schmitt, Andrea	B.S.	ADCC Administrative Director
Serrano, Geidy	Ph.D.	Anatomist
Shill, Holly	MD	Principal Investigator
Sparks, D. Larry	Ph.D.	Principal Investigator
Sue, Lucia	B..S	Neuropathology Core Coordinator
Walker, Douglas	Ph.D.	Principal Investigator
Liudmila Y. Zakharova	Ph.D.	Staff 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 aging and Alzheimer's Disease is in prevention, early detection and defining mechanisms of AD. On the cellular level, the Cellular Metabolism laboratory (the work of Dr. Maalouf continued by Dr. Jiong Shi) studies the problems in metabolism that can be a mechanism in Alzheimer's Disease development and proposes molecules that can be neuroprotective against the disease. Using advanced magnetic resonance imaging protocols in the BNI's Keller Center for Imaging Innovation, Dr. Baxter investigates of the earliest signs of pathological brain changes and imaging indicators of brain health that could be causing these changes. Both of these studies capitalize on the integration within the Consortium institutes through ongoing Consortium collaborations allowing us to combine genetic, neuropsychological, and neurological data to assess changes in neural integrity over time.

Cellular Metabolism Studies:

The focus of our laboratory efforts 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 research program consists of three specific aims:

1) Pathogenesis of Alzheimer's disease: Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) 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 the age of onset and beta-amyloid (Aβ) neuritic plaque burden. 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-AMPK-Sirtuin3 pathway may play an important role in pathogenesis of AD. Our present objective is to further delineate the correlation between PACAP-AMPK-Sirtuin3 pathway and clinical and preclinical cognitive manifestations.

2) The neuroprotective properties of ketones: Our research clearly shows that ketones alleviate the toxicity of amyloid beta by improving mitochondrial function. Our present objective is to demonstrate the neuroprotective properties of ketones in transgenic animals that reproduce the clinical and pathological characteristics of Alzheimer's disease. We have already completed a series of experiments in triple transgenic mice that express mutant APP, PS1 and tau proteins.

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 vs. 10.53 ± 2.30, $p<0.05$) 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.

Human Brain Mapping Laboratory in the Keller Center for Imaging Innovation:

At Barrow Neurological Institute, our overarching aim is to assess 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 and track the earliest changes in people at-risk for AD. As an interdisciplinary group composed of scientist and clinicians from multiple hospitals a majority of our studies have included research participants recruited from multiple institutions from the Consortium.

Overall, we seek to investigate differences between normal aging patterns and disease-related aging. Of special interest to us is a major genetic risk factor of AD, the apolipoprotein variant (APOE ε4). Our goal is to interrogate structural and functional changes associated with normal aging and to assess the effect of APOE ε4 on brain aging in healthy cognitively intact subjects, which may allow for the detection of earliest biomarkers before the onset and progression of a disease state.

We have directed our research aims into several areas:

1) To investigate age-related differences in activation patterns in successfully (no cognitive deficits) and unsuccessfully (slight memory impairments) aging adults using functional magnetic resonance imaging (fMRI)

2) To measure and track changes in brain integrity over time in persons at-risk for AD using whole-brain and regional morphometric measures. This is a multi-institutional project with Dr. Caselli at Mayo Clinic, Arizona.

3) To determine the effects of APOE ε4 in a population of patients suffering from Multiple Sclerosis (MS) using a longitudinal, multi-modal approach of structural and functional imaging techniques. This is a study in collaboration with Dr. Shi, Department of Neurology, at Barrow Neurological Institute.

Below is a brief description of study interests:

1) The human brain undergoes structural and cognitive decline associated with the normal aging process. In order to better understand brain changes associated with the aging process, we assessed 23 young and 42 older adults to evaluate and assess brain areas of activation. Our results, which were recently submitted for publication, indicate differences in functional recruitment patterns in subjects who are successfully aging compared to individuals who show slight memory problems, but are still well within the normal range.

2) To date, we have data from approximately 120 participants, primarily participants from Dr. Caselli's APOE cohort who are cognitively normal and genetically characterized at-risk for AD. As part of this study we have included a subset of patients with MCI and AD to determine the trajectory of changes in some of the experimental neuroimaging techniques implemented in this study. Some of the scan procedures are measures that are commonly used in studies of aging and AD, including region of interest morphometrics, cortical thickness and volume, and voxel-based morphometry measures of gray and white matter. However, we have also included other measures that are not commonly available on such a large group of well-characterized participants, including non-invasive arterial spin labeling perfusion MRI, 3-D FLAIR imaging, and resting-state functional MRI. These measures can be used as functional measures of blood flow and microscopic tissue integrity to allow for assessment of early and subtle changes that may help create not only possible measures of early changes for efficacy trials, but also discover mechanisms of change that could influence preventative or early intervention clinical trials. We have found that at risk individuals show changes in white matter as well as cortical thickness in key brain regions well before any signs of cognitive impairment. In order to determine the progressive nature of aberrant aging patterns in subjects at-risk for AD it is imperative to assess subjects longitudinally. This year, we have collected the second timepoint of longitudinal data in a subset of these participants in order to determine cognitive and neuroimaging parameters that best capture the rate of change in brain structure and function that occurs in participants at risk for AD

3) We are recruiting 80 MS subjects to determine how APOE genotype affects cognitive and structural changes in MS. An increasing amount of studies suggest a deleterious affect of the APOE ε4 gene and MS. We seek to investigate using a multi-modal approach of structural and functional neuroimaging techniques combined with a longitudinal study design, the role of the APOE ε4 gene relative to MS disease progression and severity.

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 the City of Phoenix senior centers which has improved both our Latino recruitment as well as the ADCC's relationship with the local City of Phoenix community. This has considerably enhanced the AARC and ADCC efforts in reaching out to underserved communities in Phoenix. About one third of the BNI's ADCC participants are Hispanic, and our population represents more than a third of total Hispanics enrolled in the AzADCC. We are currently completing data analysis of the differences in retention and patient profiles of Hispanics who are recruited through Neurology compared to those that are volunteers from the local Hispanic community. When data analysis is completed, we will submit these findings for publication.

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

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. perform a cognitive "stress test" based upon TOMM40 genotype to further test the proposal that TOMM40 is another genetic risk factor for AD
6. develop a tool that will facilitate compliance with diet and exercise based primary prevention measures, and test its success in enhancing compliance in small test cohorts

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

MAYO CLINIC ARIZONA
Key Personnel

Name	Degree	Role on Project
Caselli, Richard	MD	Principal Investigator, Clinical Core Director, Associate Director, Behavioral Neurologist
Woodruff, Bryan	MD	Co Investigator, Behavioral Neurologist
Locke, Dona	PhD	Co Investigator, Neuropsychologist
Stonnington, Cynthia	MD	Co Investigator, Psychiatrist
Geda, Yonas	MD	Co Investigator, Psychiatrist

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) research within TGen. AD has been a focus of the Division since its inception and every laboratory within the Division has performed research related to 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
Dunckley, Travis	PhD	Co-Investigator, Molecular Profiling
Henderson, Adrienne	BS	Research Associate
Huentelman, Matthew	PhD	Principal Investigator
Lechuga, Cynthia	MBA,CRA	Grants Administrator
Meechoovet, Bessie	BS	Research Associate
Reiman, Eric	MD	Consultant
Siniard, Ashley	BS	Research Associate
Van Keuren-Jensen, Kendall	PhD	Co-Investigator, Neurobiology
TGen Collaborative Bioinformatics Center		Bioinformatics and Analysis Support

UNIVERSITY OF ARIZONA
Institutional Abstract

Researchers at the University of Arizona (UA) are engaged in a collaborative, multi-disciplinary program of research focused on advancing our understanding of the major risk factors for brain aging and age-related cognitive decline, their underlying neural substrate, and ways to delay or prevent cognitive aging. To accomplish these overarching goals, a team of UA investigators that include researchers in the fields of neuroimaging, cognitive and behavioral neuroscience, neuropsychology, neurology, and statistical analysis are involved in this research program. 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 utilizes advanced magnetic resonance imaging (MRI) as a cross-cutting methodology to provide measures of brain function, structure, and regional connectivity in the context of 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, 6) to provide information to the community to advance understanding about aging, cognitive decline, and age-related neurodegenerative disease.

Program-related activities at the UAinclude threemajor 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 andAlzheimer's disease (AD). The projects focus on identifying early neurocognitive and biological markers that may signal theearly 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 processesin 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, Pagie	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
Nadel, Lynn	PhD	Investigator; Psychology, Neuroscience Program, Evelyn F. McKnight Brain Institute
Rapcsak, Steven	MD	Investigator; Neurology, Psychology, Evelyn F. McKnight Brain Institute
Ryan, Lee	PhD	Investigator; Psychology, Neurology, Neuroscience Program, Evelyn F. McKnight Brain Institute
Serio, Tricia	PhD	Investigator; Molecular and Cellular Biology
Trouard, Theodore	PhD	Investigator; Biomedical Engineering, Evelyn F. McKnight Brain Institute

Project Progress Reports

Project Progress Reports

Arizona State University

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Androgens, Menopause, and Memory: A Test Of Hormone Mechanisms. Heather Bimonte-Nelson, PhD. Arizona State University.

Project Description: The broad goal of our lab's program of research is to determine which factors influence whether hormone therapy (HT) acts as a protectant or risk factor for cognitive and brain aging. Indeed, ovarian hormone loss due to menopause has been linked with cognitive decline and increased Alzheimer's disease risk. While there is evidence that HT benefits cognition in women, several clinical trials failed to find positive effects, and some found detrimental effects, of HT. Yet, basic science evidence suggests that estrogens exert beneficial effects on cognition and related brain mechanisms. We assess variations in current HTs (such as conjugated equine estrogens, or CEE), testing whether they attenuate or exacerbate age-related cognitive changes in surgically menopausal ovariectomized (Ovx) rats, and transitionally menopausal rats using 4-vinylcyclohexene diepoxide (VCD). In VCD-treated rats estrogen is depleted and gonadotropins increase, a profile resembling non-surgically menopausal women. Despite the insight rodent models have yielded for surgical hormone loss, surgical menopause models <13% of women; the majority of women undergo non-surgical, transitional menopause. We have shown substantial differences in cognitive aging depending on whether menopause is surgical or transitional, and whether ovaries are retained or removed. These effects are related to the ovaryderived androgen, androstenedione, which is released from the menopausal ovary in rats in women.

Aim: The aim of this study is to determine the hormonal mechanism related to our observed androstenedione-induced cognitive detriments in the surgically menopausal rat.

Progress to Date: We have completed the majority of this experiment testing the hormone mechanism of our previously shown findings regarding androstenedione effects on cognition. We recently found that high levels of androstenedione, the main circulating hormone present after menopause and follicle depletion, is correlated with poor spatial memory in chemically-induced follicular depleted rats (Acosta 2009a), and impairs spatial memory when administered as an exogenous treatment (Camp 2012). Androstenedione can be converted to either an estrogen (e.g., estrone) or to another androgen (e.g., testosterone). The current study tested the hypothesis that the impairment of spatial memory found previously after androstenedione administration is due to its conversion to either estrone or testosterone. This study was conducted with the goal of elucidating the hormonal mechanism of the observed androstenedione effects on cognition by methodically blocking the conversion of androstenedione to estrone, or blocking androgen receptor activity, and evaluating changes in cognition. The previously found effects of androstenedione were supported. However, when decreasing the conversion of androstenedione to estrone (via aromatase inhibitory), the impairing effects of androstenedione were alleviated. When androgen receptor activity is blocked, there is negligible difference in comparison with the cognitive profile of androstenedione given alone. The implications of this study are important in understanding androstenedione's effects on cognition in post-menopausal women. We are currently preparing brains of the tested animals for evaluation, and writing the manuscript for publication.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Vulnerable Caregivers: The Dynamic Interplay between Caregiving and Self-Care . David W. Coon, PhD. Arizona State University.

Project Description: Informal dementia caregivers contribute an essential and highly valuable service to their families and to society, but also suffer costs. Caring for family members with Alzheimer's disease or a related dementia has been associated with elevated distress and depression, along with poorer self-reported health and detrimental changes in several physiological systems. However, most research has investigated non-Hispanic white caregivers, leaving an information deficit regarding caregiving experiences in other ethnic groups. Moreover, studies examining relations between caregiving and physiological health indicators often omit caregivers with chronic illness. Thus, little is known about the effects of caregiving on chronic illness progression or illness self-management strategies. The current study will lay the groundwork for future research to address these knowledge gaps.

The central aim of the study is to investigate how caring for someone with ADRD and managing one's own health conditions might impact one another; and to begin to develop a new or refine an existing evidence based intervention to address self-care issues. This project extends prior work by recruiting additional Latino and Non-Hispanic White caregivers with at least one of three health problems (Type II diabetes, High blood pressure, or being overweight according to NIH standards) from the Phoenix metropolitan area. Caregivers will be telephone screened; and, eligible participants will be asked to participate in an in-depth interview that gathers both quantitative and qualitative data regarding caregiving and their self-care activities.

This mixed methods project will include screening procedures and material as well as structured questionnaires based on those used in prior NIH funded studies (e.g., the NIH REACH I and II trials) such as: social support, positive aspects of caregiving, coping, depression, stress, burden, health behaviors, and illness self-management. Data collection will also involve saliva samples (cortisol response), as well as a finger stick to assess CRP, EBV-VCA.

Finally, interested participants will be recruited for focus group discussions to extend our understanding of how to develop new or refine existing family caregiver interventions to address chronic disease self management activities critical for vulnerable family caregivers, and thereby reduce negative physical health outcomes in addition to negative mental health outcomes.

Proposed One-Year and Long-Term Outcomes: This year we will build off recruitment efforts with community partners successful in the US AoA CarePRO and EPIC grants to enroll additional Latino and non-Hispanic white family caregivers with one of three health problems (Type II diabetes, high blood pressure, or being overweight according to NIH standards), and conduct analyses on data gathered in this mixed methods project. Long term outcomes include the development of family caregiver interventions to address the chronic disease self-management challenges faced by these vulnerable caregivers. The goal is to use the data collected to submit for NIH funding to support an RCT testing the new intervention.

Progress to Date: Much of the project to date has focused on rebuilding relationships with community based organization serving the Latino community in an effort to increase the number of family caregivers in the project who self-identify as Latino or Hispanic. Project staff have met with well over 20 organizations, and made presentations at a wide variety of staff meetings, health fairs and conferences serving older adults and their family caregivers. Only 15 participants have been screened and scheduled for interviews thus far with 11 fully completing the interview and biological specimen collections. Additional screens are pending. All structured interview data has been entered and cleaned, and all

audiotaped semi-structure interviews have been transcribed and verified. Similar to our experience with other projects, we have found that Latino/Hispanic families express additional concerns about research participation given the ongoing debate on immigration reform, thereby negatively impacting enrollment of these families.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

An Integrative Approach for the Discovery of Potential Therapeutic Targets for Alzheimer's Disease. Graciela Gonzalez, PhD, Matthew Huentelman, PhD, Eric Reiman, MD. Arizona State University, TGen, Banner Alzheimer's Institute.

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). Some are purely statistical, resulting in a (mostly) undifferentiated set of genes that are differentially expressed (or co-expressed), while others seek to prioritize the resulting set of genes through comparison against specific "known" targets. 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. We propose 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.

Aims and Objectives: This project advances our prior work, seeking to 1) enhance our integrated knowledge base on the biological basis of Alzheimer's Disease pathology that incorporates current knowledge from the literature and other sources, and can be dynamically updated as new information is published and directly via investigator suggestions, 2) develop a prototype interface to allow direct manipulation of the integrated knowledge by translational researchers and integration with data resulting from empirical assays, particularly microarray expression data. The outcomes of these aims will be validated with expert analysis (Huentelman) of the resulting selection of targets. Futher empirical validation (such as qrtPCR and immunohistochemestry), will be pursued by collaborators with separate funding, to their discretion.

Progress to Date: To date, we have organized knowledge from the AlzGene database (available at http://www.alzgene.org) of genes identified as relevant to Alzheimer's Disease, and integrated known interactions for the genes in the list. Sources include: the Genetic Association Db (last updated 03/2012), Drug Bank db – v3 (last updated 10/2012), PharmGKB db (last updated 10/2012), STRING db – v9.0 (last updated 03/2012), and the NCBI Gene db (last updated 03/2012).

We have completed a working version of a 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.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Detection of oligomeric beta-amyloid and tau species as sensitive, selective biomarkers for Alzheimer's Disease. Michael Sierks, PhD. Arizona State University.

Project Description: 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. Numerous studies have implicated small soluble oligomeric aggregates of Aß as toxic species in AD, and increasing evidence also implicates oligomeric forms of tau as having a direct role in AD pathogenesis and in other neurodegenerative diseases. We have developed novel highly selective antibody based reagents (nanobodies) that selectively recognize individual aggregate species of Aß and tau that have been implicated in AD [1-4]. These highly specific, very well-defined nanobodies can be useful to study the progression of AD and related neurodegenerative diseases, as potential early diagnostic markers, and as part of a therapeutic strategy that targets only the toxic morphologies of Aß and tau. Using limited sample sets we have shown that the morphology specific Aß nanobodies can distinguish between AD and healthy brain tissue and between post-mortem CSF samples from AD and healthy patients demonstrating the potential value of these reagents for diagnostic applications. Here we will continue these studies and characterize the binding specificity of additional nanobodies to different oligomeric species of Aß and tau. We will also use these nanobodies along with other nanobodies against Aß, to detect the presence of these various aggregate species in brain tissue and CSF samples obtained from the Banner/Sun Health Research Institute brain bank to demonstrate their value as biomarkers for AD.
The specific aims of this project are:
1) Grow, purify and validate binding specificity of nanobodies to different oligomeric forms of Aß and tau.
2) Test AD and healthy CSF samples for presence of selected tau and Aß species using the pool of nanobodies against oligomeric Aß and tau.

Proposed One-Year and Long-Term Outcomes: The one year outcomes are to produce the different nanobody proteins and to use them to detect the presence of specific aggregate species of Aß and tau in post-mortem patient tissue samples. We will also utilize the different nanobodies to identify which tau and Aß forms are present in post-mortem CSF and serum samples of AD and healthy patients. The longer term outcomes are that correlation of concentrations of specific Aß and tau aggregate species with AD progression can lead to identification of promising biomarkers for early detection of AD and other neurodegenerative disease. The panel of reagents can also be used to detect the presence of specific Aß and tau morphologies in animal models of AD by various different imaging protocols including PET and SPECT and eventually for human use as well.

Literature cited:
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3. Zameer, A., et al., Anti-oligomeric Abeta single-chain variable domain antibody blocks Abeta-induced toxicity against human neuroblastoma cells. J Mol Biol, 2008. 384: p. 917-28.

4. Zameer, A., et al., Single Chain Fv Antibodies against the 25-35 Abeta Fragment Inhibit Aggregation and Toxicity of Abeta42. Biochemistry, 2006. 45: p. 11532-9.

Progress to Date:

Aim 1. We validated binding specificity of two different nanobodies, one to a brain derived oligomeric form of Aß and one to an oligomeric form of tau. Both nanobodies when isolated from the antibody library contained a frame shift at the beginning of the antibody sequence. To produce the nanobody protein we needed to correct the frameshift. We successfully corrected the frameshift in both the C6T anti-Aß nanobody and in the F9T anti-tau nanobody. We then produced protein from both of these nanobodies using an E. coli host. The proteins were then purified and assayed for specificity. We verified that the C6T anti-oligomeric antibody bound AD brain derived Aß, and that it could selectively recognize brain tissue from AD mouse models, but not wild-type.

Aim 2. We utilized the nanobodies to determine whether different oligomeric forms of Aß and tau were present in post-mortem human tissue samples obtained from the BSHRI brain bank. We used three different anti-oligomeric Aß nanobodies and showed that they could readily distinguish between AD and cognitively normal brain samples. What was particularly impressive about these results is that the anti-oligomeric Aß nanobodies could clearly distinguish between AD and cognitively normal samples even when both samples contained similar plaque loads. These results provide further evidence that oligomeric Aß may be a very sensitive biomarker for AD.

Project Progress Reports

Banner Alzheimer's Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Native American Outreach Program. Roy Yaari, MD, MAS, Jan Dougherty, MS, RN, Richard Caselli, MD, Marwan Sabbagh, MD, Eric Reiman, MD, Pierre N. Tariot, 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 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 and families, strong relationships and a sense of shared ownership in the development of new educational and service programs, and to demonstrate to this vulnerable community our strong interest in serving these needs whether or not they participate in research studies. We have also provided a means by which a growing number interested members of the Urban Native American community can participate in the Arizona Alzheimer's Disease Core Center (ADCC) Clinical Core to facilitate in those studies that are of particular interest to them. We have continued to follow 9 participants in the Clinical Core for greater than 5 years with another 30 either deceased or lost to follow up. We have a tremendous interest from the Native community to participate in the Core and we anticipate doubling the enrollment in the next 12 months. While we are proud of our initial clinical core efforts, we see our primary goal as promoting a close, trusting relationship, offering educational and other relevant services, and providing a foundation to work together to address the AD-related problems faced by our Native American communities,and provide a foundation for research studies that would have the greatest impact on this understudied minority group.

Preliminary Data and Plan: Over 3300 Native Americans have participated in numerous education and outreach efforts. We continue to have a strong working relationship with 16 of the 22 Arizona tribes in addition to working with InterTribal Council on Aging, Native Health and other Urban Indian programs. We hosted the 9th Annual conference on AD in Native Americans in October drew 220 community participants.Additionally we offered the 3rd annual memory screening at the conference for participants.Our outstanding Native American personnel and our other colleagues will continue to establish close working relationships with stakeholders from different tribes and nations. In regards to the ADCC Native American cohort, we have 22 participants that have been followed and whose finding have been reported to the ADCC database. Currently there are 19 active participants with results reported to the NACC. There were 7 new participants enrolled in 2012.

Proposed One-Year and Long-Term Outcomes:

1. Continue to grow lasting relationships with Arizona tribes and decrease the disparity related to diagnosis and treatment of AD in both reservation and urban dwelling Natives.

2. Maintain the Native American cohort in the ADCC trial in the next 12-months while building a list of those interested in participation as funding becomes available for more assessment.
3. Utilize the Native American Advisory Committee to identify and prioritize possible research opportunities that include the epidemiology of AD among various tribes and culturally sensitive cognitive screening. This will include a newly funded project to improve culturally sensitive measures for memory screening and the development of a culturally sensitive brain health program.

Funds will be use in a way that conmplement 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 the Gila River Indian Community and Tohono O'odham Nation for targeted memory screening/brain health programs.

Year End Progress Summary:

Aim 1: Our relationships with the Arizona Native American communities continue to be strengthened. During the past 12 months the outreach and education efforts have reached over 2000 professional staff and paid caregivers and approximately 1300 family caregivers and community members. The 9th Annual conference on Alzheimer's disease in Native Americans reached 220 participants and a 3rd annual memory screening was provided to 55 participants. A total of 35 participants signed up for the Alzheimer's Prevention Initiative

Aim 2: We have 19 active participants enrolled in the ADCC clinical core with 7 newly enrolled participants in 2012.

Aim 3: The Native American Advisory Committee has been very helpful in assisting our team to understand various tribal needs and opportunities for additional outreach, education and possible research opportunities. We are engaged with a Navajo neuropsychologist to test culturally sensitive cognitive screening; create train-the-trainer materials to bring memory screening to identified tribal communities/organizations and to create a brain health program to promote awareness of normal memory v. Alzheimer's disease.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 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 early-onset AD 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 upcoming 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 autosomal dominant early-onset AD mutations 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 EOAD or LOAD.
Aim 3: To continue to develop registries to support future presymptomatic treatment trials.

2012-2013 Progress: **1)** In May 2012 we received grant funding from the NIA to conduct a presymptomatic trial/surrogate marker development program in autosomal dominant early-onset AD mutation carriers within 15 years of their estimated age at clinical onset. This five-year study is anticipated to cost more than $100M USD, with funding consisting of approximately $16M in NIH funding, $15M in philanthropic support, and the lion's share from industry. Funding was announced by Secretary of Health and Human Services, Kathleen Sebelius, and referred to by the NIH as the cornerstone in the national plan to address Alzheimer's disease. Scientific American named the API as one of the ten world-changing ideas in 2012. We have secured an agreement with our industry partner, Genentech, to release all of the data and biological samples to the scientific community following completion of the trial, a paradigm that others are now adopting. This license enabling trial, which requires extensive preparations, is slated to begin later in 2013. **2)** Two manuscripts were published in Lancet Neurology (Reiman et al., 2012; Fleisher et al., 2012), providing groundbreaking information about the age-related trajectory of brain and cerebrospinal fluid (CSF) changes that precede cognitive impairment in individuals from the world's largest autosomal dominant Alzheimer's disease kindred. For instance, we demonstrated that amyloid deposition begins approximately 17 years prior to mild cognitive impairment (MCI) and approximately 23 years prior to dementia onset, and there may be even earlier brain and CSF changes. Future studies are planned starting later in 2013 to better understand the trajectory of these measures. 3) We submitted two manuscripts to a high impact journal in late 2012 describing our work using a novel exhaustive search strategy in longitudinal cohorts from Rush University and the University of Antioquia find the most sensitive combination of cognitive test scores to track the preclinical stages of AD, anticipate clinical onset, controlling for practice and aging effects, and evaluate presymptomatic 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 presymptomatic AD trial, and it is now being considered by several other groups as they plan their own presymptomatic treatment trials. Based on this work, Dr. Ayutyanont received funding in July 2012 from the Arizona Alzheimer's Consortium for her pilot grant to extend this approach to other datasets, and a manuscript is in preparation based on this effort. **4)** We are two-thirds to our goal of enrolling 3,300 autosomal dominant kindred members into the Colombia API Registry, which includes extensive information on memory and thinking tests, DNA and genetic test results. Of the 2,300 people enrolled members, approximately 28% carry the genetic mutation. We anticipate enrolling 3,300 kindred members into this registry by end of 2013. **5)**We launched 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 mid-2015 and currently has approximately 9,500 members, 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 submitted an Arizona AD Center pilot study based on the Registry and plans to pilot an apolipoprotein E (APOE) ε4 genotyping and disclosure program.**6)** We submitted a grant to the NIA in January 2013 (anticipated funding start in September 2013) in support of the API's next prevention trial in 60-75 year-old cognitively healthy *APOE* ε4 homozygotes. We intend to have industry and potential philanthropic support, having already secured a major commitment from an industry company to pay for the entire cost of the amyloid PET scans collected during the trial. As with our first API trial in autosomal dominant Alzheimer's disease, we will convene an expert advisory committee to help us vet the candidate amyloid-modifying treatment options.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Arizona Alzheimer's Research Registry. Jessica B. Langbaum, PhD, Pierre N. Tariot, 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. In addition, the Registry was designed to serve as the prototype for a larger (at least 100,000 enrollee), national Registry focused on Alzheimer's Prevention treatment trials as part of the Alzheimer's Prevention Initiative (API). The current AAR relies on paper-based forms and annual telephone-based cognitive assessments, both of which are costly and inefficient, nor are appropriate for thecurrent Alzheimer's Prevention Registry. As a result, separate efforts are being made move the current AAR into the current online Registry. The goals of the current project proposal are to continue to alert and enroll current Arizona registrants into the new online Registry, to offer online Registry participants a range of online surveys and appropriate Alzheimer's prevention study opportunities, as well as newsletters regarding the progress of Alzheimer's Prevention research developments.

Specific Aims:

Aim 1: To establish an efficient mechanism to alert and encourage persons in the AAR to enroll in the online Alzheimer's Prevention Registry.

Aim 2: To promote the Alzheimer's Prevention Registry to consortium researchers and to the general public who attend consortium-led events

Aim 3: To develop specific online Registry content, eblast newsletters and online surveys designed keep participants involved and engaged in the Registry, as well as assess their self-reported memory status and risk factors for AD.

2012-2013 Progress: We have developed an online Registry enrollment system and website (www.endALZnow.org) that is open to anyone over the age of 18, with a target audience is healthy adults over the age of 50. The Registry aims to enroll 250,000 people by mid-2015 and currently has approximately 9,500 members. The Registry is intended to be a shared resource to accelerate enrollment in the range of prevention trials.Enrollment into the Registry requires minimal contact and demographic information, username and passwordand offers access to a personalized homepage for each member.The personalized homepage allows enrollees to view personalized announcements, study and survey opportunities, de-identified graphics of select demographics of all enrollees, and current and archived editions of the Alzheimer's Prevention Bulletin created by Alzforum specifically for this Registry. Enrolleesreceive eblasts for study opportunities as well as lay-oriented quarterly newsletters that focus on the progress of Alzheimer's prevention research development.The online registration system went live in March 2012 and the personalized profile dashboard component of the Registry went live in May 2012. 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, Mr. Kyle Brown, 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, Banner Alzheimer's Foundation, GBGBAI and other stakeholders help promote the Prevention Registry through national and local communications. An overview of the Registry's progress will be presented at the 2013 Alzheimer's Association International Conference. Dr. Langbaum submitted an Arizona AD Center pilot study based on the Registry and a program to pilot an apolipoprotein E (APOE) ε4 genotyping and disclosure program.

Current AAR enrollees have received personalized invitations to join the new Alzheimer's Prevention Registry beginning in April 2012. As of March 2013, 1873 paper invitations to join the Registry have been sent to AAR members, as well as 1172 email invitations.We launched the first online survey for the Prevention Registry in October 2012 in partnership with colleagues at Mayo Clinic Arizona. 2135 Registry members responded to the survey in the first month it was offered. Results from this survey will be presented at the 2013 Alzheimer's Association International Conference. In addition, a free online webinar focused on Alzheimer's prevention was offered to Registry members in November 2012. 225 members attended, and a recording of the webinar was made available to all members.

The importance of the online Registry have become even more apparent as the Alzheimer's Prevention Initiative (API), which is led by Banner Alzheimer's Institute, recently submitted a grant application to the NIA to conduct its second prevention treatment trial in approximately 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 will in-large part rely on referrals from the Registry.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

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

Project Description: 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.

Aims: 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.

2012-2013Progress: 1) We continued our collaboration with the group of researchers from Italy who, aftertheir last year's adoption of our hypometabolism convergence index (HC) algorithm for distinguishing AD from normal controls, slow AD progression from fast progression, and MCI patients who converted to AD from those who did not, worked with us to compare a number of imaging based biomarkers including HCI for their use in clinical trials. Among the FDG-PET based biomarkers, it was found that HCI is with highest sensitivity. This finding was submitted to AAIC 2013 as an abstract recently.In our continued efforts to improve HCI and to generalized its applicability, we examined the HCI differences in cognitively normal but as amyloid positive as assessed using florbetapir PET vs those who wer not. We discovered that HCI is higher in the amyloid positive normal control group, suggesting that brain functions were impacted more in them. The generalization of the HCI to a longitudinal index (we referred it as metabolic decline convergence index, or MDCI) is written up as a manuscript near

completion. It will be submitted soon. We further refined our IPCA method, used it for examining the differences among AD, MCI and NC, and estimated sample size for clinical trial. The finding is accepted for publication by Journal of Neuroscience and Biomedical Engineering (NBE). 2) Also continuing our last year efforts, we started the drafting of our regional HCI (rHCI) findings as a manuscript and calculated HCI for ALL FDG-PET images available for ADNI, ADNI-GO and ADNI-2 projects. Continuing our efforts from last year, we are applying HCI, ACI and rHCI to a number of projects and some interesting findings are obtained including one we summarized submitted to Alzheimer's Association International Conference (AAIC) 2013.This findings reported that cognitively normal subjects who had higher amyloid burden (amyloid positive) had significant reduced CMRgl (higher HCI) than those who are amyloid negative, implying the abeta-amyloid could have very early-on impact on the brain functions. Further supporting this, we also found that HCI is negatively associated with neuropychological measures only in the amyloid positive normal subject group. These findings are further confirmed by the use of our own developed multi-modal partial least square (MMPLS) technique, which was also submitted as an abstract to AAIC 2013. Last year, we extended the general 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, we found covarying patterns whose corresponding subjects scores distinguished AD from normal controls, AD from MCI, AD from early MCI (eMCI), MCI from normal controls, MCI from eMCI and eMCI from normal controls all with great statistical significance. Moreover, we found that these subjects' scores are significantly correlated with cognitive test scores. As we stated in our last year's report, though ICA is not novel as an analytic tool, its use as a global index for PET data is yet our continued efforts methodologically to find imaging based biomarkers which is multiple comparison free and yet with high sensitivity and specificity. We have started preparing the data and other materials for possible write-up of these findings. 3) We continue to make available the computer software packages/proceduresdeveloped in house to researchers in our Arizona Alzheimer's Consortium. We are pleased to note the publication of the increased amyloid burden in memory decliners compared to non-decliners using the Monte-Carlo simulation procedure developed in our lab, for Dr. Cynthia Stonnington (who are the first author of the study), Mayo clinic.. The finding of the association between high fasting serum glucose and the lower cerebral metabolic rate for glucose was also accepted for publication (first author Christine Burns from U of A) with the use of our techniques. In addition, we assisted, statistically or imaging processing wise, several publications from researchers at Sun Health. These publications were on the cardiovascular risk of AD (Dr. Alex Roher) and the Down syndrome (Dr. Marwan Sabbagh).. 5) With the state funding, we are able also to investigate a number of other techniques for analyzing resting-state fMRI using Bayesian Network (BN). We also developed multivariate ROC and found it is with increased power for detecting abnormalities (disease status). Finally, we note our accomplishments in defining the industry first autopsy-associated thresholds for determining amyloid PET positivity, defined effects of age and APOE4 on F18 amyloid PET, defined composite endpoint measures and published pilot data in Lancet Neurology describing age-related trajectories of amyloid PET findings and contributing to the launch of API's first presymptomatic treatment trial.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Development of Composite Cognitive Endpoints for Presymptomatic AD Trials. Napatkamon Ayutanont, PhD, Jessica B.S. Langbaum, PhD, Suzanne B. Hendrix, PhD, Kewei Chen, PhD, Eric Reiman, MD. Banner Alzheimer's Institute, Pentara Corporation, University of Arizona, Translational Genomics Research Institute, Arizona State University, and Arizona Alzheimer's Consortium.

Project Description: "Development of Composite Cognitive Endpoints for Presymptomatic AD Trials" is a multi-institutional collaborative project developed to establish a composite cognitive endpoint most sensitive to longitudinal cognitive decline for presymptomatic AD trials. To help accelerate the evaluation of presymptomatic AD treatments, we have begun to use longitudinal data sets that have followed individuals from cognitive normality to the clinical onset of AD (i.e., to mild cognitive impairment or probable AD) to empirically identify the combination of neuropsychological test scores that track presymptomatic AD decline with greatest statistical power and then apply these endpoints to at-risk populations to estimate sample sizes that the Alzheimer's Prevention Initiative (API) and others are now planning. In this current project we proposed to extend the work we have previously begun to a) determine the extent to which the composite endpoints' statistical power can be improved by weighting strategy, b) establish the generalizability of such endpoints to other datasets, c) prepare for their use as primary endpoints in presymptomatic AD trials planned by us and others and d) set a foundation for a further grant application.

Aims: 1) determine the extent to which a test score weighting strategy improves the statistical power of our empirically generated composite endpoint to track preclinical AD and evaluate presymptomatic AD treatments in our currently used longitudinal late-onset Ad (LOAD) and early-onset AD (EOAD) data sets. 2) establish the extent to which the composite cognitive endpoint is associated with comparable power to track preclinical AD in other available data sets. 3) provide sample size estimates for several planned presymptomatic AD trials, 4) set the stage for their use as primary endpoints in at least two presymptomatic AD trials that are likely to begin in 2013, and 5) provide a foundation for a grant application to further develop, test, and use the composite cognitive endpoint in the preclinical study and treatment of AD.

2012-2013 Progress: 1) We have significantly improved the statistical power of our empirically generated composite endpoint to track preclinical AD in our current EOAD dataset by implementing a test score weighting strategy, resulting in significantly smaller sample sizes required. The same approach is in progress for the LOAD dataset. 2) We have confirmed that the power of the pre-specified composite cognitive endpoint, generated using our current LOAD dataset, to track preclinical AD is comparable to that of an independent larger multi-center dataset provided by National Alzheimer's Coordinating Center (NACC), establishing the LOAD composite cognitive endpoint. Analyses of other independent datasets provided by our collaborators are underway. 3) Using NACC dataset, we have provided the optimal age range of enrollment with maximum statistical power and sample size estimates to Alzheimer's Prevention Initiative (API)'s second trial, an LOAD prevention trial. An NIA grant application was submitted in January 2013 and is currently under review. This public-private partnership will include significant funding from the NIA (contingent on approval), the Banner Alzheimer's Foundation, and industry. 4) The EOAD composite cognitive endpoint is currently being used as a primary endpoint in the API's first trial, an EOAD prevention trial, with the first-patient-in scheduled in 2013. We have continued the process of refining the composite endpoints for their use as primary endpoints in the preclinical AD trials using several independent datasets. 5) The progress we have made and the resulting findings have, and

continued to, provided us with a foundation for future grant applications. Initial findings from this project will be presented at the Alzheimer's Association International Conference and two manuscripts will be submitted in May 2013.

Project Progress Reports

Banner Sun Health Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

A Novel Therapeutic Directed at Mitochondrial Energetics and Epigenetics. Paul Coleman, PhD, Sidney Hecht, PhD. Banner Sun Health Research Institute, Arizona State University

Specific Aims: Our goal is to understand the involvement of mitochondria in the regulation of epigenetic molecules in neurons. The specific objective of this proposal is to analyze the effect of oligomericabeta on the mitochondria and correlate these effects with the up or down regulation of epigenetic transcripts and chromatin structure. The central hypothesis is that oligomeric Aβ perpetuates cellular senescence in mitochondria, yielding a bioenergetic system unable to meet the energy demands required by the epigenome. We will peruse these studies in three specific aims:

Aim 1) Analyze the effects of oligomeric Aβ treatment on mitochondrial function in a human cell culture model.

Aim 2) Determine if oligomeric Aβ treatment recapitulate epigenetic modification observed in AD at the transcript level (Figure 1), and correlate transcription status with chromatin structure.

Aim 3) Determine if the effects of oligomeric Aβ treatment on the mitochondria can be reversed with a novel water soluble Co-enzyme Q analogue, and restore ATP production and epigenetic expression to normal levels.

Background and Significance: Deficiencies in energy metabolism have been shown to be a central event in Alzheimer's disease pathophysiology[1]. Epigenomic modification of nuclear DNA (nDNA) requires a constant consumption of calories. Mitochondrial oxidative phosphorylation is a key factor which drives an organism's energetic demands. This system convert environmental calories into ATP, acetyl-Coenzyme A (acetyl-CoA), S-adenosylmethionine (SAM) and reduce NAD^{+2}. When calories are abundant the potential energy generated by ATP and acetyl-CoA drive epigenetic mechanisms to phosphorylate and acetylate chromatin[3, 4], resulting in active nDNA transcription, as well as maintenance of the methylation status on genes which require suppression (i.e. imprinting genes). When calories are less abundant, as seen in AD[5], phosphorylation and acetylation mechanisms are suppressed and methylation mechanisms altered, as we have shown in AD brains, and in monozygotic twins discordant for AD[6, 7]

It is well established that amyloid is a major player in AD pathophysiology, but recent evidence implicates the more oligomeric forms of Aβ as the more toxic species [8]. Furthermore, recent work has demonstrated in a mouse model that oligomeric Aβ is toxic to mitochondria both at the level of the synapse and in the cytosol, an insult that precedes synaptic degeneration [9]. Because bioenergetics provides the link between the environment and the epigenome, we propose to analyze the effects of amyloid load on mitochondria in a human cell culture model and determine whether caloric input is affected via ATP generation in cells treated with or without oligomeric Aβ-42. We'll attempt to mitigate the effects of amyloid load on mitochondria with the addition of a novel water soluble Co-enzyme Q analogue, which aids in ATP production by capturing electrons that have "leaked" from defective mitochondria and returning them to the electron transport chain. The compounds thereby normalize ATP production in cells with defective mitochondria. Because the compounds also suppress ROS and lipid peroxidation in a *catalytic cycle*, they also confer cytoprotection to cultured cells. Collectively, these data will reveal the importance of bioenergetics in regulating the epigenome, and may provide the framework for future therapeutic intervention.

Preliminary Data:

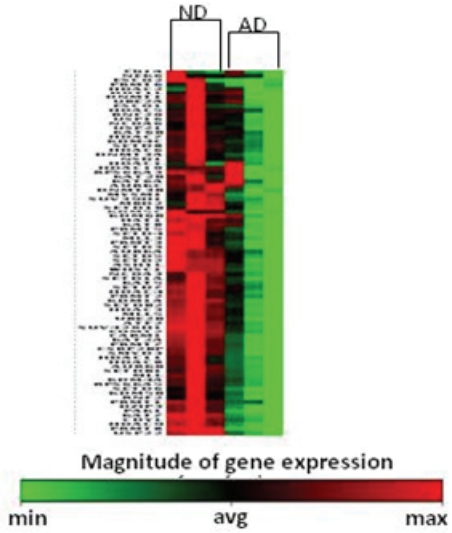


Figure 1: Clustergram analysis of Epigenetic profiler PCR array, 3AD and 3 ND, temporal cortex. Separation between groups indicate significant epigenetic drift in AD.

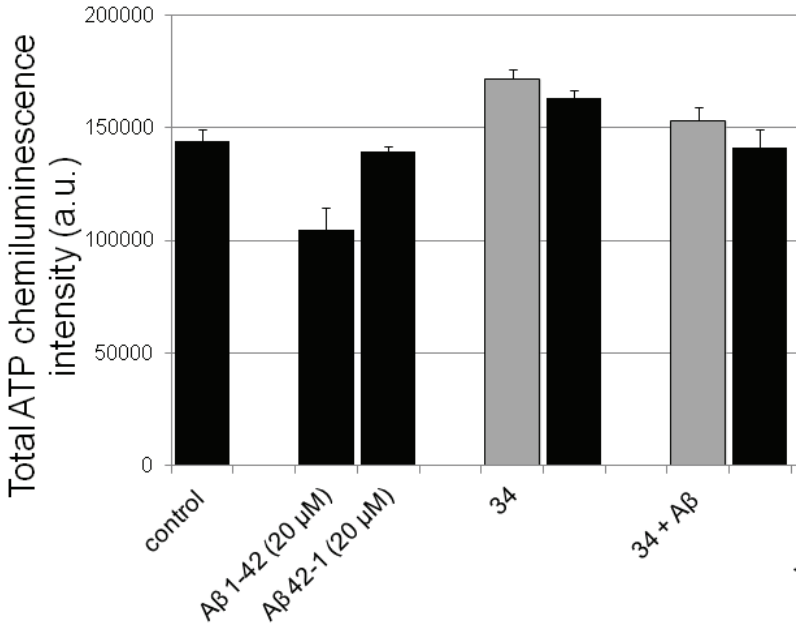


Figure 2: Aβ42 treatment of differentiated SH-SY5Y reduce ATP levels. Novel CoQ compound restore ATP levels, and aid in additional ATP production at the 1μM

Experimental Designs and Methods: Fullydifferentiated SH-SY5Y, for method see [10]; will be treated with or without a standard dose of oligomeric Aβ-42 (1uM), and each condition will be treated with four separate doses of the Co-enzyme Q analogue. All experiments will be carried out in triplicates, and analyzed in two ways; 1) bio-energetically and 2) epigenetically. Bioenergetic analysis of the mitochondria will be carried out using Mitochondrial ToxGlo™ assay (Promega), which will analyze

mitochondrial membrane integrity and cellular ATP production. Epigenetic analysis of chromatin structure will be analyzed in two ways. 1) Analysis of 85 epigenetic transcripts that regulate chromatin condensation and relaxation, using HumanEpigenetic Chromatin Modification Enzymes RT² Profiler™ PCR Array (Qiagen) and, 2) gene specific chromatin analysis using EPiQ™ Chromatin analysis kit (Bio-Rad). Genes that will be analyzed will include: synaptic genes, mitochondrial genes, epigenetic genes, genes associated with inflammation and disease specific genes. In addition to the molecular work, cellular localization of key epigenetic factors will be evaluated histochemically.

Proposed One-Year and Long-Term Outcomes: A one-year outcome will provide preliminary data for a subsequent RO1 application. Long-term outcomes include federal and external funding, and provide a possible novel therapy in the fight against Alzheimer's disease.

2012-2013 Progress: New Figure 1 (below) shows that sy5y cells treated with Abeta correlate with Alzheimer brain with a significance of 0.0019 with r=0.33. These arrays investigate enzymes responsible for modulating chromatin configuration. These data show that KAT6b (block D11 in both heat maps of Fig 1) emerges as a significant player in both AD brain and in Abeta treated cells. KAT6b is a histone lysineacetyltransferaseand, as such, plays a major role in chromatin structure by modulating histone acetylation.

New Figure 2 (below) shows that exposing Abeta treated sy5y cells with either compound A or compound B from S. Hecht at ASU reverses the effect of Abeta treatment toward an expression profile that more closely resembles vehicle treated cells. Both compound A and compound B are water soluble Co-enzyme Q analogues synthesized by S. Hecht.

Future Plans: We are preparing a manuscript describing these novel compounds and their effects for potential submission to PNAS. We will use these data as Preliminary Data for a submission to the Alzheimer Drug Discovery Foundation (due 5 June).

Figure 1

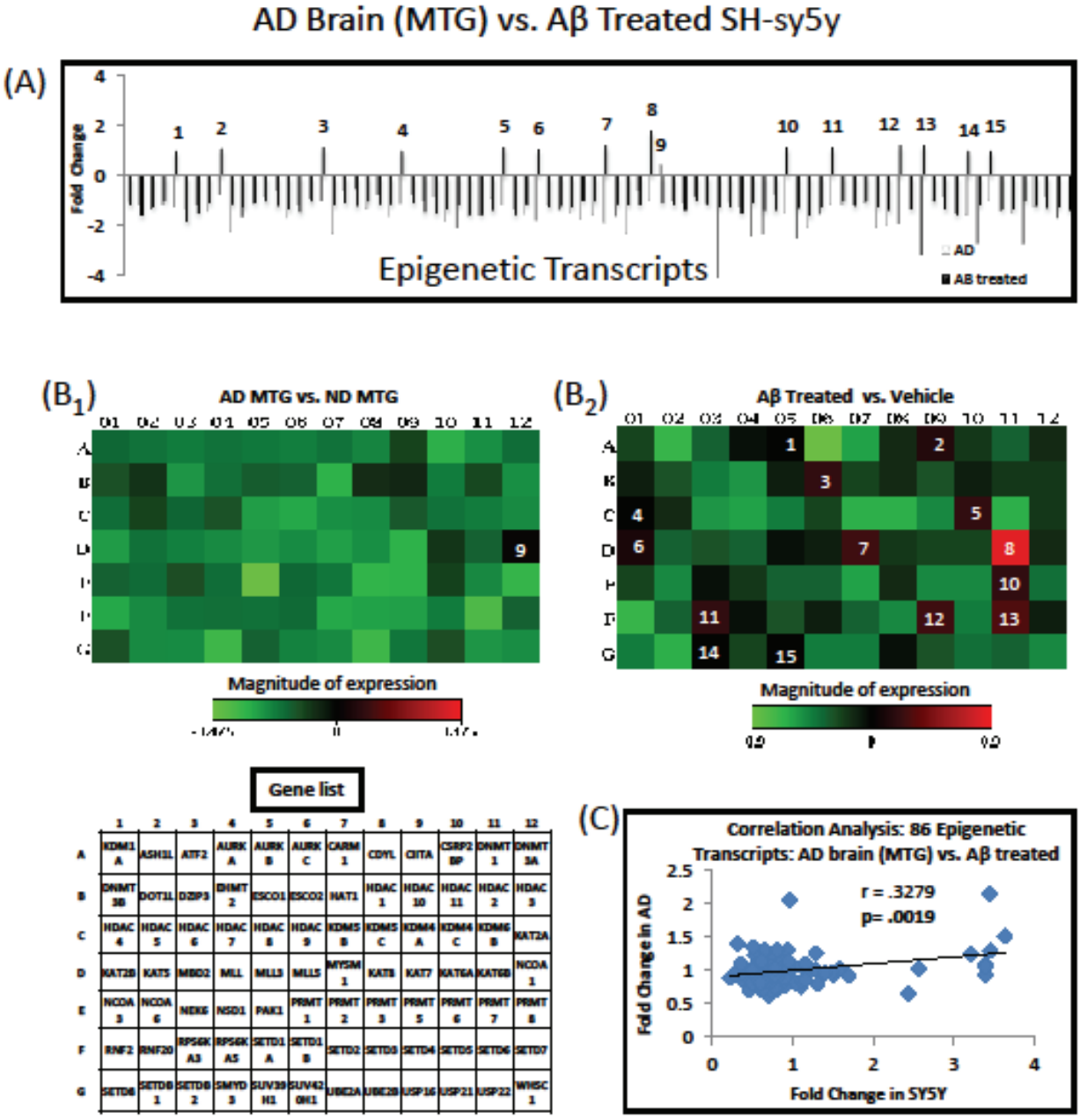
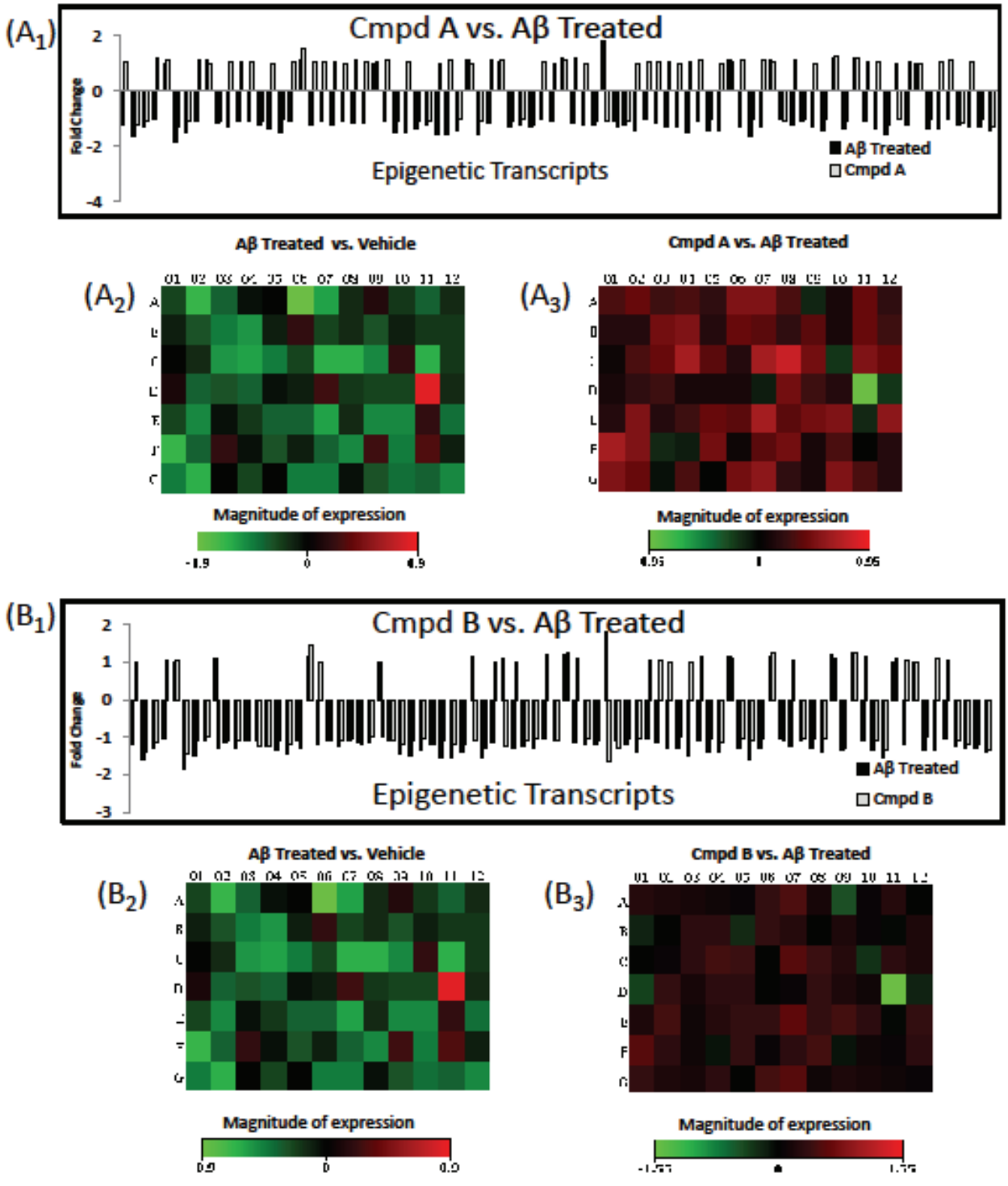

AD Brain (MTG) vs. Aβ Treated SH-sy5y
(A)
Fold Change
Epigenetic Transcripts
AD
AB treated
(B1)
AD MTG vs. ND MTG
Magnitude of expression
(B2)
Aβ Treated vs. Vehicle
Magnitude of expression
Gene list
(C)
Correlation Analysis: 86 Epigenetic Transcripts: AD brain (MTG) vs. Aβ treated
r = .3279
p= .0019
Fold Change in AD
Fold Change in SY5Y

Figure 2


(A1)
Cmpd A vs. Aβ Treated
Fold Change
2
0
-2
-4
Epigenetic Transcripts
Aβ Treated
Cmpd A
Aβ Treated vs. Vehicle
(A2)
Magnitude of expression
Cmpd A vs. Aβ Treated
(A3)
Magnitude of expression
(B1)
Cmpd B vs. Aβ Treated
Fold Change
2
1
0
-1
-2
-3
Epigenetic Transcripts
Aβ Treated
Cmpd B
Aβ Treated vs. Vehicle
(B2)
Magnitude of expression
Cmpd B vs. Aβ Treated
(B3)
Magnitude of expression

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Inflammatory role in insulin-signaling dysregulation in Alzheimer's disease and 3XTg-AD mice. Lih-Fen Lue, PhD. Banner Sun Health Research Institute.

Specific Aims: Aim 1: To characterize the differences in the expression profiles of inflammatory and insulin signaling pathways in diabetic Alzheimer's disease (AD) and non-diabetic AD brains. **Aim 2:** To model the interaction of inflammation and insulin signaling dysregulation in streptozotocin (STZ)-treated 3XTg-AD mice.

Background and Significance: Both type-2 diabetes mellitus (T2DM) and AD are leading causes for high morbidity and mortality in elderly population. Emerging evidence also indicated that these two diseases are risk factors for each other, which could be further compounded by another metabolic disorder, obesity, a risk factor for developing T2DM and cardiovascular diseases [1,8,12,15,18,21,22]. The incidence rates of these diseases are of great concerns. A lack of comprehensive preventive and intervention strategies for these interlinked diseases could lead to a severe crisis for the healthcare cost and patient care [9]. Regardless of recent research progress, the understanding of how these diseases interact mechanistically is still emerging. The major mechanisms through which T2DM may influence the pathogenesis of AD include insulin resistance, impaired insulin receptor (IR) and insulin growth factor (IGF) signaling, glucose toxicity, advanced glycation endproducts (AGE) and the receptor for advanced glycation endproducts (RAGE), cerebrovascular injury, peripheral vascular injuries and inflammation [4,6,7,12,19]. ***Although there have been studies characterizing AD pathology in AD with T2DM, whether T2DM enhances the severity of hallmark pathology in human postmortem brains remains controversial*** [2,3,5,16,20]. Furthermore, chronic inflammation is a shared feature in the pathogenic processes of AD and T2DM. ***It is currently unclear if the occurrence of peripheral inflammation is a contributing factor to central insulin-signaling dysregulation in AD***. Research to bridge these gaps in knowledge has potentials to facilitate the design and development of novel treatments which could be beneficial for the patients who develop both diseases.

Preliminary Data: To begin to address this issue, we first analyzed biochemically total expression levels of amyloid β (Aβ) and phosphorylated tau (ptau) in inferior temporal cortices of AD with T2DM (ADDM) and AD who were matched for the neuropathological diagnosis, last MMSE scores, age, and gender: **Aβ** Mean±S.E.): 1.64±0.25 from 16 AD; and 0.93±0.13 from 17 ADDM, $p<0.05$; **ptau** (Mean±S.E.): ***4.13±0.96*** from 16 AD, ***5.29±1.06*** from 17 ADDM, $p>0.05$. We also analyzed inflammatory markers and insulin receptor signaling molecules. The results showed significant increases in the expressions of inflammatory markers (astroglial activation marker, glial acidic fibrillar protein, GFAP) and toll like receptor (TLR) 2, when one way ANOVA was used to compare ADDM to AD, ND (non-demented controls) with and without T2DM. Negative associations between inflammation (ICAM1 and TLR2) and the level of phospho-insulin receptor substrate 1 (***p-IRS1***), a key component to initiate insulin receptor signaling, was also detected. Based on our preliminary findings, we propose to test the ***hypothesis*** that inflammation could contribute to insulin-signaling dysregulation in ADDM.

Experimental Design and Methods:

Aim 1: We will complete the measurements of insulin/insulin growth factor signaling in inferior temporal cortical samples from which we have already made significant progress, and a selected panel of the markers will be measured in an additional brain region known to develop low glucose use in AD detected by FDG-PET, cingulate gyrus. The T2DM cases are defined by receiving drug treatment specific for DM

from medical record of SHRI brain donor database and case selection will consult with our neuropathologist Dr. Beach. Various measurements will be performed according to our published ELISA and western blotting procedures [13,14].

Aim 2: Triple transgenic mice, 3XTg-AD, have been well characterized in their pathological development [17]. Hyperglycemic condition will be induced by i.p. injections of STZ and inflammation by lipopolysaccharides (LPS) using published methods [10,11]. Eight male 7-month old 3XTg-AD mice (Jackson Lab, shipped at 8 wk old and aged in SHRI facility) will be used in each group: vehicle control; STZ-alone, LPS-alone, and STZ and LPS combined treatments. Briefly, a single dose of STZ (50 mg/kg body wt) will be injected i.p. for 5 consecutive days. Blood glucose, insulin, and HbA1c will be monitored in tail-vein blood samples at various time points. Six weeks after hyperglycemic induction, LPS (0.5 mg/kg) will be i.p. injected once to mimic low degree inflammatory responses. Mice will be sacrificed at 9.5 months old to assess the effect of inflammation and STZ on insulin signaling, A□, ptau, and synaptic changes both biochemically and immunohistochemically.

Proposed One-Year and Long-Term Outcomes: The outcomes will advance the understanding of interactive mechanisms between inflammation, insulin signaling, A□, and ptau which can lead us to a strong position to apply for NIH-RO1 grant funding; of which we plan to include micro-PET imaging and treatment tests.

2012-2013 Progress:

Specific Aims: Aim 1: To characterize the differences in the expression profiles of inflammatory and insulin signaling pathways in diabetic Alzheimer's disease (AD) and non-diabetic AD brains.

We have obtained brain tissues in a total of 57 autopsy cases from the Banner Sun Health Research Institute brain bank. The cases were selected according to neuropathological criteria for the diagnosis of Alzheimer's disease (AD) and the medical documentation of the diagnosis of diabetes mellitus type II (DM). Classified by these criteria, the cases that we have received were divided into AD (without DM), ADDM, ND (non-demented controls without DM), and NDDM (non-demented controls with DM). The following table shows the mean and standard error (SEM) and the number of the cases (N) under each disease category in the features of age at autopsy, postmortem delay, total plaque scores, total tangle scores, temporal cortical scores, temporal tangle scores, cerebral amyloid (CAA) scores, and Braak scores.

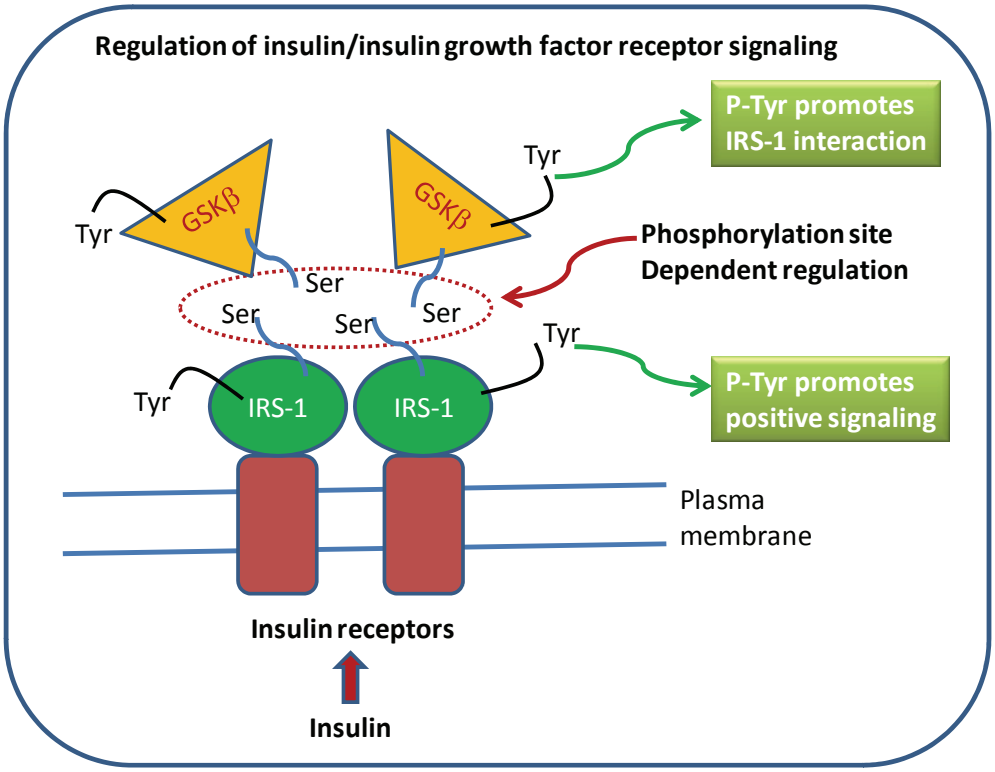
Table 1. Demographic summary of the autopsy cases used in this study

	diseases											
	AD			ADDM			ND			NDDM		
	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM
Age at death (years)	16	81.937	1.9610	17	84.882	1.3281	12	80.917	3.4344	12	78.000	2.5436
Postmortem interval (hrs)	16	3.195	0.1958	17	3.135	0.2079	12	3.353	0.3992	12	2.610	0.1537
Total plaque scores	16	14.344	0.3498	17	13.574	0.4167	12	0.250	0.1443	12	1.417	0.7226
Total tangle scores	16	13.875	0.4390	17	13.029	0.8095	12	4.083	0.7829	12	2.792	0.7189
Temporal cortical plaque scores	16	2.969	0.03125	17	2.882	0.05302	12	0.167	0.09401	12	0.375	0.2053
Temporal cortical tangle scores	16	2.875	0.08539	16	2.625	0.2213	12	0.458	0.1893	12	0.208	0.09650
Temporal cortex CAA scores	15	1.000	0.2928	17	0.353	0.1471	12	0.000	0.0000	12	0.167	0.1124
Braak Scores	16	5.437	0.1281	17	5.235	0.2016	12	2.833	0.3445	12	2.167	0.3658

The brain tissues from both temporal cortex and cingulate cortex were processed and subjected to analysis according to our original experimental design which aimed for insulin receptor signaling molecules, AD pathological changes, inflammation, and neurodegeneration markers: insulin receptor/ insulin growth factor signaling (IRS-1, phospho-IRS-1, insulin growth factor receptor, GSK-3beta, and phospho-GSK3beta), inflammation (glial acidic fibrillary protein, toll-like receptor, and mitochondrial 18kD translocator protein, and , AD pathological changes (Abeta, and phosphorylated tau), inflammation (astrocyte activation marker glial fibrillary acidic protein, microglial activation toll-like receptor), and neuronal degeneration (synaptic proteins, synaptophysin, PSD90).

First, we focused on the insulin signaling protein IRS-1 because this is a crucial molecule that has multi-facet effects on insulin/insulin growth factor receptor signaling determined by its phosphorylation activities: phosphorylations on Serine/Threonine residues lead to negative signaling, whereas phosphorylation on Tyrosine residue leads to positive signaling. We also investigated the final enzyme that catalyzes the synthesis of glycogen, glycogen synthase kinase (GSK) beta 3, a serine/threonine phosphorylation kinase. Nevertheless, the phosphorylation on different residues on GSK beta kinase itself could lead to changes in the kinase-substrate binding ability, through which the GSK beta kinase activity can be regulated. For examples, the phosphorylation of serine residue 9 of GSK beta molecule decrease binding site activity, leading to inhibition of the downstream targets. GSK beta 3 can phosphorylate IRS-1. In the following illustration, we showed the concept of the phosphorylation site dependent regulation of insulin receptor-signaling. IRS-1 is a necessary molecule for intracellular propagation of insulin

signaling. When tyrosine residues are phosphorylated, a positive signaling is induced. When serine/threonine (denoted by "ser") residues are phosphorylated, a negative signaling is induced. IRS-1 has many phosphorylation sites, and kinases responsible for phosphorylation. One of them is GSK beta 3. However, GSK beta 3 activity is also phosphorylation site-dependent. Tyrosine-phosphorylation on GSK beta 3 increases substrate binding whereas serine residue phosphorylation reduces the binding with substrate such as IRS-1. Through these mechanisms, insulin signaling could be regulated.



We have analyzed these key molecules in human brain tissues and cultured human adult astrocytes. In the experimental system of cell cultures, we sought to determine how inflammatory cytokines affected the phosphorylation of the serine/threonine on IRS-1 and GSK beta 3 on serine 9. We have obtained a large set of the data from human brain tissues which are currently being analyzed.

Based on our results from the study of postmortem brain tissues, astrocyte activation was increased in the AD cases with DM. To begin to determine how inflammatory stimuli change astrocyte response to glucose and insulin fluctuation, a series of experiments in cultured human astrocytes were conducted. First, cells were exposed to glucose concentrations at normal and high levels (low, normal, and high glucose) for short (24 hrs) and long (72 hrs) period of time with the treatments of IL1 beta and TNF alpha, inflammatory cytokines that could induce insulin resistance. The increases in these inflammatory cytokines in the AD pathological brain region have also been well documented in previous literature. Cells were lyzed when the experiments were terminated, and cell lysate were collected and analyzed by western blot to detect the insulin/insulin growth factor receptors signaling molecules such as IRS-1 and IRS-1 kinase, GSK beta 3.

We first summarized the findings from IL-1 beta treatment in astrocytes. IL-1beta significantly increased the levels of phosphor-IRS-1 in normal glucose containing medium at 24 hrs. However, IL-1 beta effects significantly reduced the ratio of p-IRS-1 to t-IRS-1 in 72 hours treatment and in normal glucose medium. The reduction of this ratio was due to a significant increase in the level of total IRS-1 without increasing the phosphor-IRS-1. This means that IL-1 beta treatment could increase the

availability of IRS-1 as the kinase substrate in 72 hours experiment. Whether IL-1 beta changed the ability of GSK beta to act on its substrate was measured by the availability of the phosphor-GSK beta 3 (serine 9) in the same cell lysates. The lower the amount of phosphor-GSK beta 3 (serine 9), the higher the chances for GSK beta 3 to be phosphorylated at tyrosine residue; which could in turn increase the kinase interaction with IRS-1. The results showed that at 72 hour IL-1 beta did not affect either total GSK beta 3 or phosphorylated GSK beta 3 in normal glucose medium. Nevertheless, in the short-term treatment (24 hrs), IL-1 beta significantly increased the amount of phosphor-GSK beta 3 without increasing the total levels of GSK beta 3. This could still have potentials to exert negative effects on the ability of GSKbeta 3 to interact with IRS-1. Thus, 24 hrs treatment IL-1 beta could indirectly facilitating tyrosine phosphorylation on IRS-1 protein, thus leading to insulin signaling. In summary, IL-1 beta caused treatment time-dependent differential effects in IRS-1 and GSK beta 3 in normal glucose containing medium.

We also examined the effects of TNF-alpha. Our results showed that TNF-alpha did not affect all of the measures in IRS-1 system regardless of glucose concentrations in the medium and duration of treatment time. When GSK beta 3 proteins were analyzed, we found that TNF alpha induced significantly both the amount of phosphorylated GSK beta 3 and the ratio in 24 hrs treatment in normal glucose medium. This result suggested that TNF alpha could also facilitate insulin signaling by increasing the chance to phosphorylating tyrosine on IRS-1. This is due to increases in phosphorylation of GSK beta 3 at serine 9 would reduce its binding with IRS-1 as kinase substrate, which would then increase the chance for IRS-1 to be phosphorylated at tyrosine.

In summary (Table 2), our findings demonstrated that inflammatory and insulin resistance inducing cytokines such as IL-1 beta and TNF alpha could cause disturbance in the insulin signaling regulation in astrocytes. These cytokines are also known to change astrocyte activation states through autocrine and paracrine mechanisms. Therefore, we proposed that inflammation in AD could lead to abnormal regulation of insulin signaling. These results have been written as an abstract to submit to 2013 AARC annual conference.

Table 2. Summary of the biochemical findings in human astrocytes

Normal glucose medium	**IL-1 beta**		**TNF alpha**	
	24 hr	**72 hr**	**24 hr**	**72 hr**
IRS-1	Increased p-IRS1	Increased the ratio of p-IRS-1 to t-IRS-1	No effects	No effects
GSK-beta 3	Increased p-GSK beta 3	No effects	Increased p-GSK-beta 3; and ratio of p-GSK beta 3 to t-GSK-beta 3	No effects

Aim 2: To model the interaction of inflammation and insulin signaling dysregulation in streptozotocin (STZ)-treated 3XTg-AD mice.

We have purchased 100 of 2 months old male 3XTg-AD mice. Due to a delay in the processing of the order, the mice arrived 3 months later after our originally anticipated date. Currently, these mice are housed and aging in the animal facility of Banner Sun Health Research Institute. There were 4 accidental death without apparent bite, fight, or illness. The experiment will be conducted when the mice are at 7 months following the experimental design described in the IACUC approved protocol and the funded grant proposal. We plan to complete the experiments and obtained the data by the end of September.

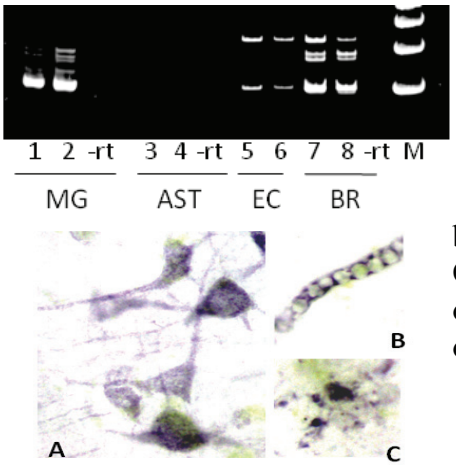
ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Studies of CD33, a new genetic risk factor for Alzheimer's Disease, in human brain. Douglas Walker, PhD. Banner Sun Health Research Institute.

Specific Aims: **Aim 1**. To correlate CD33 disease risk polymorphism with a) Alzheimer's disease pathology and b) CD33 mRNA, protein and cellular localization in brain tissue samples. **Aim 2**. To determine whether CD33 disease risk polymorphism affects human microglia responses to Aβ.

Background and Significance: CD33 (also known as Siglec-3) is considered a myeloid cell specific marker having as its primary function to mediate anti-inflammatory signaling (Crocker et al, 2012; Gonzalez et al, 2012). This membrane protein contains an immunoreceptor tyrosine-based inhibitory motif whose activation with sialic acid-modified ligands inhibits cytokine production. It also can function as an endocytic receptor for sialic acid-modified ligands. Recently, genome wide association studies have associated a polymorphism in CD33 with increased risk of Alzheimer's disease (AD) (Carrasquillo et al, 2011;Hollingworth et al, 2011;Naj et al, 2011). CD33 is located on chromosome 19, where the major AD risk factor gene apolipoprotein E (apoE) is located. The polymorphism (rs38654444) resulting in a C/A substitution is located 373 bp upstream from the closest exon of CD33. The minor allele A polymorphism is present at a frequency of 23.8% in all ethnic groups sampled with up to 35% in some Caucasian populations [11], and 30% in the population studied in report [3]. Although two other Siglec genes map in this vicinity, as they are 71,179 bp and 94,396 bp distant (Carrasquillo et al, 2011) from this polymorphism, it is likely that CD33 is the gene affected. In recent years, a number of new AD polymorphisms besides CD33 have been identified, including ABCA7, BIN1, CD2AP, CLU, CR1, EPHA1, MS4A4E/MS4A6A, and PICALM, that have been associated with increased risk of AD. At present, the biological properties of the products of these genes now need to be studied to determine how they might be involved with AD. We will focus on CD33 and the risk polymorphism because of its properties as an anti-inflammatory mediator, which fits with our long-standing interest in inflammatory regulatory molecules in AD brains, such as CD200 and suppressor of cytokine signaling proteins (SOCS) (Walker et al, 2009b). It is known that CD33 can be regulated by SOCS-3 (Orr et al, 2007). How much of a risk factor to AD is possession of the CD33 polymorphism requires further study in combination with other genetic risk factors, but since there is nothing known about CD33 function in human brain, our proposed studies are significant due to an urgent need to understand **any** new potential molecular target in AD. A review article published this week highlights the need for studies looking at the effects of polymorphisms/mutations on AD neuropathology calling them "*new era of neurodegenerative research*" [12].

Preliminary Data: We have already made some significant discoveries about CD33 expression in preliminary studies. It has been stated that Siglec-11 is the only molecule of this class expressed by microglia (Wang and Neumann 2010). This is not true as we demonstrate CD33 mRNA expression by cultured microglia (MG) and brain vascular endothelial cells (EC), but not by astrocytes. Expression of multiple forms of CD33 mRNA in human brain (Br) is also seen (Top figure). The multiple bands are consistent with known transcript variants of CD33 (Perez-Oliva et al, 2011). The figure represents results of PCR amplification of cDNA derived from the indicated sources. We also made the novel observation of CD33 immunoreactive neurons in human brain sections



(lower figure, panel A), but only in the control cases. There were also endothelial cells (B) and microglia (C) showing CD33 immunoreactivity in these sections. The microglia cluster shown represents a group of cells also immunoreactive for CD14. As CD22 (Siglec-2), a molecule closely related to CD33 and with similar function, can be expressed by neurons (Mott et al, 2004), there is precedent for our finding of CD33 neuronal expression.

Hypothesis: We will examine the hypothesis that the CD33 risk polymorphism will result in enhanced levels of AD pathology in tissues, and enhanced response to Aβ *in vitro* as a result of lower expression of CD33. We also hypothesize that CD33 levels will be lower in AD affected brain tissue.

Experimental Design and Methods:

Aim 1. We will select 25 cases of neurologically normal controls and 25 Alzheimer's disease(AD) cases for study. These age-, gender- and apoE-matched cases will have been diagnosed by our neuropathologist and will either contain 25 non-demented control cases with limited AD-like pathology or 25 cases with severe AD pathology and a history of dementia. As the scale of this project is limited, only one brain region will be studied (inferior temporal cortex). From tissue, we will prepare DNA, RNA and protein extracts for biochemical measurements, and tissue sections for immunostaining with antibodies to CD33, Aβ, phosphorylated tau, HLA-DR to define activated microglia and GFAP to identify reactive astrocytes. DNA from these cases will be amplified with gene specific primers for the region of the CD33 polymorphism rs3865444. The amplified DNA will be sequenced by Retrogen Inc (CA) to identify the polymorphism. From these matched cases, RNA will be used in real time PCR measurements of CD33 mRNA expression and protein levels will be quantified by western blots [6]. Tissue sections from each case will be stained by immunohistochemistry to identify cellular localization of CD33 in relation to AD pathology, including activated microglia. We will correlate CD33 polymorphism with AD status and degree of AD pathology in this series of neuropathologically and clinically confirmed cases. We will also correlate levels of expression of CD33 mRNA and protein with disease state, degree of pathology and cellular expression patterns. In particular, we will be able to answer the question whether CD33 expression in an AD affected brain region is affected by the CD33 polymorphism.

Data Analysis and Expected Outcomes: Data will be analyzed for presence and absence of AD status and for features of AD pathology with CD33 polymorphism by two-way Analysis of Variance (ANOVA). Correlation analysis will be carried out to determine how CD33 expression levels affects features of AD pathology (plaques, tangles, microglia scores) across disease categories. Our hypothesis expects disease risk polymorphism and AD status will be associated with lower levels of CD33 expression.

Aim 2. To address the question how the rs3865444 CD33 polymorphism affects functional microglia responses, we will use microglia isolated from at least 12 human cases using our established techniques of culturing these cells directly from human postmortem brains (Walker et al, 2009a). As shown in preliminary studies, we can readily detect CD33 mRNA expression in isolated microglia. Based on current work, this number of cultures is achievable during a one-year time period. These microglia cultures will be from either elderly neurologically normal cases or AD cases; based on the allelic frequency of the rs3865444 polymorphism, we can expect both to be present in this series. As CD33 is an immune regulatory molecule, this aim will be informative of its role in AD inflammation. Each case will be genotyped for apoE and CD33 polymorphism. To determine how this CD33 polymorphism affects responses to Aβ, cultures will be stimulated with 2 doses of aggregated Aβ42 (0.5 μM and 2 μM) for 24 and 48 hours. Two outcomes will be measured, firstly how microglia respond to Aβ in terms of degree of inflammatory activation, and secondly how microglia interact and process/degrade Aβ. Both experiments can be carried out on the same set of cultures. The media from stimulated cultures will be assayed for IL-1β, TNF-α, IL-10 and IL-18 by ELISA to determine how the inflammatory responses are affected by CD33 polymorphism and level of CD33 protein. As CD33 has been suggested also to be an endocytic

receptor, protein extracts from the microglia cultures will be used to measure CD33 protein in control and Aβ stimulated cultures, and to measure Aβ levels and breakdown fragments to correlate CD33 polymorphism and protein levels with uptake and degradation of Aβ.

Data Analysis and Expected Outcomes: Data will be analyzed by two-way ANOVA with CD33 polymorphism as one independent variable and Aβ stimulation as the other. We will be able to show whether CD33 polymorphism affects responses to Aβ, CD33 expression levels and how they affect Aβ uptake and degradation. We hypothesize that either disease polymorphism or Aβ stimulation will reduce CD33 levels resulting in enhanced inflammatory responses. We need to consider whether apoE genotype of the cases used for isolation has an effect on these parameters. We and others have shown higher levels of inflammatory activation with possession of apoE4. We will be able to measure how the two measures interact.

Proposed One-Year and Long-Term Outcomes: This project has both short and long term potential to address issues important to understanding Alzheimer's disease, namely the functioning of proteins expressed by risk-associated genes and their effect on pathology and inflammation. By the end of one year of funding, we will know if the CD33 polymorphism affects features of this protein in human AD brains, and in brain derived microglia. In aim 1, the number of cases should be large enough to detect disease related statistical significance. In aim 2, if the number of cases is too small for statistical analysis, this aim will give valuable pilot information for power analysis for a larger study. Even if an effect of CD33 polymorphism on AD pathology is unresolved, we will have a greater understanding of CD33 in human brain, in inflammation, and also define how CD33 expression in neurons is involved in AD. As these studies are highly innovative and potentially significant, the results obtained will be suitable pilot data for a request for federal funding.

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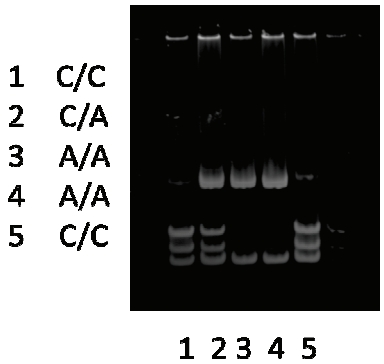
Progress Report

Goal: The goal of this project is to understand the role of CD33 in the AD brain using the CD33 single nucleotide polymorphism (SNP) rs38654444 as a variable to categorize the human brain and microglia cases being studied. This SNP is present in a non-coding sequence adjacent to the CD33 gene. Possession of the A polymorphism has been shown to be a moderate increased risk factor for AD. CD33 has been characterized as an anti-inflammatory receptor that can control inflammation if it engages the appropriate sialic acid containing ligand. Although this SNP as a risk factor for AD is moderate, its association has been repeatedly shown to be statistically significant in most published studies. However, the role of CD33 in human brain has never been studied, nor its expression in human microglia. So the potential outcome of this project is to understand how, if CD33 is a risk factor for AD and a known anti inflammatory protein, CD33 expression changes with expression of the rs38654444 polymorphism and whether this affects AD pathology. We have hypothesized that decreased expression of CD33 would result in less control of inflammation and therefore might contribute to enhanced AD pathology.

Modifications to project: It was initially proposed to carry out the CD33 rs38654444 genotyping using a contract sequencing service. However, we have developed a simple and cheap method in the laboratory utilizing restriction endonuclease polymorphism. PCR amplification of genomic DNA from our collection of neuropathologically diagnosed cases using primers that amplify a region that spans the genomic sequence of rs38654444 with digestion with the restriction endonuclease **NlaIII** results in a DNA fragment pattern that can be used to distinguish between the C/C, C/A and A/A forms of this polymorphism. An example of the gel pattern is shown below. The cases selected for study were a larger series than initially proposed (this was possible due to the cost saving on the genotyping) and were separated into non-demented (ND) cases (with or without an apoE ε4 allele) and AD cases (with or without an apoE ε4 allele). For this initial pass, we excluded the cases that had two apoE ε4 alleles as there were no ND cases for comparison, and also this genotype has such a strong effect on AD pathology to likely overshadow any effect of this CD33 risk polymorphism. Another criteria for inclusion in the study was that there is brain tissue available for protein studies and mRNA studies.



Due to the cost saving on CD33 genotyping, we decided to use the DNA samples selected above for screening for another newly discovered single nucleotide polymorphism (SNP) (mutation) rs75932628 in the gene of triggering receptor expressed on myeloid cell (TREM)-2. Possession of this SNP has also

been shown to be associated with increased risk of AD. Both CD33 and TREM-2, the proteins encoded by these genes have similar properties as anti-inflammatory receptors. Activation of TREM-2, similar to CD33, results in induction of anti-inflammatory signaling through a common protein called DAP12. We developed a restriction endonuclease fragment length polymorphism (RFLP) technique for the rs75932628 SNP. In this case, the presence of the TREM-2 risk polymorphism resulted in loss of DNA cleavage by the enzyme **Hha I**. These results will be discussed below.

Research Results

CD33

a) Presence of the AD risk rs3465444 CD33 polymorphism in a series of human brains with available neuropathological diagnoses

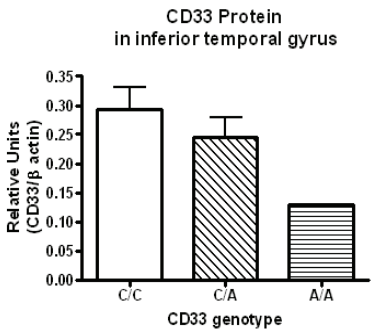
Table 1

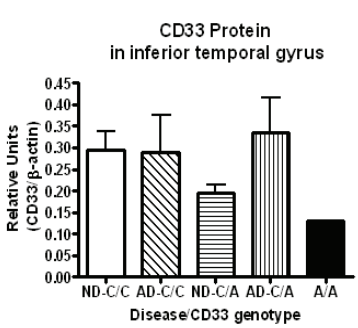
	ND (n=37)			AD (n=46)		
	C/C	**C/A**	**A/A**	**C/C**	**C/A**	**A/A**
% of Cases	**48.7**	**32.4**	**18.9**	**36.9**	**54.4**	**8.7**

These results shown in Table 1 in our studied population showed some interesting trends. Firstly, the C/A genotype was more represented in the C/A group in the AD cases as expected, though surprisingly, the higher risk A/A genotype was underrepresented. Alteration in the genotype distribution did not reach statistical significance, but we have the opportunity of adding additional cases to the study. One of the problems has been getting sufficient power for these analyses as we have not only had to divide them into 2 disease groups, but each disease group has three genotype groups (total 6). Initial estimations of numbers of cases to be studied appears to have been underestimated, so we propose to expand the number of cases so that we can assess the role of apoE ε4 allele on disease presentation and CD33 polymorphism. We particularly need a greater number of cases with A/A genotype, as at present the numbers are small (11 out of 83 cases). A/A represents the genotype with enhanced AD risk, but our data has shown higher representation in the ND cases. This raised the critical issue of how CD33 rs3865444 polymorphism affected levels of AD pathology.

Further analysis was carried out for the presence of Alzheimer's pathology in the ND group using data obtained from the BSHRI neuropathology department. As these cases were all from aged subjects, a certain amount of plaque and tangle pathology can be present. We restricted our study to the elderly ND group, as many of these cases could be considered as possible pre-AD. Our analyses indicated that the A/A ND group had approximately 50% higher plaque load than the C/A group, but with identical load of tangles. This finding is consistent with our hypothesis that A/A genotype will result in enhanced AD pathology. This difference did not reach statistical significance but indicates that larger numbers of cases are needed for this study. The incidence of A/A genotype in our patient population has been less than expected.

b) Does CD33 genotype affect expression of CD33 protein in human brains?

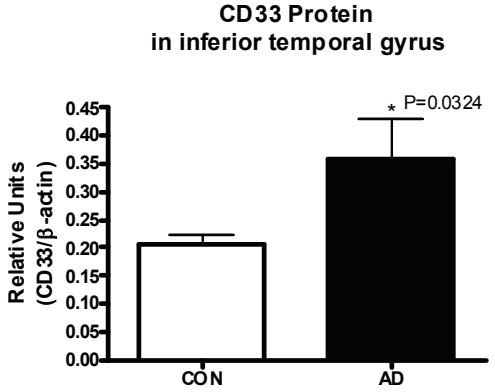




Our results are preliminary but as presented below, there is an indication of a trend for differential expression of CD33 in inferior temporal gyrus, an AD affected brain region with

CD33 genotype. The left hand figure showed the combined result of all cases studied and separated according to CD33 rs3865444 polymorphism. The right hand figure showed that there was a difference in expression with C/A genotype between control and AD cases, but not with C/C genotype. These results do not have statistical difference at present, and further cases will be added to the study. As in the section above, it is clear that a larger number of genotyped cases are needed for these protein studies. The group used for western blot detection of CD33 in human brains represented a subset of those screened in the preceding section. At present, we had only a single A/A case for protein analysis. In this protein study, the single A/A genotype case was from an AD subject. This is the first documentation of CD33 expression in human brains, so this result is significant in itself.

c) Are levels of CD33 in inferior temporal gyrus affected by AD pathology?



Using the above series of cases, we also addressed the question of whether CD33 protein level, irrespective of genotype, was altered with the presence of AD pathology. The adjacent figure shows that there was a significantly increased amount of CD33 protein in the AD brains. This is a novel finding and suggestive that inflammatory events ongoing in the AD brain, generally assumed to be classical inflammatory activation, results in increased levels of CD33, probably as a control mechanism. This is the rationale for studying CD33 in human microglia at the cellular and molecular level.

d) CD33 expression by human microglia

We have prepared materials from 6 different human microglia cases for studying regulation of CD33. Cells were isolated from human brains and grown according to our standard protocols. We have stimulated these cells with relevant cytokines or with A□peptide and will measure the expression of CD33 mRNA and protein as proposed in Aim 2. These 6 cases have not been CD33 or apoE genotyped as yet, but this will be completed in the near future. We are hoping for an additional 6 cases of microglia to complete this study during this last 4 month period. To address the hypothesis, we need to be able to work with microglia from CD33 A/A cases, but these cases are proving rarer than expected. In addition, we do have RNA and protein samples from more than 30 microglia cases that were stimulated with the above listed reagents; these were collected during the course of other projects. These cases will be reviewed to determine if they can be used for this study. DNA can be obtained for genotyping any of these previous cases.

At present, we have confirmed CD33 mRNA expression by human microglia and by human vascular endothelial cells. This is a novel finding and can be reported.

e) Identification of AD case with TREM-2 rs75932628 polymorphism

Using the above listed DNA samples from ND and AD cases, we also screened them for the TREM-2 rs75932628 polymorphism. As this C/T polymorphism results in an amino acid substitution of histidine for arginine, it could be considered as a mutation. One positive AD case, out of 52 screened had a single copy of the R47H substitution. This case was an 87 year old male with AD and a single allele for apoE ε4. Tissue is available from this case for protein and mRNA studies. Although other SNPs for TREM-2 that are associated with AD have been identified, the increased risk for this rs75932628 polymorphism is the most significant. We also screened 64 ND cases and found no positive cases for this polymorphism in this non-AD group.

Plan for Completion of Study: To complete this project, we plan to screen further cases, in particular to identify subjects with A/A mutation. Our original estimation of numbers of cases needed for Aim 1 was too low. As we have collected sufficient numbers of human microglia cases to address Aim 2, this will be initiated. We will determine how CD33 expression and function is regulated in microglia and whether the rs3865444 risk genotypes affect levels of expression and function of CD33 in these critical cells. These analyses should be completed over the next 3-4 months.

Outcome of Project: The potential for this project is to establish CD33 rs38654444 polymorphism as a functional risk factor for AD, and demonstrate its involvement in AD pathological processes, as well as demonstrate what functions CD33 might be having in human brains or in human microglia. These outcomes if positive should form the basis for application for further funding as it will demonstrate the rationale for mechanistic studies of translational significance.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Investigation of the methylation of APP in Aging and Late-Onset Alzheimer's disease Brain. Andrew Grover, PhD, Alex Roher, MD, Paul Coleman, PhD. Banner Sun Health Research Institute.

Specific Aims: It is our aim to demonstrate that the APP molecule, and possibly its proteolytic fragments, are methylated at lysine and/or arginine residues, and identify whether methylation levels of these peptides are altered in LOAD.

Background/Significance: For more than 20 years the amyloid cascade hypothesis has formed a central part of our understanding of the etiology of LOAD. Formation of Aβ requires one of two potential cleavage events of APP. The α-secretase ADAM10 cleaves APP after K686 to release sAPPα peptide, whereas BACE1cleavage after M670 releases the 16-amino acid shorter sAPPβ peptide. The remaining membrane bound C-terminal fragment (CTF), is then cleaved by γ–secretase to release either P3 or Aβ. Therefore the events that determine whether ADAM10 or BACE1 cleaves APP determine whether or not Aβ is produced. Given that there is a significant increase in Aβ production in LOAD the factors that influence this are critical to the etiology of LOAD.

Post-translational modifications of APP have been identified including N- and O-glycosylation, and phosphorylation, and there is some evidence that post-translational modifications can alter APP processing.

Protein methylation is a post-translational modification that has recently been examined in the context of LOAD. Recent studies have shown that methylation changes in LOAD influence function of the Tau protein phosphatase PP2A and abnormally methylated Tau protein has been isolated from the paired helical filaments of LOAD tangles. This may be linked to the accumulation of methyltransferases inhibitor S-adenosylhomocysteine (SAH) in the brain tissue of LOAD cases relative to cognitively normal controls. Also, multiple families of lysine- and arginine-specific methyltransferases, and demethylases, expressed in brain cells and tissue show altered expression in microarray profiling studies of neurons from cognitively normal and LOAD brain.

No reports of methylation regulating APP proteolysis have been published to date, particularly in the context of aging and LOAD. Within APP, Lysine residues occur near the β-secretase cleavage site and at the α-secretase cleavage site, conveniently positioned to regulate these events. It is tempting to hypothesize that these cleavage events could be regulated through methylation. As preliminary data we showed a Western blot (WB) of lysine- and arginine-methylated proteins isolated from brain cell lysate by immunoprecipitation (IP). Probing the blot with anti-APP antibody showed the presence of a band at ~110 kDa, the correct size for APP, representing the first evidence that APP might indeed be post-translationally methylated. It is our aim to demonstrate that the APP molecule, and possibly its proteolytic fragments, are methylated at lysine and/or arginine residues, and identify whether methylation levels of these peptides are altered in LOAD.

2012-2013 Progress: As previously described, our initial experiment identified APP by WB in a pool of methylated proteins isolated from human brain lysate by IP. We have now determined that APP isolated by IP from human brain lysate is immunoreactive for methylated lysine residues, confirming the preliminary data in the pilot application and demonstrating that this post-translational modification of APP can be detected by IP in both directions. Preparation of the brain tissue lysates required for this project is in progress and these experiments should be completed before the end of the period covered by this award. However, a number of technical aspects have had to be addressed in order to optimize IP of the APP fragments as proposed in this Aim.

1) The anti-APP antibody (Clone 22C11) proposed for IP of the N-terminal APP peptides was unsuitable for this purpose due to 3^{ary} structure of APP in its native state, as were the other commercially available antibodies tested. Antibodies raised against the APP C-terminal fragment (CTF) captured the full length holoprotein, in addition to the CTF, but not the sAPP fragments which represent an important fraction of the APP peptide population. We have now obtained a suitable antibody tested for this purpose, from an overseas collaborator, which will be employed to capture all the sAPP/holoprotein peptides by IP from brain lysates to test for lysine and arginine methylation levels as proposed.

We should note that confirmation of APP methylation status was obtained by probing WB of CTF IPs from brain lysates with anti-methyl Lysine. Therefore the holoprotein of APP at least is lysine-methylated; methylation of sAPP will be confirmed by completion of this experiment.

2) For the Aβ and CTF IPs we have been able to perform both efficiently in brain lysate. However, signal from probing with anti-methyl Lysine and Arginine antibodies has not indicated the presence of methylation of these fragments. It is conceivable that the methylation signal from these short fragments is weaker due to fewer methylation sites per molecule. In addition, we have not yet tested methylation levels of Formic-Acid extracted Aβ, which has not yet been performed, but which will be necessary to determine methylation levels of aggregated Aβ.

Finally, the data generated to date will be used as preliminary results in a grant application to the Alzheimer's Association, which will be followed up by applications to additional funding agencies, and may also be sufficient for an initial manuscript in support of these grant applications.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

White Matter Alterations Associated with Presenilin Mutations. Alex E. Roher, MD, PhD.
Longtine Center for Neurodegenerative Biochemistry, Banner Sun Health Research Institute

Project Description: Mutations in the presenilin (PS) genes are associated with early-onset dementia known as familial Alzheimer's disease (FAD). We propose to investigate the biochemical profile of the white matter (WM) in individuals that carry PS1 and PS2 mutations.

Specific Aims: Our objective is to characterize and quantify key markers of WM structural integrity and function in 10 PS1 mutations: E280A, A79V, A260V, F105L, Y115C, A431E, V261F, V261I, M146L, P264L as well as one PS2 mutation: N141I. The PS subjects will be compared to 4 sporadic AD (SAD) and 4 non-demented control (NDC) age-matched cases to assess the deviations between pathology and normal aging.

The molecules to be investigated will comprise those associated with myelin (myelin basic protein, proteolipid protein, 2'3'-cyclic nucleotide 3'-phosphodiesterase) and with fast and slow axonal transports (dynein, dynactin, kinesin, α-tubulin, β-tubulin, tau, neurofilaments (NF): NF-light, NF-medium, NF-heavy) and structural proteins (actin, myosin, glial fibrillary acidic protein). Molecules associated with acute phase responses, including full length and C-terminal amyloid-beta precursor protein (APP) peptides, amyloid-beta (Aβ), α-synuclein and apolipoprotein E (ApoE), will also be examined. In addition, 2-dimensional difference gel electrophoresis (2D-DIGE) proteomics will be implemented to identify other molecules that are altered in the WM among PS subjects and to compare them to SAD and NDC cases.

Background and Significance: Although ground-breaking prospective studies utilizing a PS carrier population are underway, very little is known about the natural history, pathophysiology and intrinsic variability of these autosomal dominant mutations that lead to FAD. In addition, few comparative studies of human PS mutation biochemistry have been conducted. Presenilin mutations confer substantial phenotypic variability on brain biochemistry [1,2] and have profound variable effects on clinical outcomes [3-5], suggesting a possible diversity in responses to immunotherapy or other disease-modifying treatments. Furthermore, this potential variability suggests that analysis of therapeutic outcomes in FAD cases needs to be done on individual bases. This diversity is expected from a molecular complex (γ-secretase) that plays a pivotal role in membrane-bound protein degradation and, more important, in the generation of multiple transcription factors that modulate the expression of multiple genes that dictate survival and adaptability. Presenilin/γ-secretase has been found to mediate proteolytic cleavage of ~90 different substrates [6]. To date, 197 PS1 and 25 PS2 mutations have been discovered (http://www.molgen.ua.ac.be/ADMutations), the vast majority resulting in deleterious phenotypes.

Presenilins are indispensible for the embryonic and fetal development since they are essential for neurogenesis [7-9], somitogenesis [10,11], angiogenesis [12] and cardiac morphogenesis [13]. The constraints imposed by natural selection upon the γ-secretase are enormous since no living cases of homozygous PS-mutated individuals are known. A PubMed search for the topic of "presenilin and white matter" yielded about 40 articles, many of them related to transgenic mice, while the subject of "presenilin mutations" alone produced over 2100 entries. At present, there is a debate on whether PS mutations express a gain of function or a loss of function [14,15]. Some limited information exists about the involvement of some PS on dysfunctional axonal transport [16-19] and MRI abnormalities [20-25]. However, there is no information related to a comprehensive and systematic molecular investigation of human WM in the context of PS mutations as we propose.

Our study will contribute toward a comprehensive understanding of the molecular pathological alterations associated with an array of PS mutations. These mutations are known to exert profound consequential effects on the WM [20-24,26]. Although comparatively neglected by AD investigators, the WM is both indispensable to healthy cognitive function and dramatically impacted during the course of dementia. Healthy myelin sheets are necessary for efficient saltatory transmission of action potentials and the preservation of axonal flow is vital for synaptic fitness and neural communication. A basic knowledge regarding WM disease progression will be essential for the rational design and assessment of therapeutic interventions in both FAD and SAD. Failing to comprehend the full spectrum of phenotypic diversity and the complete scope of pathology attending PS mutations may lead to potential errors in outcomes evaluations. Our study will be complementary to the recently funded Alzheimer's Prevention Initiative [27] in so far as it will yield a plethora of data regarding PS WM pathology as well as the biochemistry of amyloid and neurofibrillary tangles (NFT) and their roles in the pathogenesis and evolution of FAD and SAD.

Preliminary Data: The proposed study will extend our previous investigations of individuals carrying PS mutations [1,28], which revealed that the gray matter (GM) is severely impacted during the course of these neurodegenerative disorders. Our studies demonstrated a large degree of heterogeneity among the different PS mutations in the neuropathology and in the quantities and degradation patterns and of APP, Aβ (Aβ42:Aβ40 ratios), Notch, N-cadherin and Erb-B4 (substrates of γ-secretase) as well as in the distribution of amyloid deposits and NFT. The proposed study will allow comparison between FAD and our previous studies on SAD that showed alterations in myelin proteins and cholesterol [29] as well as severe demyelination and WM dilated periarterial spaces (etat criblé) and cortical Aβ levels when grouped for ApoE genotype (R=0.97) and between the number of enlarged periarterial spaces and the ratio of their diameters to blood vessel diameter (R=0.70) [30]. Our ultrastructural WM studies also indicate that in SAD there are fewer (25% less; n = 3) and smaller axons, thinner myelin sheets and enlarged astrocytes (astrocytosis) as well as a significant reduction in blood vessels and cell numbers (glia) when compared to NDC individuals (n = 3) [31]. We have available a unique collection of frozen tissues from 11 PS mutations for comparison among themselves and against SAD and normal aging individuals.

Experimental Designs and Methods: We will utilize deep WM from the frontal lobes of the PS1 and PS2 mutations. These brains are already in our possession. In addition, control brain tissues from SAD and NDC cases will be obtained from our Brain Donation Program at Banner Sun Health Research Institute, Sun City, AZ. Our laboratory possesses all the equipment and experience necessary to achieve our goals. Denatured brain WM homogenates will be submitted to Western blot using specific antibodies against target proteins of WM structure and function (see Specific Aims), and the protein bands will be quantified by scanning densitometry as described in detail elsewhere [32]. ELISA will also be used to determine the quantity of proteins of interest. To enrich myelin proteins, we will utilize the recently published technique of Nair et al. [33] which uses detergent thermodynamics (ASB-14-4) for the direct precipitation of myelin proteins for 2D-DIGE proteomic analysis. Proteins of interest will be isolated, tryptic digested, analyzed by mass spectrometry and the information then submitted to a bioinformatics databases for identification. Proteins of special interest will also be purified by column chromatography (size-exclusion, reverse-phase and ion-exchange). Confirmatory quantification of proteins found to be altered in the 2D-DIGE analyses will be also performed by ELISA or Western blot [32].

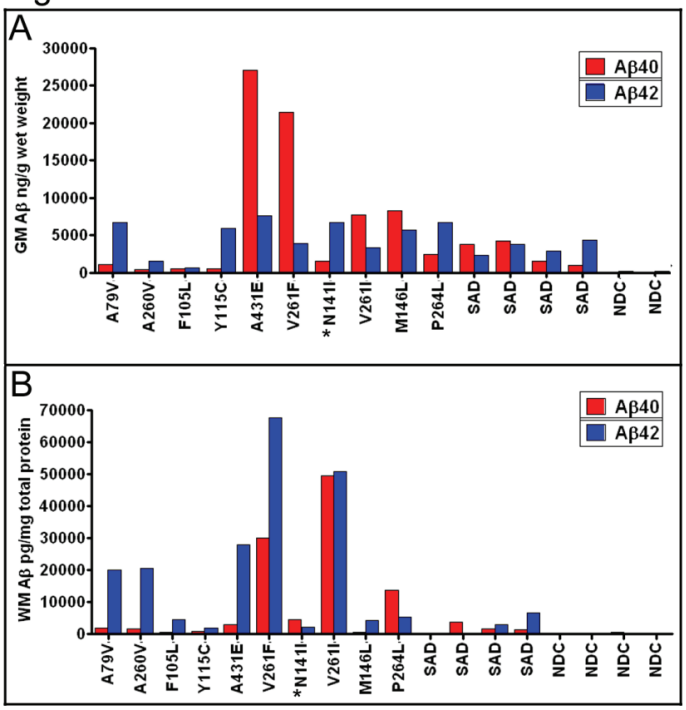
Proposed One-Year and Long-Term Outcomes: The investigation we are proposing, while intensive in labor terms, can be completed in one year, which will elicit the production of at least 1 or 2 scientific publications. We expect to gather data of paramount importance for the design of therapeutic interventions that may modify the course of FAD and SAD. We anticipate that this study will also provide preliminary

information on specific molecular cascades that will need to be investigated in more detail and therefore will provide the scientific bases for the application of a R01-NIH grant proposal.

2012-2013 Progress: We characterized and quantified the levels of Aβ40 and Aβ42 peptides by ELISA as well as a battery of 23 proteins by Western blot in the WM of 10 subjects harboring different PS mutations. These were the same cases in which our group previously studied the GM [1]. For the current study, we selected the WM because this area of the brain is greatly affected in PS-FAD. As a comparative frame of reference, we also determined the levels of these proteins obtained from 4 NDC cases as well as 4 subjects with SAD.

Aβ peptides. The histograms illustrated in **Figures 1A** and **1B** show the levels of gray matter (GM) and WM Aβ peptides, respectively, in 9 PS1-FAD and 1 PS2-FAD (denoted by asterisk) mutation carriers compared to SAD and NDC cases. Consideration should be given to the fact that there are ~1000 times less Aβ levels in the WM than in the GM (ng vs. pg) which suggests that the synthesis and accumulation of the Aβ peptides mainly occurs in the neuronal bodies. Thus, the presence of Aβ in the WM of SAD and PS-FAD is probably due to interstitial fluid diffusion from the GM or alternatively it represents an intracellular axonal pool that is elevated in SAD and PS-FAD, since these peptides were not increased in the NDC cases.

Figure 1



The GM Aβ42:40 ratios of the 10 PS-FAD mutations in which the PS-FAD A431E, V261F, V261I and M146L mutation carriers exhibited enriched Aβ40 levels **(Figure 1A)**. These values have been previously reported by our group [1]. Interestingly, two of the SAD cases also appear to have higher relative levels of Aβ40 compared to Aβ42 [1]. On the other hand, in the WM, only two PS-FAD cases (N141I and P264L) contained more Aβ40 than Aβ42 which was also the case for one of the SAD cases **(Figure 1B)**. The mean total GM Aβ (Aβ42+Aβ40) for the PS-FAD cohort was 12 µg/g wet weight, two-fold higher than the SAD mean (6 µg/g wet weight), and, as expected, significantly higher that of the NDC mean (Kruskal Wallis, $p = 0.039$) [1]. The same trends are observed for the WM in which PS-FAD cases had a mean total Aβ of 31 ng/mg total protein and the SAD cases had a mean of 4.2 ng/mg total protein while the NDC group had a mean of 0.22 ng/mg total protein (Kruskal Wallis, $p = 0.004$). Two important conclusions can be drawn from our data: 1) The PS-FAD mutations do not produce a uniform increase in the relative levels of Aβ42, as is widely believed, and 2) the PS-FAD mutations have, in general, higher amounts of Aβ peptides over SAD which may play a role, besides other factors, in the devastating dysfunction of the brain.

Western blots. One of the challenges in the present study was to determine how direct comparisons on a number of different biomarkers could be made. Since several of the biomarkers use different scales of measurement, direct comparisons of the raw values were not practical and did not allow for meaningful interpretations of the data. One of our interests was to determine whether the biomarker levels of the studied PS-FAD cases were different from those with SAD and also from NDC. We were also interested in examining the inter-individual variability of the biomarkers among the different PS-FAD cases. In

order to carry out these analyses, we converted the raw scores of the PS cases' biomarker levels into z-scores to standardize the raw score of a variable against the mean and standard deviation of a dataset. The quantitative advantage of this method is that the value of 0.00 becomes the reference point, thus permitting the determination as to whether biomarker phenotypes deviations were higher (positive z-scores) or lower (negative z-scores) among the PS-FAD cases relative to the SAD and NDC groups. This method also allowed the examination of the heterogeneity of biomarker phenotypes between the individual PS-FAD mutation cases.

Figure 2 through **Figure 8** displays the PS-FAD individual z-scores when compared to the NDC group, and also displays the PS-FAD mutations individual z-scores when compared to SAD groups. Molecules investigated by Western blot were grouped as follows: 1) direct substrates of PS1 in the WM (**Figure 2,** Notch-1, N-cadherin, Erb-B4, APP and its C-terminal fragments(CTF)), 2) WM apolipoproteins (**Figure 3,** ApoE and ApoA-1), 3) WM axonal transport participants (**Figure 4,** α-tubulin, β-tubulin, kinesin, dynein, dynactin), 4) proteins performing cytoskeletal functions in the WM (**Figure 5,** neurofilament (NF)-light, NF-medium, NF-heavy and tau), 5) proteins related to structural functions in the WM (**Figure 6,** GFAP, α-synuclein and myelin basic protein), 6) WM neurotrophic proteins (**Figure 7,** PEDF and VEGF) and 7) GM synaptic proteins (**Figure 8,** neurexin and neuroligin). For the NDC vs. PS-FAD comparisons, kinesin z-scores were not available for the PS1 cases carrying the mutations: A79V, A260B, F105L and V261F because the levels of kinesin were below the limit of detection **(Figure 4A)**. Likewise, for the SAD vs. PS-FAD comparison, kinesin z-scores were not available for the PS1 cases carrying the mutations: A79V, A260V, F105L and V261F **(Figure 4B)**.

Figure 2

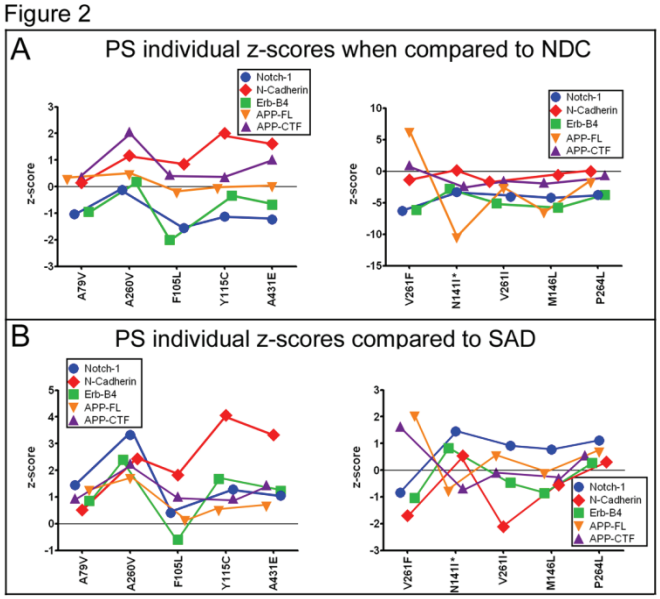


Figure 3

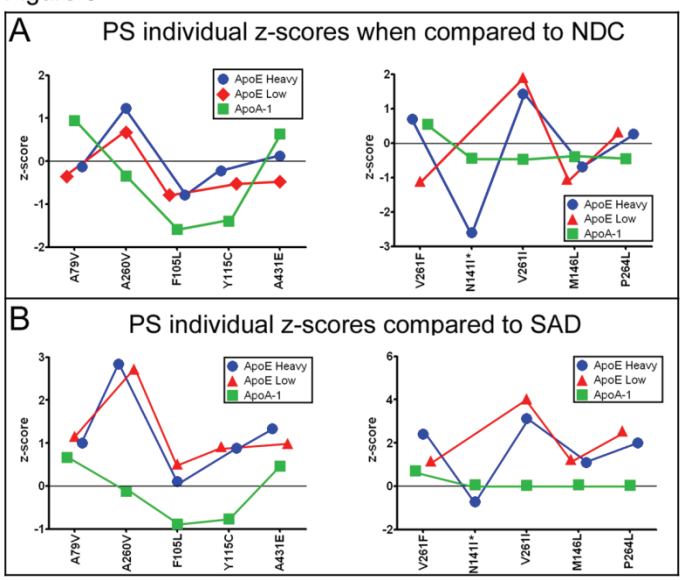


Figure 4

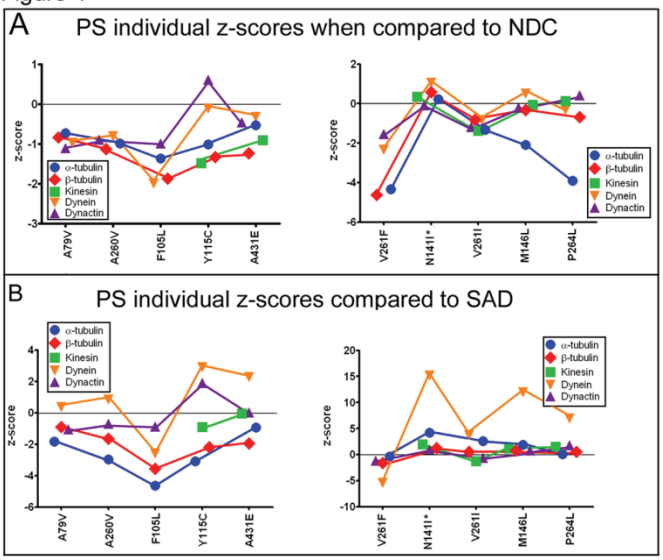


Figure 5

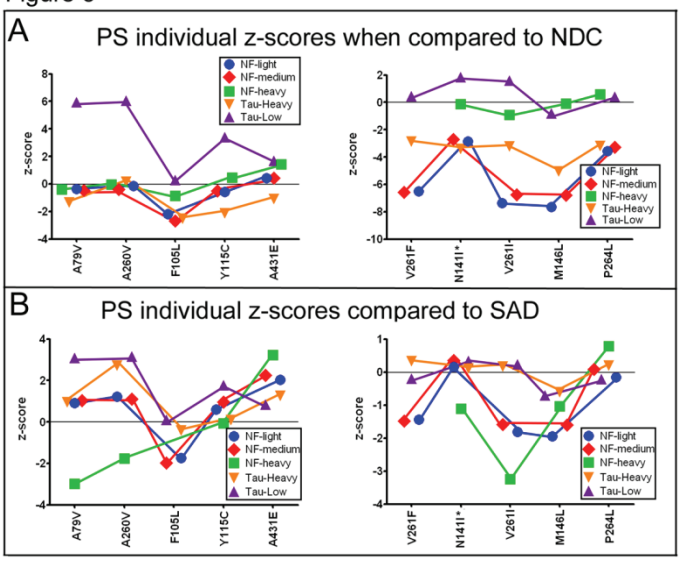


Figure 6

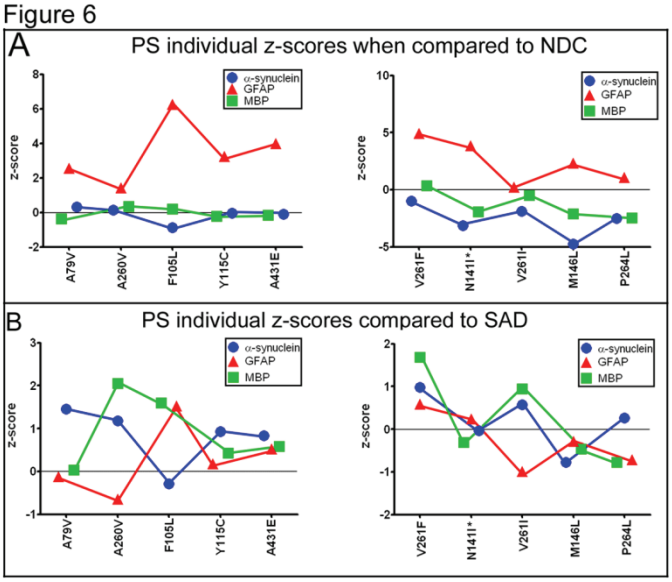


Figure 7

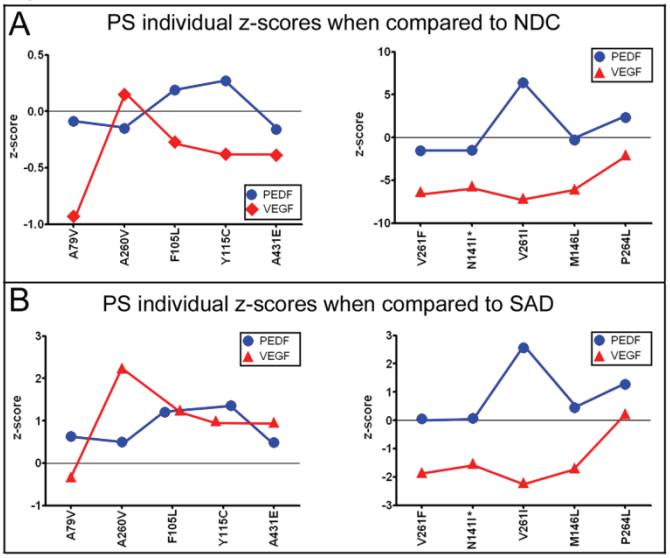
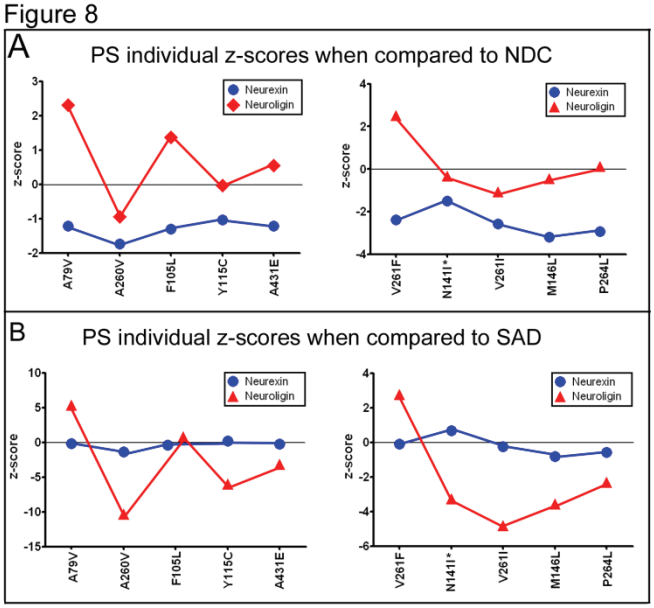


Figure 8



Intriguingly, the amounts of a specific marker were very different among the PS-FAD mutations. It is important to consider that all SAD and PS-FAD cases were at the end-stage of the disease process. Hence, the biochemical damage was at maximum levels of expression. This may account for the gross alterations observed in the integrity of neuronal and glial cells, which grossly perturbed the structure and function of vital systems such as axonal transport, synaptic integrity, cytoskeleton scaffolds, transmission of action potentials and neurotrophic factor levels. One can further argue that the individual phenotypic characteristics of the diverse PS-FAD mutations result from unique alterations of multiple substrates and their corresponding complex pleiotropic interactions that are ultimately expressed as common cellular dysfunctions. Thus, the observed early age of onset, fast course of the disease and severe neuropathological presentation of the PS-FAD mutations cannot be solely the result of APP/Aβ misprocessing, but rather the end-product of the cumulative effects of multiple pathological changes exerting cascading consequential effects on a large number of molecules and cellular functions.

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Project Progress Reports

Barrow Neurological Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Using multimodal MRI to investigate early brain changes in presymptomatic APOE ε4 Carriers. Leslie Baxter, PhD, Richard Caselli, MD, Kewei Chen, PhD, Josef Debbins, PhD, Yalin Wang, PhD. Barrow Neurological Institute, Mayo Clinic Arizona, Banner Alzheimer's Institute, Arizona State University.

Project Description: 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 are currently acquiring longitudinal scans of our previously scanned participants to determine the rate of change as correlated with their cognitive profile. We also have partnered with ASU and BAI collaborators to investigate imaging methodology that will capture subtle changes in brain integrity.

Aims: 1) To determine the age at which subtle brain changes associated with Alzheimer's Disease can be observed in APOE e4 carriers compared to noncarriers using multi-modal MRI methods. Regional brain changes in the APOE carriers are expected in the regions critical for memory functioning, including mesial temporal and posterior cingulate. On a group level, APOE carriers are expected to show decreased brain integrity compared to noncarriers prior to age 60. 2) To determine if different MRI methodologies can detect neuropathological changes reflecting the mechanism(s) underlying the increased risk of Alzheimer's Disease in the APOE carrier group.

2012-2013 Progress: We currently have baseline MRI data from 94 well-characterized, cognitively normal participants. At the time of this report, we have scanned 51 of these participants at a second time point, with an additional 20 scheduled for scanning at the time of this report. 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 individuals between the ages of 50 and 75 years of age, but not in younger, or indeed in older individuals. We are in the process of finishing the collection of the second timpoint for the MRI study to examine the relationship between longitudinal brain changes and cognitive functioning in the APOE cohort. We are collaborating with Dr. David Frakes in the ASU department of Bioengineering to analyze the relationship between vascular integrity (flow in Circle of Willis and nearby vessels) and cortical/white matter changes. Dr. Yalin Wang in the Computer Sciences Department at ASU submitted an R21 including our baseline structural MRI data and recently received a favorable score for funding.

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Enhancing mitochondrial complex I activity with the ketones acetoacetate and β-hydroxybutyrate alleviates soluble Aβ1-42 toxicity. Pengcheng Han, Junxiang Yin, Marwan Maalouf, Jiong Shi. Barrow Neurological Institute.

Project Description: We have previously shown that soluble Aβ42 aggregates inhibit neuronal excitability and long-term potentiation, increase levels of reactive oxygen species and oxidized proteins, and decrease mitochondrial respiration driven by complex I. In contrast, Aβ42 monomers do not exhibit any toxicity. Aβ42 aggregates do not affect intracellular calcium levels or mitochondrial respiration driven by complex II but 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 increase 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. We will immunoprecipitate intracellular Aβ from cells treated with human Aβ42, ketones or both and identify proteins that are associated with Aβ by mass spectrometry. 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.

2012-2013 Progress: Pituitary Adenylate Cyclase Activating Polypeptide (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 the age of onset and beta-amyloid (Aβ) neuritic plaque burden. 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.

In addition to investigating the molecular mechanisms underlying the effects of Aβ42 and ketones, 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 3xTgAD 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.

Project Progress Reports

Mayo Clinic Arizona

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Normal and Pathological Aging (Preclinical Alzheimer's Disease). Richard J. Caselli, MD. Normal and Pathological Aging; Mayo Clinic Arizona.

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

Specific Aims:

A. To maintain and grow a unique cohort of human aging in which we characterize the effect of APOE gene dose (a risk factor for Alzheimer's disease) on age-related changes in:
   1. Mentation (neuropsychological measures of cognition and behavior; subjective assessments by observers and self; sleep parameters)
   2. Brain Imaging (structural brain changes [MRI], functional [FDG-PET], PIB-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 and medical outcomes

D. To create a biobank of serum, plasma, DNA, frozen viable lymphocytes, and immortalized cell lines of this cohort.

E. To function as a core resource collaboratively supporting other investigators

Background and Significance: Even at the earliest clinical stages of Alzheimer's disease (AD), amyloid pathology has nearly peaked yet neither symptoms nor brain atrophy correlate well with amyloid burden. 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, so that we plan to differentiate normal from pathological aging, and discover factors that influence the diversion of individuals from the normal to the pathological pattern.

Preliminary Data: To date we have completed APOE genetic testing on over 2400 participants from which were selected our study population for further testing. We have completed one or more epochs of neuropsychological testing on 697 individuals including 402 APOE e4 noncarriers, 214 e4 heterozygotes, and 79 e4 homozygotes. Of these, 516 have completed two or more epochs of testing, providing data for longitudinal studies. 363 have been followed for at least 5 years, and 181 for at least 10 years. We have stored serum and plasma on 353 of these individuals, and DNA on all. 497 have immortalized cell lines established including all with brain imaging. We established memory aging trajectories for each of 3 APOE genotypes (Caselli RJ et al. New Engl J Med 2009; Alz Dem 2013 in press), 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 that in turn may impact selection of experimental therapeutic targets. We have completed, or are well on the way to completing all of our stated one year 2012 goals including:

1. Generate comprehensive longitudinal neuropsychological profile of preclinical AD
2. Explore the sensitivity of newer experimental measures including:
   a. the Parra binding task
   b. the Cogstate one-back (and related) tests
   c. the Iowa Gambling Task
3. Test the hypothesis that depression escalates during preclinical Alzheimer's disease
4. Correlate subjective measures of decline (observer-based and self-based) with neuropsychological and clinical outcome measures (to test the hypothesis that subjective perceptions may precede objective neuropsychological decline)
5. Continue our collaboration with Dr. Leslie Baxter (BNI), to perform longitudinal MRI-based studies of cerebral volumes, white matter integrity, and blood perfusion measures to identify the sequence of events that correlate with the preclinical memory decline we have identified
7. Pursue funing for new image analysis algorithms developed by Dr. Yalin Wang (ASU) with Dr. Baxter
8. Continue our collaborations with Drs. Coleman (epigenetics) and Huentleman (whole genome analysis) in exploring the basis for our "exceptions"

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. Survey public opinion about preclinical genetic and biomarker testing for Alzheimer's disease and compare public responses obtained via a public website with responses from APOE cohort study participants
2. Within the APOE cohort, correlate perceptions regarding preclinical testing with genetic, demographic, neuropsychological, and psychological characteristics
3. Perform a pilot study, in collaboration with Drs. Huentelman and Coleman of unexpectedly young onset Alzheimer's disease patients involving whole genome and epigenetic analyses
4. Support collaborative studies of new investigators including
   a. Cynthia Stonnington: the effects of lorazepam on memory performance in individuals and correlate these effects with TOMM40 genotype
   b. Yonas Geda: development of a large Latino cohort

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Brain-derived Neurotrophic Factor (BDNF) and Physical Activities among Hispanic-Americans in Phoenix, Arizona. Yonas E. Geda, MD, MSc. Mayo Clinic Arizona

Project Description: Between 2009 and 2011, the two co-investigators on this application (Dr. Larry Mandarino and Dr. Gabriel Shaibi) collaborated with stake holders in the Latino community of Phoenix, Arizona. 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 had administered a survey on physical exercise. At the same time, they had also biobanked plasma, DNA, RNA, and immortalized lymphoblastoid cell lines. We are now planning to conduct analysis on the stored sample in order to investigate the association between physical exercise and neurotrophic factors.

Neurotrophins are key regulators of cell fate in the life and death pathways of vertebrate nerve cells (Bibel and Barde 2000). Brain Derived Neurotrophic Factor (BDNF) is one of the major regulators of synaptic plasticity, neuronal survival, and phenotypic maintenance of mature, fully developed neurons (Binder and Scharfman 2004; Zuccato and Cattaneo 2009).

The overarching goal of the project is to utilize stored biospecimens in order to examine the association between a survey-based measurement of physical activity, and the plasma protein BDNF from a stored blood sample of 357 Latino adults aged 30-85 years. The preliminary data generated from this pilot study will be used to support a future prospective extramural grant application.

Specific Aims:
Primary Aim: To examine the association between BDNF (a biomarker of neurocognitive health) in a stored biospecimen, and self-reported physical exercise data.
Secondary Aims:

- To characterize the BDNF genotype and explore whether the BDNF gene mediates the association between serum BDNF and physical activity.
- val66met SNP polymorphism is the most widely investigated SNP. We will conduct SNP genotyping of the BDNF gene
- To conduct Whole Exome Sequencing of the BDNF gene.

Background and Significance: We and others have reported that physical exercise is associated with decreased odds of having cognitive impairment (Verghese, Wang et al. 2007; Geda, Roberts et al. 2010). In addition to cognitive outcomes, physical exercise is also associated with changes in biomarkers of neuroplasticity such as BDNF (Carro, Nunez et al. 2000; Cotman and Berchtold 2002). Central and peripheral levels of BDNF are elevated in response to exercise (Carro, Trejo et al. 2001; Murer, Yan et al. 2001; Gold, Schulz et al. 2003). BDNF expression is considerably reduced in the hippocampus (Phillips, Hains et al. 1991) and parietal cortices (Holsinger, Schnarr et al. 2000) of patients with Alzheimer's dementia. In view of this, BDNF is hypothesized to be the mechanism linking physical activity and cognitive function (Mattson M. 2006). In view of this, we sought to examine if the peripheral serum BDNF level is more elevated in the exercising group versus the non-exercising group.

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Preliminary Data: To date we have completed assay of the Serum BDNF on biospecimen collected from the 357 Hispanic study participants. We also completed the SNP genotyping of the BDNF gene. Sequencing of the BDNF gene is pending.

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: Biomarker, genotyping and sequencing study on a stored biospecimen collected from 357 adults who had completed a physical exercise survey.

Proposed One-Year and Long-Term Outcomes:

1- To get IRB approval in order to conduct sequencing of the 5 Exons of the BDNF gene.

2- To analyze the serum BDNF assay and examine its correlation with the self-reported physical activity of Hispanics in Phoenix.

3- To analyze the data generated by genotyping of SNPs in BDNF gene.

4- Prepare manuscripts on the above three results of analysis.

5- In collaboration with Dr James Levine, we have submitted an R21 to conduct a prospective cohort study. We will respond to the critiques and feedback and resubmit in the July of 2013.

6- Dr Geda, and his newly hired research associate(Dr Jazmin Acosta) have started attending the meeting of the steering committee that is leading the design and conduct of a Hispanic cohort (PI : Larry Mandarino). It is anticipated that starting in 2013, about 500 Hispanic participants per year will be recruited. The recruitment phase will continue over a four years period thus the cohort will eventually reach an n =2000.

Project Progress Reports

Translational Genomics Research Institute

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Novel biomarker and genetic risk factor identification in Alzheimer's disease. Matthew Huentelman, PhD, Travis Dunckley, PhD, Kendall Van Keuren-Jensen, PhD. TGen.

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 above mentioned 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 a 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. 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.

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.

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.

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.

Project Description:

Aim 2 – Identify differences in the methylated genome between Alzheimer's disease cases and controls. Using genome-wide methylation profiling approaches we will identify those regions in the genome of Alzheimer's disease patients with differential DNA methylation profiles compared to matched control individuals. Methylated regions of the genome have been shown to be differentially altered between case and control individuals in other human diseases however no one has demonstrated a clear influence of methylation on AD risk. We will utilize genomic DNA from AD cases and matched controls and either an array-based or sequencing based approach to profile their methylation profile. Statistical analysis of the differences in methylation levels between cases and controls will enable us to identify those regions in the genome that are potentially altered, regulated, or could serve as biomarkers for AD risk.

Progress Report

In collaboration with Mayo Clinic, Arizona (Dr. Driver-Dunckley, MD and Dr. Caselli, MD), we prospectively recruited age and gender matched Alzheimer's disease (AD), Parkinson's disease (PD) and controls free of neurodegenerative disease. We characterized the global methylation profiles of blood from these patients to identify potential differences that may be specific to either AD or PD. Methylation profiles were obtained on blood samples from 15 neurologically normal controls, from 10 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). 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. 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 biomarkers to track disease progression or aid in disease diagnosis. These results were recently presented at the 11th International Conference on Alzheimer's and Parkinson's Diseases.

Project Description:

Aim 3 - Identify miRNA species that are associated with AD neurodegeneration. 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 Report

We have analyzed the miRNA data generated from 50 CSF and serum samples from control patients with no disease upon postmortem neuropathological evaluation. We compared this data to 50 CSF and serum pairs from patients diagnosed with Alzheimer's disease or 50 CSF and serum samples from Parkinson's disease patients. All patient diagnoses were made postmortem. The total number of samples examined was greater than 300. We generated a significant data set that can be used and analyzed in many different ways. We list some of the findings that we find interesting thus far.

1) Among the significant miRNAs differentially expressed between AD and control patient CSF were miR-122 (lipid metabolism, previously shown to be upregulated in AD), miR-30c (associated with neurodegeneration), miR-9 (associated with BACE function and hippocampal neurodegeneration). Among the significant differentially expressed miRNAs found in the serum samples between AD and control patients: miR-34b (upregulated during ageing), miR-197 (involved in BACE regulation).
2) Some of the significant miRNAs that differentiated AD patients from PD patients were: miR-19b, 19a, miRNAs known to regulate BACE, and APP (miR-101). There were no significant miRNAs in serum.
3) Braak stages showed a decrease in miR 9 (binds in the 3' UTR of PSEN1) and miR 708.

We have analyzed the data in several different ways and we are working on validation of the hits with qRT-PCR. We are planning to write a manuscript by the end of April.

Project Progress Reports

University of Arizona

ARIZONA ALZHEIMER'S CONSORTIUM
2012-2013 Scientific Progress Report

Risk Factors for Brain Aging & Cognitive Health. Gene E. Alexander, PhD, Carol Barnes, PhD, Lee Ryan, PhD, Ted Trouard, PhD, Geoff Ahern, MD, PhD, Paul Coleman, PhD, G. Alex Hishaw, MD, Matthew Huentelman, PhD, Steven Rapcsak, MD. University of Arizona, Banner Sun Health Research Institute, Translational Genomics Research Institute, and Arizona Alzheimer's Consortium.

Project Description: The focus of this project is to conduct multi-disciplinary, translational research to advance our understanding of how common health-related factors in the elderly impact brain aging and associated cognitive health. To accomplish this goal, we have included a collaborative group of Arizona Alzheimer's Consortium (ADC) investigators, including leading researchers in the fields of neuroimaging, neuropsychology, behavioral neuroscience, genetics, and epigenetics. Using an integrative approach, this work will investigate the impact of health-related factors, including hypertension, exercise, and traumatic brain injury (TBI), on the neural systems supporting cognitive function during aging.

The population of older adults is expected to grow rapidly over the next two decades. It is well established that aging is associated with declines incognitive functions. Hypertension is a common health risk factor for the development of cognitive decline in the elderly, increasing the risk for cerebrovascular disease and is also associated with an increased risk for Alzheimer's disease (AD). The experience of traumatic brain injury (TBI) represents another important and common health-related risk factor in the elderly, with a large proportion of the estimated 1.4 million people in the United States experiencing TBI annually being elderly. Further, there is growing concern that TBI in older adults may be an important factor influencing the course of cognitive aging and the risk for AD. In contrast to health-related risk factors contributing to cognitive decline during aging, exercise has emerged as an important factor that may help mitigate or improve cognition and brain function during the lifespan. Studies investigating the effects of these health factors are critically needed to help advance our understanding of cognitive aging and the risk of AD.

Research in human and non-human animal models of aging and common risk factors for cognitive decline provide an important opportunity to elucidate the neural systems and underlying molecular mechanisms associated with poor cognitive outcomes in the elderly. This work is expected to inform and lead the way to new treatment approaches and interventions that may ultimately delay or prevent age-related cognitive decline. To support this effort, we have proposed two overarching sets of highly integrated, translational research study aims: 1) human studies to evaluate the effects of aging, exercise, hypertension, and TBI in the elderly on functional and structural brain networks supporting cognitive processes; and 2) studies of animal models of hypertension and brain aging in rats and healthy aging in non-human primates (bonnet macaques) to determine the impact of hypertension and aging on brain-behavior relationships and their associated gene expression and epigenetic mechanisms. This novel, integrative approach will provide the opportunity to translate findings between animal models and human studies to investigate the impact of age-related health risk factors on the neural systems altered during cognitive aging. Our overall hypothesis is that health-related risk factors of hypertension and TBI, as well as the beneficial effects of exercise, interact with the effects of healthy aging by altering the structure and function of brain networks important for cognitive processes that depend on frontal and selective temporal brain regions and the integrity of connecting white matter. Further, we expect that the combination of these health-related factors and aging will lead to altered gene expression and epigenetic changes in these key brain regions for aging-related candidate genes.

Aims: 1) To investigate the age-related, functional brain networks associated with increasing memory load and executive functions in healthy human aging from late middle age to elderly adulthood; 2) To

determine how health factors of hypertension, TBI, and exercise interact with the effects of aging to modify human brain function and cognitive performance; 3) To investigate the effects of hypertension, TBI, and exercise on human structural brain integrity and associated cognitive functions; and to determine how these effects are altered in the context of aging; 4) To evaluate the effects of age on structural brain integrity in the bonnet macaque and evaluate their relation to measures of learning and memory; 5) To investigate the effects of age and hypertension on brain integrity in rats; and to evaluate their association with memory and learning performance; and 6) To determine the effects of aging and hypertension on gene expression in the rat for aging-related candidate genes in brain regions affected by aging (i.e., frontal and selective temporal regions).

Secondary Aims: This multi-disciplinary study will provide substantial added value with our plan to 1) acquire a battery of neuroimaging scans in clinically well-characterized human cohorts to advance the collaborative development of new multi-modal image analysis methods to evaluate the effects of aging and age-related health factors on brain structure and function, 2) translate findings between human, monkey, and rat models to advance understanding of the neural systems preferentially affected by brain aging and age-related cognitive decline, 3) store DNA and tissue samples that will be available for future multi-institutional collaborative studies across the state of Arizona, and 4) support community outreach, education, and recruitment efforts with the development and implementation of an annual conference on successful aging.

2012-2013 Progress: During this year, we have implemented a number of important methodological developments to support our translational research efforts in studying risk factors for brain aging and cognitive health. In addition, our UA ADC investigators have been actively involved in the submission of numerous new grant proposals in the past year and have collectively been included as authors or co-authors on 66 manuscripts published or in press in support of this multi-disciplinary research project. Drs. Barnes, Glisky, Ryan, and Alexander participated in a workgroup effort to review and propose measures to assess cognitive profiles of aging with the potential to support translation between human and non-human animal studies. This effort led to the publication of six invited manuscripts with UA ADC investigators contributing as authors on five of these articles as part of a special issue of *Frontiers in Aging Neuroscience* (Alexander et al., 2012; Bizon et al., 2012; Burke et al., 2012; Engle et al., 2012; Roberson et al., 2012). From this effort, a new set of cognitive tasks have also been developed and implemented using E-Prime computer software in Dr. Ryan's lab in collaboration with Drs. Glisky and Alexander to assess specific components of executive function, memory, and processing speed for use in our human studies of age-related cognitive decline and to evaluate the effects of the aging related health factors of hypertension, TBI, and exercise. 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.

In this past year, a new stand-alone translational neuroimaging research facility was established at the UA, including research-dedicated magnetic resonance imaging (MRI) scannersto support human and small animal imaging. This facility includes a newly installed state-of-the-art Siemens Skyra 3T MRI scanner with 20 and 32 channel coils for human and non-human primate studies, as well as a pre-existing Bruker 7T MRI system for rodent imaging. With these two imaging scanners in place, we now have the capabilities to conduct our studies of aging with full research access to both imaging systems 24 hours a day, seven days a week. For the human studies, we have worked on actively implementing and refining our battery of state-of-the-art anatomical and functional neuroimaging scans on the newSiemens 3T Skyra MRI system for use in our studies of aging, health risk factors, and age-related neurodegenerative disease, as part of this project. Dr. Trouard's lab has led efforts to implement and evaluate scan sequences for the new scanner for structural MRI, diffusion tensor MRI, ASL perfusion, FLAIR for white matter lesions, functional MRI, functional connectivity MRI, susceptibility-weighted imaging (SWI) for investigating the

presence of cerebral microbleeds, and myelin mapping scans. A selected set of similar pulse sequences have been implemented on the 7T Bruker small animal MRI system at the University of Arizona to provide the potential for comparative measures of brain anatomy and functional and structural connectivity in the rodent. In addition, a new phantom was developed for the 7T Bruker instrument by Dr. Trouard's lab in collaboration with Dr. Alexander to provide standardization of acquisition across studies and over time for the scans acquired on this small animal MRI system, allowing comparability to phantoms used for standardization in human studies. A manuscript reporting on the development and proposed use of this phantom has been accepted for publication (Yoshimaru et al., 2012).

Using cognitive and neuroimaging methods, we have continued to make great progress in our human aging studies. 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/nocturalvariation in blood pressure and a manuscript on these findings has been submitted (Haws et al., submitted). Evaluation of diurnal blood pressure variability in relation to brain imaging effects is currently underway. Additionally, pilot data using a new fMRI source memory task with variable cognitive load, developed by Drs. Ryan in collaboration with Dr. Alexander, has shown age-related regional differences in brain activation, with full analyses in progress and a manuscript on these findings in preparation. Dr. Ryan led a study of aging effects on neural systems supporting a novel complex object discrimination task that showed age differences in the ability to engage the perirhinal cortex and a manuscript of these findings has been published (Ryan et al., 2012). In the past year, we re-submitted our Program Project Grant application (PI: Alexander; co-PIs: Barnes, Billheimer, Coleman, Huentelman, Ryan, Trouard), which was scored but not funded. We have been encouraged by NIA to submit the individual subprojects as R01 grant applications and this effort is now underway with plans for submission of the human studies in the Spring, 2013. In addition, we submitted a pre-application proposal (PI: Alexander) to the Department of Defense (DOD) Convergence Science Research Award program to investigate the use of neuroimaging methods to detect brain differences related to mild TBI and the risk for cognitive decline and AD dementia. The proposal further establishes collaborations between Drs. Glisky, Hishaw, Ryan, Trouard, and Alexander together with investigators in the UA Trauma Center. Our pre-proposal was approved and we were invited to submit a follow-up full proposal to the DOD, which is currently pending review. Dr. Hishaw (PI) working with Dr. Alexander submitted a proposal and received funding for a UA Faculty Seed Grant to provide pilot data to support our plans for an R01 grant submission on TBI and aging in the spring, 2013. In addition, a NIH R21 grant (PI: Alexander) has also been developed for submission 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 is in progress and will support plans for a collaboration between Drs. Alexander Raichlen, Ryan, and Glisky to investigate how exercise impacts brain function, structure, and connectivity in the context of aging. A proposal for a UA Faculty Seed Grant (PI: Raichlen, co-PI: Alexander) was submitted and funded to support plans for submission of an external grant proposal in the summer, 2013 to evaluate aging and exercise fitness. In addition, our investigators have plans to leverage the data collected from the current project to support several grant submissions planned in the spring and summer to NIH and NSF, related to further identifying important risk factors for brain aging, their underlying neural mechanisms, and associated ways to intervene or prevent age-related cognitive decline.

In our non-human animals studies of aging and age-related disease, we have completed acquisition of a pilot study of brain aging in the rat with structural MRI and multivariate network analysis has been applied. In collaborative work by Drs. Barnes, Trouard, and Alexander, a regional network MRI pattern that distinguishes the young from old rats was observed, characterized by reductions in gray matter

inregions within the medial temporal lobe and frontal cortex that is associated with poorer maze learning performance. Further work has been performed to additionally refine our MRI processing and analyses methods for small animal studies and a manuscript for this work is in preparation. In addition, Dr. Barnes in collaboration with Drs. Billheimer, Coleman, Huentelman, Trouard, and Alexander have been working on evaluating the use of a novel rat model for the gradual induction of hypertension with Cyp1a1-Ren2 transgenic rats. These rats are on a F-344 background (the species most widely used in aging research), have the cytochrome P450 promoter (Cyp1a1) inserted to drive the expression of the mouse renin (Ren-2) gene. The promoter can be activated by the dietary addition of the aryl hydrocarbon indole-3-carbinol (I3C). We obtained permission to acquire these animals from Kenneth Mitchell at Tulane University School of Medicine, and have had great success in slowly elevating blood pressure in the treated animals by our feeding procedures which included 0.15% I3C in the diet. The Barnes lab obtained weights, blood pressure measurements, and cognitive tests before and after treatment in all animals that we have obtained from Tulane, and in 9 I3C-treated and 8 untreated transgenic rats MRI scans before and after hypertension induction were obtained by Dr. Trouard working in collaboration with Dr. Alexander. Initial analyses of the structural MRI scans comparing rats receiving the I3C diet versus those without the augmented diet showed regional differences in gray matter in multiple cortical regions. Theseinitial MRI analyses were performed as part of Master's thesis work by Megan Fitzhugh, a graduate student in Dr. Alexander's lab, and an abstract of the initial findings have been presented (Fitzhugh, et al., 2012) with plans for a manuscript for publication underway. Further work in the analysis of the DTI scans collected with these transgenic rats is planned. Because we know that the treated animals showed a gradual induction of hypertension as indicated by elevated systolic and diastolic blood pressure measurements, were slower to learn the spatial location of an escape platform on the Morris swim task but not on cued versions of the task compared to animals without gene induction, and had increased kidney weights, heart weights as well as aortic hypertrophy, we believe that this will be the preferred model to use to evaluate hypertension effects in the brain in rodents. We plan to further examine the parameters mentioned above, and also in collaboration with Matt Huentelman and Paul Coleman, plan toexamine the transcriptional profiles (Huentelman) and the methylation status of selected genes to test epigenetic mechanisms associated with aging and hypertension (Coleman).

Dr. Barnes hascontinued to make great progress in the past year in studies with MRI scanning of cognitively tested young and old bonnet macaques (7 young adult and 9 geriatric). Structural and DTI scans were obtained from all but one of these animals. Dr. Trouard, working with Dr. Alexander, has been implementing and testing methods to analyze the DTI scan data. Further work on these data are planned to include network analyses of the volumetric changes across the brain in relation to specific cognitive tests that assess medial temporal lobe and frontal cortical functions. In addition, the Barnes lab is collaborating with Dr. Katalin Gothard, an expert in amygdala and orbitofrontal cortical function in nonhuman primates at the UA, to selectively target volumetric measurements of these structures in relation to reinforcer devaluation behavioral tests conducted on these animals. We expect that the data collected should allow for variability in behavioral performance to be associated with structural integrity of these brain regions.

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 mild cognitive impairment (MCI), Alzheimer's disease, 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. Drs. Rapsak and Ahern continue efforts to increase the number of Hispanic participants in the Clinical Core. Members of our ADC research group, including Drs. Ryan, Glisky, Ahern, Alexander, Barnes, Hishaw, and Rapsak have also participated in UA efforts for community outreach to meet with and provide lectures for primary care providers, geriatricians, local neurologists,

and the general public to increase awareness of age-related cognitive changes, Alzheimer's disease, and the ADC research program.In addition, Drs. Ryan and Alexander spearheaded efforts to establish an Annual Conference on Successful Aging (ACoSA) at the UA campus, providing members of the Tucson-metro area community with up to date information and new research findings on ways to enhance and support cognitive functions as we age. Our first annual daylong conference exceeded all expectations including nearly 300 participants with presentations by UA ADC investigators, including Drs. Ryan, Alexander, Barnes, Glisky, and Kaszniak. Plans for our next year's conference are currently underway.

2012– 2013

Publications, Manuscripts,

& Grants

2012 Publications and Manuscripts

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Current and Pending Grants

Current Grants

Ayutyanont, Napatkamon (PI)	7/1/12-6/3013
AARC	$30,000 Annual DC
Development of composite cognitive endpoints for presymptomatic AD trials	
Caselli, Richard (co-PI)	
ADHS12-010553-1	7/1/11 – 6/30/13
Arizona Alzheimer's Consortium	0.6 calendar (5%)
Normal and Pathological Aging (Preclinical Alzheimer's Disease	$197,603
Caselli, Richard (co-PI)	
P302P30 AG019610-1	8/15/11 – 6/30/16
National Institute on Aging	0.6 calendar (5%)
Arizona Disease Core Center	$101,715
Woodruff, Brian (PI)	
ABE4869g-1	10/26/11-10/25/14
Genentech Incorporated	0.36 calendar (3%)
	$259,050
Woodruff, Brian (PI)	
12-001623/ CR20	7/19/12 – 7/18/2014
	2.4 calendar (20%)
CR20 - Clinical Research, 20% PI Effort	$121,358
Cognitive, Occupational and Psychosocial Outcomes of Adults on the Autism Spectrum	
Caselli, Richard (co-PI)	
Mayo Clinic Arizona	7/1/10 – 6/30/13
Mayo funds: Center for Individualized Medicine	0.6 calendar (5%)
Normal and Pathological Aging, the "Arizona APOE Cohort"	$230, 913
Caselli, Richard (co-PI)	
ADHS12-010553-2	7/01/11 – 06/30/13
Health Resources and Services Administration	0.6 calendar (5%)
Normal and Pathological Aging (Preclinical Alzheimer's Disease)	$197,603
Stonnington, Cynthia (PI)	
Mayo Clinic Arizona	2/1/13 – 1/31/14
Internal Funding	0.6 calendar (5%)
The Cognitive Effects of Lorazepam in Healthy Older Individuals with TOMM40 Variable-length Polymorphisms	$158, 693

Caselli, Richard (co-PI)
R01 AG031581-14 — 4/01/08 - 3/31/13
National Institute of Neurological Disorders and Stroke — 1.68 calendar (14%)
PET, APOE & the Preclinical Course of Alzheimer Disease — $85,605

Caselli, Richard (PI)
Mayo Clinic Arizona — 7/1/10 - 6/30/13
Mayo Center for Individualized Medicine — 0.12 calendar (1%)
Title: Neuroscience Theme/Aging and Alzheimer's Disease — $134,846

Caselli, Richard
P302P30 AG019610-1 — 8/15/11 - 6/30/2016
National Institute on Aging — 1.8 calendar (0.8%)
Arizona Disease Core Center — $74,996
Role: Associate Director and Clinical Core Director.

Caselli, Richard (PI)
ADHS12-010553-1 State of Arizona, DHS — 7/1/11 – 6/30/13
Arizona Alzheimer's Research Center (Consortium) — 0.69 calendar (6%)
Normal and Pathological Aging (Preclinical Alzheimer's Disease) — $197, 603

Caselli, Richard (PI)
12-005324 — 8/27/12 – 8/26/13
Preclinical Testing: Personality Profiles and Other Factors — 0.12 calendar (1%)

Caselli, Richard (co-PI)
Department of Defense — 1/1/13 – 12/31/14
13-092/W81XWH-12-1-0583 — 0.12 calendar (1%)
Oligomeric Neuronal Protein Aggregates as Biomarkers for TBI and AD — $14,822

Chen, Kewei (PI) — 7/1/12-6/30/13
AARC — $49,965 Annual DC
State of Arizona
Advanced Image Analysis Techniques for the Detection and Tracking of Alzheimer's disease

Chen, Kewei (co-PI) — 2/15/11-3/31/13
Mayo Clinic Arizona via Mayo Foundation — $30,161 Annual DC
Predicting Cognitive Decline for Individuals Using Supervised Machine Learning and Combined Imagine and Neuropsychological Data

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

Fleisher, Adam (co-PI) 1/1/13-11/30/13
NIH/NIA AG010483 $21,978 Annual DC
Alzheimer's Disease Cooperative Study

Langbaum, Jessica (PI) 7/1/11-6/30/12
AARC $12,149 Annual DC
State of Arizona
Arizona Alzheimer's Registry

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 (PI) 7/1/11 - 6/30/16
NIA 2P30 AG19610 $1,196,386 Annual DC
Alzheimer's Disease Core Center

Reiman, Eric (PI) 7/1/11-6/30/12
AARC $167,436 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) 7/1/03-6/30/13
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-PI) 9/30/09-8/31/12
NIH/NIA U01AG024904 Weiner (PI) $148,060 0Annual DC
Amyloid Imaging, VMCI and Analysis, for ADNI

Reiman, Eric (co-PI) 3/1/09-8/31/13
Avid Clinical Study Agreement $23,550 Annual DC
Avid Radiopharmaceuticals, Inc.

Reiman, Eric (PI) 9/30/09-8/31/13
NIH 1RC-2AG036535 via N. Calif. Inst. Research & Education $280,907 Annual DC
Amyloid Imaging, VMCI and Analysis for ADNI

Reiman, Eric (PI) 1/28/10-1/27/15
NIH/NCRR1C 06RR030610-01 $6,530,203 Total Costs
Cyclotron, PET and MRI Facility Improvement: A scientific Resource for Arizona

Reiman, Eric (PI) 6/10/10-6/9/13
NIH/NCRR 1S1RR02923-01 $2,652,275 Total Costs
The GE PETtrace Cyclotron: A Scientific Resource for the State of Arizona

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

Huentelman, Matthew (co-PI)
2 P30 AG019610 07/01/2011 - 06/30/2016
NIH 0.48 calendar mo.
Arizona Alzheimer's Disease Core Center $13,294

Huentelman, Matthew (PI)
SU2C (Jeffrey Trent) 04/01/2012 - 03/31/2015
American Association for Cancer Research 1.2 calendar mo.
Personalized Medicine for Patients with BRAF wild-type (BRAFwt) Cancer $1,302,921

Huentelman, Matthew (PI)
Grant 07/01/2012 – 06/30/2013
DHS 2.28 calendar mos.
$165,000

Huentelman, Matthew (co-PI)
Schatzberg, Scott (co-PI/mentor)
Morris Animal Foundation 01/01/2011 - 12/31/2013
Mapping Genes Associated with Necrotizing Meningoencephalitis in Dogs 0 calendar mo.

Yaari, Roy (PI) 7/1/11-6/30/12
AARC $56,387 Annual DC
State of Arizona
Native American Outreach and Native American Clinical Core

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) 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) 9/25/12-9/24/13
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 (Phase 1 of 2 Phases)

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

Shi, Jiong (PI) 07/01/11 - 06/30/12
State of Arizona/Barrow Subcontract $120,000 (TC)
Enhancing mitochondrial complex I activity with the $120,000 (BNI Match)
ketones acetoacetate and β-hydroxybutyrate alleviates soluble Aβ1-42 toxicity

Beach, Thomas
U24 (Beach) 9/1/11-6/30/16
NIH $1,012,965 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 $162,978 Annual DC
Arizona Alzheimer's Disease Core Center

Beach, Thomas
TGEN (Huentelman) 3/1/08 to 3/31/13
Genetic Variation in KIBRA & its Role in Episodic Memory $9,582 (Beach/ BBDP Annual Direct Costs)

Beach, Thomas
Schering-Bayer Pharmaceuticals, Inc. 11/1/09 to 10/30/14
Postmortem Correlation for Amyloid Imaging Ligand Bay 94-9172 $98,000 Beach Total DC

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

Beach, Thomas
MJFF (Adler) 9/1/11-8/31/14
Michael J. Fox Foundation for Parkinson 's Research $78,100 Beach Total DC
Transcutaneous Submandibular Gland Biopsy: A Diagnostic Test for Early Parkinson's Disease

Beach, Thomas
R43 (Seligman) 4/1/11 to 7/31/13
HT Genomics $25,000 DC/year
qBead Assessment of miRNA in Alzheimer's Disease

Beach, Thomas
National Alzheimer's Coordinating Center (NACC) (Beach) 7/1/12-6/30/13
NACC via Washington University $12,069 Annual DC
Optimization of Neuropathologic Assessment of Alzheimer's Disease

Beach, Thomas
U01 (Scherzer) 9/30/12-9/29/17
Brigham and Women's Hospital $12,500 Annual DC
Biomarkers for early detection and intervention in Parkinson's disease

Beach, Thomas
1R21AG044068-01 (Walker) 11/1/12-8/31/14
NIH $150,000 Annual DC
Is Toll-like receptor-3 signaling involved in Alzheimer's disease?

Belden, Christine
P30 AG019610 (Reiman) 7/1/11-6/30/16
NIH/NIH $96,510 Annual DC
Arizona Alzheimer's Disease Core Center – Clinical Core Core B-SHRI

Belden, Christine
U24 (Beach) 9/1/11-6/30/16
NIH $1,021,965 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Belden, Christine
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

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.

Coleman, Paul
3R01AG036400-02S1 9/15/10-8/31/14
NIH/NIA $63,291 Total DC

Coleman, Paul
FY2013 Award (Reiman) 7/1/12-6/30/13
Arizona Alzheimer's Consortium (Coleman, project PI) $45,556 Total Costs
A Novel Therapeutic Directed at Mitochrondrial Energetics and Epigenetics

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) 07/01/12-06/30/13
NIH/NIA ADC Pilot (DeCourt) $29,412 Total Costs
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

Dugger, Brittany
1U24NS072026 (Beach) 9/01/11-6/30/13
NIH/NINDS $1,012,965 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 $78,100 Beach Total DC
Transcutaneous Submandibular Gland Biopsy: A Diagnostic Test for Early Parkinson's Disease

Dugger, Brittany
National Alzheimer's Coordinating Center(NACC) 7/1/13 – 6/30/14
NACC– NACC Junior Investigator Award $25,000
Relationship of cardiovascular risk factors to dementia subtypes

Gaballa, Mohamed
R01AG027263 (Gaballa) 1/1/08 to 6/30/13 (NCE)
Aging Effects on Cellular Therapy for Heart Failure $205,000 Annual DC

Gaballa, Mohamed
Grant (Gaballa) 8/1/10 – 7/31/14
Sun Health Foundation Funding $656,470 Annual DC
Heart Failure Research Project at BSHRI

Geda, Yonas (PI)
European Union (FNUSA-ICRC) 1/1/2011 – 12/31/2015
St. Anne's University Hospital Brno 2.04 calendar (17%)
Neuroepidemiology – Aging, Pre-Clinical Alzheimer's Disease and Dementia $149,565

Petersen, Ron (co-PI)
U01AG 06786-27 9/1/2009 – 8/31/2014
National Institute on Aging 0.60 calendar (5%)
Alzheimer's Disease Patient Registry $1,204,434

Caselli, Richard (co-PI)
INTERNAL (Mayo) 7/1/2010 – 6/30/2013
1.20 calendar (10%)
Mayo Clinic $134,846
Center for Individualized Medicine/Normal and Pathological Aging, the "Arizona APOE Cohort"

Geda, Yonas (PI)
69831-1 2/15/2012 – 2/14/2013
3.36 calendar (28%)
Robert Wood Johnson Foundation $116,751
The Neuropsychiatry of MCI and Pre-MCI in Geographically and Ethnically Diverse Populations

Caselli, Richard (co-PI)
ADHS12-010553-1 7/1/2011 – 6/30/2013
Arizona Alzheimer's Consortium 0.60 calendar (5%)
Normal and Pathological Aging (Preclinical Alzheimer's Disease) $197,603

Petersen, Ron (co-PI)
5U01AG 006786-26-1 9/1/2011 – 8/31/2012
National Institute on Aging 0.44 calendar (3.6%)
Alzheimer's Disease Patient Registry $8,971

Jacobson, Sandra
U24 (Beach) 9/1/11-6/30/16
NIH $1,012,965 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 $96,510 Annual DC
Arizona Alzheimer's Disease Core Center – Clinical Core Core B-SHRI

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
AARC (Reiman, Project PI Walker) 7/01/12- 06/30/13
State of Arizona and Sun Health Foundation (match) $60,000 Annual DC
Arizona Alzheimer's Research Center

Lue, Lih-Fen
AARC (Reiman, Project PI Lue) 7/01/12- 06/30/13
State of Arizona and Sun Health Foundation (match) $90,000 Annual DC
Arizona Alzheimer's Research Center
New Insights into microglial activation in Alzheimer's Disease

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

Lue, Lih-Fen
R21AG034409-01A1 (Walker) 8/15/10-7/31/13 (NCE)
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?

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

Roher, Alex
R01 AG19795-09A1 (Roher) 8/1/01-5/31/14
NIH $205,000 Annual DC
APP/Abeta/Tau biochemistry in transgenic mice, familial and sporadic AD

Roher, Alex
Arizona Alzheimer's Research Commission 7/1/12-6/30/13
AARC $68,487 Annual DC
White matter alterations associated with Presenilin mutations.

Sabbagh, Marwan
P30 AG019610 (Reiman) 7/1/11-6/30/16
NIH/NIH $96,510 Annual DC
Arizona Alzheimer's Disease Core Center – Clinical Core Core B-SHRI

Sabbagh, Marwan
U24 (Beach) 9/1/11-6/30/16
NIH $1,012,965 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 DC
Study on Thalidomide as BACE1 inhibitor in Alzheimer's disease

Sabbagh, Marwan
1123 (Sparks) 01/01/11 – 3/31/14
Arizona Biomedical Research Commission $181,451 Annual DC
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

Shill, Holly
IETF 2013 7/1/12-6/30/13
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
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
U24 (Beach) — 9/1/11-6/30/16
NIH — $1,012,965 Annual DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Sparks, D. Larry
1123 (Sparks) — 01/01/11 – 3/31/14
Arizona Biomedical Research Commission — $181,451 Annual DC
Longitudinal Changes in Circulating TAU Correlates with Changing Cognitive Performance

Sparks, D. Larry
R01AG023211 (Scheurs) — 06/01/09-5/31/14
NIA (West Virginia University) — $37,109 Annual DC
Cholesterol and Copper Affect Learning and Memory

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

Walker, Douglas
R21AG034409-01A1 — 8/15/10-7/31/13(NCE)
NIH — $120,000 DC year 1
Are the suppressors of cytokine signaling involved in Alzheimer's disease?

Walker, Douglas
5U24NS072026-02 (Beach) — 4/1/11 to 3/31/15
NIH – NINDS — $881,419 DC
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders

Walker, Douglas
5 P30 AG019610 (Reiman) — 7/01/12 – 06/30/13
NIH/NIA — $158,666 DC/yr
Arizona Alzheimer's Disease Core Center — (Neuropath Core)

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

Walker, Douglas
AARC (Reiman, Project PI Walker) — 7/01/12- 06/30/13
State of Arizona and Sun Health Foundation (match) — $60,000 Annual DC
Arizona Alzheimer's Research Center

Walker, Douglas
AARC (Reiman, Project PI Lue) — 7/01/12- 06/30/13
State of Arizona and Sun Health Foundation (match) — $90,000 Annual DC
Arizona Alzheimer's Research Center
New Insights into microglial activation in Alzheimer's Disease

Huentelman, Matthew (co-PI)
Grant — 07/01/2012 – 06/30/2013
2.28 calendar mos.
DHS — $165,000

Bimonte-Nelson, Heather (PI)
RO1 Grant, RO1 AG028084 — 10/07-9/12
NIA — $1,653,769 Total DC

Bimonte-Nelson, Heather (PI)
Barrow Neurological Institute — 9/01/11-1/1/13,
Stimulating cognition? Deep brain stimulation as a mnemonic enhancer during aging. — $54,943 Total DC

Bimonte-Nelson, Heather (co-PI) — 08/11-present
Acosta, Jazmin (co-PI) — Fall 2011 award =$3135
Western Alliance to Expand Student Opportunities (WAESO) — Spring 2012 award =$3284
Mechanism of androstendione effects on cognition.

Bimonte-Nelson, Heather (co-PI) — 08/11-present
Acosta, Jazmin (co-PI) — Fall 2011 award =$3103
Western Alliance to Expand Student Opportunities (WAESO) — Spring 2012 award = $5600
Timing of conjugated equine estrogen administration in a transitional model of menopause.

Cohen, Ann (PI) — 07/11-6/16.
Klunk, William (Mentor)
Bimonte-Nelson, Heather (Collaborator)
K01AG037562
National Institute on Aging. Effects of Environmental Enrichment on Cognitive Survival: Role of Aβ & Metabolism.

Bimonte-Nelson, Heather (PI) 1/13-1/14.
Arizona State University $25,000 Total DC
Impact of exogenous hormone treatment on age-related memory changes

Hiroi, Ryoko (PI) 07/01/11 – 06/30/14
Bimonte-Nelson, Heater (co-mentor)
Handa, Robert (co-mentor)
F32 MH093145 Postdoctoral NRSA
National Institute of Mental Health.
Regulation of the Tryptophan Hydroxylase-2 Promoter by Estrogen

Sierks, Michael (PI)
1R21AG042066-01 8/1/12 – 7/31/14
National Institutes of Health.
Developing Diagnostic Nanobodies Against Aggregated TDP-43 Species

Sierks, Michael (PI)
W81XWH-12-1-0583 9/25/12 – 9/24/13
Department of Defense
Oligomeric neuronal protein aggregates as biomarkers for TBI and AD

Coon, David (PI)
CarePRO Translating Evidence-based ADRD Direct Services Research into Practice 9/30/09 09/30/13 (NCE)
$856,640 Total
U.S. Administration on Aging's Alzheimer's Disease Supportive Services Program
(Additional funding pending).

Coon, David (PI)
NevadaCARE (CarePRO Nevada)
Translating Evidence-based ADRD Direct Services Research into Practice 9/30/09-09/30/13 (NCE)
U.S. Administration on Aging's Alzheimer's Disease Supportive Services Program $173,435 Total

Coon, David (PI) 9/30/09-12/31/12
Innovation Award Funded by the U.S. Administration on Aging's $360,514 Total
Alzheimer's Disease Supportive Services Program from

Coon, David (co-PI) 8/1/08 – 6/30/14 (NCE)
The Caregiving Trajectory for Community-Dwelling Mexican-American Elders. $1,791,804
National Institute for Nursing Research

Coon, David (co-sponsor) 08/15/11 – 08/14/13
Post-Caregiving Transitions in African American Caregivers.
National Institutes of Health/National Institute of Nursing Research $38,145 TC

Coon, David (co-mentor) 07/01/11 – 06/30/2013
Post-Caregiving Transitions in African American Caregivers $100,000 TC
John A. Hartford Foundation Building Academic Geriatric Nursing Capacity

Coon, David (mentor) 04/01/11 – 03/31/16
Transdisciplinary Training in Health Disparities Science (TTHDS)
National Institute of Health /National Institute of Nursing Research $1,334,662 TC

Jensen, Kendall (co-PI)
1 R01 NS076006(Hollis Cline) 08/01/2011 - 07/31/2014
NIH 1.2 calendar mos.
Transcriptome Analysis of Identified Cells in Developing X. laevis CNS $100,000

Jensen, Kendall (co-PI)
Grant (Matthew Huentelman) 07/01/2012 – 06/30/2013
4.2 calendar mos.
DHS $165,000

Ahern, Geoffrey (co-PI; PI Reiman) 07/01/12 – 06/30/13
NIH 1 P30 AG019610 $68,175 TC
Arizona Alzheimer's Disease Core Center - UA Clinical Core

Ahern, Geoffrey (PI) 2010 - 2012
Elan Pharmaceuticals, Inc. $43,491/patient
A Phase 3 Extension, Multicenter, Double-Blind, Long Term Safety and Tolerability Treatment Trial of Bapineuzumab (AAB-001, ELN115727) in Subjects with Alzheimer's Disease who Participated in Study ELN115727-301 or in Study ELN115727-302.

Ahern, Geoffrey (PI) 2011 - 2012
Elan Pharmaceuticals, Inc. $11,901/patient
A Long-Term Follow-Up Study of Oral ELND005 (AZD-103) in Subjects with Alzheimer's Disease.

Ahern, Geoffrey (PI) 2011 - 2013
Janssen Alzheimer Immunotherapy $62,791/patient
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center, Biomarker, Safety, and Pharmacokinetic Study of Bapineuzumab (AAB-001) Administered Subcutaneously at Monthly Intervals in Subjects with Mild to Moderate Alzheimer's Disease.

Ahern, Geoffrey (PI) 2011 - continuing
Pfizer Pharmaceuticals $56,039/patient
A Phase 2, Multicenter, 24-Month, Randomized, Third-Party Unblinded, Placebo-Controlled, Parallel-Group Amyloid Imaging Positron Emission Tomography (PET) and Safety Trial of AAC-001 and QS-21 Adjuvant in Subjects with Early Alzheimer's Disease.

Ahern, Geoffrey (co-PI)
Eisai Pharmaceuticals 2012 - ongoing
A Placebo-controlled Double-Blind Parallel-group, Bayesian Adaptive Randomization Design and Dose Regimen $70,517/patient

Alexander, Gene (PI) — 04/01/07 – 07/31/13 (NCE)
NIA 1 RO1 AG025526 — $2,129,598 TC
Neuroanatomical Substrates of Aging and Cognitive Decline

Alexander, Gene (UA Subcontract PI; PI: Reiman) — 07/01/08 – 06/30/13
NIMH/NIA 2 RO1 MH57899 — $114,122 (Sub Annual
PET, APOE and he Preclinical Course of Alzheimer's Disease — DC)

Alexander, Gene — 07/01/12 – 06/30/13
State of Arizona/Banner Subcontract Grant — $165,000 Annual TC
Risk Factors for Brain Aging and Cognitive Health — $165,000 (UA Match)

Alexander, Gene (co-PI; PI: Raichlen) — 06/01/12 – 5/31/13
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 — $292,967/year TC
Cell Assemblies, Pattern Completion and the Aging Brain

Barnes, Carol (PI) — 05/01/10 – 04/30/15
5 RO1 AG003376 — $753,153/year TC
Neurobehavioral Relations in Senescent Hippocampus

Barnes, Carol (co-PI; PI: Zhou) — 09/01/10 – 07/31/15
4 R44 AG035446 — $72,787/year TC
Whole-brain fluorescence and brightfield imaging at single-cell level

Barnes, Carol (co-PI; PI: Reiman) — 07/01/11 – 06/30/16
5 P30 AG019610 — $20,502/year TC
Arizona Alzheimer's Disease Core Center – Ad Hoc Review

Beeson, Pelagie (PI; co-PI: Rapcsak) — 02/01/11 – 01/31/16
2 RO1 DC07646 — $35,785/yr TC
Developing Evidence-based Treatment Continuum for Spoken and
Written Language

Billheimer, Dean (co-PI; PI: Nelson) — 03/01/10 – 02/28/15
1 RO1 DK082542 — $52,267 TC
Population-Based Proteomic Investigation of Type 2 Diabetes Melitus

Billheimer, Dean (co-PI; PI: Guerra) — 04/01/11 – 03/31/13
1 P50 HL107188 — $22,440 TC
Validation of Serum Biomarker Signatures Predictive of Incident COPD

Billheimer, Dean (co-PI; PI: Snyder) — 07/01/11 – 06/30/16
1 RO1 HL108962 — $47,089 TC
Gene-By-Gene Interactions and Lung Field Balance in Patients with Heart Failure

Billheimer, Dean (co-PI; PI: Nelson) 08/05/11 – 07/31/15
1 R24 DK090958 $51,691 TC
Team Approach to Translate Novel Biomarkers for Diabetes

Billheimer, Dean (co-PI; PIs: Martinez/Wright) 04/01/12 – 03/31/17
2 RO1 HL056177 $88,675 TC
Childhood Predictors of Airway Structure, Function and Disease in Adult Life

Billheimer, Dean (co-PI; PI: Lau) 04/01/12 – 03/31/17
NIEHS $9,589 TC
Southwest Environmental Health Sciences Center

Kaszniak, Al (co-PI; PI: Reiman) 07/01/12 – 06/30/13
2 P30 AG019610 $75,432 TC
Arizona Alzheimer's Disease Core Center – Education and Information Core

Hishaw, G. Alex (PI; co-PI: Alexander) 06/01/12 – 05/31/13
University of Arizona Faculty Seed Grant $9,935 TC
Effects of Mild Traumatic Brain Injury on the Aging Brain

Kaszniak, Al (PI) 01/01/12 – 12/3/13
John Templeton Foundation $64,938 TC
Mind and Life Summer Research Institute and Varela Awards

Kaszniak, Al (co-PI; PI: Reiman) 04/01/12 – 03/31/13
R01 MH57899 $9,839 TC
PET, APOE, & the Preclinical Course of Alzheimer disease

Nadel, Lynn (co-PI: Edgin) 01/01/11 – 12/31/13
Sleep Disturbance, Cognition, and Behavior in Down Syndrome $349,470
Thrasher Research Fund

Nadel, Lynn (co-PI: Edgin) 06/01/11 – 05/31/12
The Neuropsychology of Down Syndrome $30,000
Research Down Syndrome

Nadel, Lynn (co-PI: Edgin) 06/01/11 – 05/31/12
A Down Syndrome Virtual Center for Basic and Translational Studies – $85,030
Cognition Testing Network...ARC Expression and Hippocampal Deficits
Johns Hopkins University (sub DSRTF) 6/11-5/12

Nadel, Lynn (co-PI: Edgin) 06/01/11 – 05/31/12
A Down Syndrome Virtual Center for Basic and Translational Studies - $55,000
Cognition Testing Network...ARC Expression and Hippocampal Deficits
Johns Hopkins University (sub DSRTF)

Nadel, Lynn (co-PI: Edgin) 07/01/11 – 06/30/12
The Neuropsychology of Down Syndrome $195,000
Down Syndrome Research and Treatment Foundation

Nadel, Lynn (co-PI: Edgin) 06/01/12 – 05/31/13
The Neuropsychology of Down Syndrome $185,000
Down Syndrome Research and Treatment Foundation

Nadel, Lynn (co-PI: Edgin) 07/01/12 – 06/30/13
The Neuropsychology of Down Syndrome $50,000
Down Syndrome Research and Treatment Foundation

Nadel, Lynn (co-PI: Edgin) 08/10/12 – 08/09/15
High density EEG Biomarkers of Memory Dysfunction in Down Syndrome $44,879
Jerome LeJeune Foundation 8/12-8/15

Rapcsak, Steven (co-PI; PI: Reiman) 07/01/12 – 06/30/13
NIH 1 P30 AG019610 $69,216/yr TC
Arizona Alzheimer's Disease Core Center - UA Clinical Core

Serio, Tricia (PI) 02/01/06 – 05/31/13
RO1 GM069802 $851,381 TC
Prion Regulation in Vivo

Serio, Tricia (PI) 09/01/12 – 08/31/16
R01 GM100740 $1,118,941 TC
The Role of Competitive Forces in Prion Propagation and Appearance

Serio, Tricia (Sponsor; NRSA for Christine Langlois) 9/1/11 – 8/31/14
F31 GM099383 $83,841 TC
Oligopeptide Repeats and Prion Propagation

Serio, Tricia (Sponsor; NRSA for Janice Villali) 1/15/11 – 1/14/14
F32 GM096582 $152,766 TC
Pathway of Protein Misfolding Initiation in vivo

Trouard, Ted (PI) 07/01/12 – 06/30/13
NIA RO3 $50,000/yr DC
3D UTE Imaging in Alzheimer's mice

Trouard, Ted (co-PI) 04/15/13 – 06/30/13
UA TRIF $150,000 TC
Equipment for Stimulus Presentation, Response Collection and Patient Monitoring for fMRI

Trouard, Ted (PI) 01/01/12 – 12/31/16
RO1 CA161534 $3,226,496 TC
Insaid Effects on Clinical and Imaging Breast Biomarkers

Pending Grants

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

Caselli, Richard (PI)
R01R01 AG031581-15 7/1/13 – 6/30/18
National Institute on Aging 1.8 calendar (15%)
PET, APOE & the Preclinical Course of Alzheimer Disease $93,085

Caselli, Richard (PI)
Arizona Alzheimer's Disease Center 1/1/13 – 6/30/13
National Institute of Health 0.12 calendar (1%)
Plasma/Serum Storage at MCA Biorepository $11,024

Fleisher, Adam (co-PI) 3/1/13-9/19/12
NIH SBIR via Brain Biosciences, Inc. $148,562 TC
Dedicated Brain PET Scanner for Alzheimer's Aging

Fleisher, Adam (co-PI) 7/1/13-6/30/18
NIH/NIA R01 via Banner Sun Health Research Institute $656,096 TC
Translating Hemodynamic Biomarkers into Early Diagnosis and Prognosis

Reiman, Eric; Tariot, Pierre (Multi-PI) 9/1/13-8/31/18
NIH/NIA R01 $158,535,039 TC
Alzheimer's Prevention Initiative APOE4 Trial

Reiman, Eric (Co Investigator) 7/1/13-6/30/16
NIH/NIA R01 via Yale University $374,857 TC
Fyn Inhibition y AZDO530 for Alzheimer's Disease

Reiman, Eric (Co Investigator) 9/1/13-8/31/18
NIH/NIA R01 via Duke University $555,669 TC
MCI-2-AD Study Delaying MCI Progression using Pioglitazone

Beach, Thomas
U18 (Sierks) 11/1/12-10/31/15
Arizona State University $17,336 Year 1 DC
Detection of toxic oligomeric protein species in CSF and serum as biomarkers for PD

Beach, Thomas
R01 (Dunkley) 12/1/12- 11/30/17
NIH R01 via TGen $16,700 Annual DC
Next-generation characterization of neuronal vulnerability in Alzheimer's disease

Beach, Thomas
P50 (Standaert) 7/1/12 – 6/30/17
NIH P50 via Alabama (sub to Beach) $12,000 Annual DC
Alabama Udall Center of Excellence for Parkinson's Disease Research

Beach, Thomas
NIH (Duggar) 9/1/12-8/31/116
NIH Director's Early Independence Award (DP5) $250,000 Annual DC
The peripheral immune system in Alzheimer's disease

Beach, Thomas
R01 (Kanaan) 4/1/14-3/31/18
Michigan State University $11,000 Year 1 DC
Tau-mediated disruption of axonal transport in Alzheimer's disease tauopathies

Beach, Thomas
R21 (Lue) 7/1/13-6/30/15
NIH/NIA $125,000 Annual DC
Are there beneficial or detrimental roles for microglia TSPO in disease brain?

Beach, Thomas
IIRG 1/1/14-12/31/15
Alzheimer's Association (Sierks) $40,000 TC
Identifying specific Abeta and tau morphologies diagnostic for Alzheimer's

Beach, Thomas
R21 (Sierks) 12/1/13-11/30/14
NIH via ASU $40,000 TC
Nanobodies selective for oligomeric Tau species isolated from AD brain

Beach, Thomas
R01 (Peng) 9/1/13-8/31/17
NIH $79,000 TC
Systems Biology Approaches to Alzheimer's disease

Beach, Thomas
R01 (Dunckley) 9/1/13-8/31/15
NIH $31,600 TC
Identification of novel druggable gene pathways for AD

Beach, Thomas
R01 (Scherzer) 9/1/13-8/31/16
NIH $55,300 TC
Interdisciplinary target identification in Alzheimer's disease

Coleman, Paul
R21 (Dartmouth PI is Yeh) 9/1/12 – 8/31/13
NIH R21 via Dartmouth College $71,543 Annual DC
DNA Methylation in Single CNS Neurons Defined by Transmitter Phenotype

Coleman, Paul
IIRG 9/1/13-8/31/16
Alzheimer's Association $72,727 Annual DC
Manipulation of DNA methylation and expression of AD related genes

Dugger, Brittany
Arizona Alzheimer's Disease Core Center Pilot Study 7/1/13-6/30/14
ADCC $47,400 TC
Relation of brain microglial densities to cerebrospinal fluid levels of IL-6

Dugger, Brittany
American Parkinson Disease Assocation 9/1/13-8/31/14
APDA $35,000 TC
Inflammatory CSF Profile as a Biomarker for Concurrent Alzheimer's disease in Parkinson's Disease Dementia

Geda, Yonas (PI)
FP00072595 1/21/2013 – 11/30/2015
National Institutes of Health 1.80 calendar (15%)
Window of Opportunity in Ethiopia: Exercise, Cognition and Rapid Economic Change $102,323

Grover, Andrew
R03 9/1/13-8/31/15
NIH/NIA $50,000 Annual DC
Nucleosome positioning in the APOE gene linked to DNA methylation changes in LOAD

Grover, Andrew
5P30 AG019610-12 (Reiman) 7/1/13-6/30/14
Arizona Alzheimer's Disease Center Pilot (Grover) $30,000 Annual DC
Pure cell type isolation from rapid PM brain tissue for epigenetic profiling

Grover, Andrew
NIRG 9/1/13 to 8/31/15
Alzheimer's Association $45,455 Annual DC
Altered protein methylation and APP processing in Alzheimer's disease brain

Caselli, Richard (co-PI)
2P30 AG19610-1 9/30/01 - 6/30/16
National Institute on Aging 1.08 calendar (9%)
Arizona Disease Core Center $101,715
Caselli, Richard (co-PI) 4/01/08 - 3/31/13
R01 AG031581 0.48 calendar (4%)
National Institute of Neurological Disorders and Stroke $83,605
PET, APOE & the Preclinical Course of Alzheimer Disease

Caselli, Richard (PI)
1R01 NR012419 (Greenaway & Locke) 5/21/10 – 4/30/13
National Institute of Nursing 4.20 calendar (35%)
A Multicenter Rehabilitation Intervention for Amnestic Mild Cognitive Impairment $119,574

Caselli, Richard (co-PI)
ADHS12-010553-2 State of Arizona, DHS (Caselli) 7/1/11 – 6/30/13
Arizona Alzheimer's Research Center (Consortium) 0.60 calendar (5%)
Normal and Pathological Aging (Preclinical Alzheimer's Disease) $197,603
OVERLAP: None

Lue, Lih-Fen
R21 7/1/13 – 8/31/15
NIH $125,000 Annual DC
Are there beneficial or detrimental roles for microglia TSPO in disease brain?

Lue, Lih-Fen
IIRG 9/1/13 to 8/31/15
Alzheimer's Association $240,000 TC
How does microglial TREM2 function affect Alzheimer's disease?

Macias, Mimi
IMHR Pilot Study 9/1/13-8/31/14
Institute for Mental Health Research $20,000 Annual DC
A Cell System for Mechanistic Studies of Pharmacologic Inhibitors of BACE1

Macias, Mimi
5P30 AG019610-12 (Reiman) 7/1/13-6/30/14
Arizona Alzheimer's Disease Center Pilot Study (Macias) $30,000 Annual DC
A Cell System for Mechanistic Studies of Pharmacologic Inhibitors of BACE1

Nural, Hikmet
AHA (Nural) 7/1/13 to 6/30/15
American Heart Association $49,000 Annual DC
Myocardial infarction is associated with development of AD-like neuropathology

Locke, Dona (co-PI) 12/1/13 – 11/30/18
External Grant ID (Roarke) 0.6 calendar (5%)
National Institute of Health $89,146
Multi-Center Comparative Effectiveness Research (CER) on clinical impact of brain PET (FDG, Amyloid) evaluation of mild decline in cognition

Roher, Alex
13321032 6/1/13-5/31/16
Department of the Army USAMRAA $497,273 Total DC
The Relevance of Alzheimer's Disease Pathology and Biochemistry to Traumatic Brain Injury in Military Personnel

Roher, Alex
1R01AG045577 7/1/13 – 6/30/18
NIH/NIA $565,932 Total DC
Translating Hemodynamic Biomarkers into Early Diagnosis and Prognosis of AD

Sabbagh, Marwan
DS/AD IIRG 9/1/13 to 8/31/16
Alzheimer's Association $90,909 Annual DC
Longitudinal assessment of amyloid, FDG-PET and MRI imaging in DS and DS/AD

Sabbagh, Marwan
NACC (Reiman/Sabbagh) 7/1/13 – 6/30/15
National Alzheimer's Coordinating Center $63,292 Total DC
Comparison of Alzheimer's disease and Down syndrome post-mortem brain biomarkers

Walker, Douglas
R21 (Lue) 7/1/13 – 8/31/15
NIH $125,000 Annual DC
Are there beneficial or detrimental roles for microglia TSPO in disease brain?

Coon, David (PI)
National Institute on Aging Submitted 02/2013
EPIC: Translation of a Group Early-Stage AD Intervention into Diverse Communities. $3,274,695 Total

Coon, David (co-PI)
National Institute on Aging (Diane F. Mahoney) Submitted 03/2013
Development of a Responsive Emotive Sensing System (DRESS) ASU Budget $211,512.

Coon, David (co-PI)
National Institute on Aging (Fei Sun) Submitted 10/2012
Develop and Test Tai Chi Chuan or Wii Activity-Based Interventions to Improve Brain Health in Older Chinese Americans. ASU Budget $154,250.

Coon, David (co-PI)
National Institute of Nursing Research — Submitted 09/2012
EPIC: Early-State AD Intervention for Sociodemographically Diverse Care Partners. — ASU Budget $2,701,087.

Coon, David (PI)
National Institute of Nursing Research (LuAnne Lilly) — Submitted 09/2012
Demographic and Contextual Factors of Lesbian and Gay ADRD Caregivers — ASU Budget $330,239.

Woodruff, Brian (PI)
12-007739/ 18F-AV-45-A18 — 2/1/13 – 1/31/2015
Avid Radiopharmaceuticals — 0.12 calendar (1%)
A Randomized, Multicenter, Multicountry, Study to Evaluate the Effectiveness of Florbetapir (18F) PET Imaging in Changing Patient Management — $38,030

Woodruff, Brian (PI)
Government Grant — 9/1/13 – 8/31/18
National Institute of Health — 1.8 calendar (15%)
Aerobic Exercise as Secondary Prevention in Alzheimer Disease — $393,242

Woodruff, Brian (co-PI)
Government Grant (Roarke) — 12/1/13 – 11/30/18
National Institute of Health — 0.6 calendar (5%)
Multi-Center Comparative Effectiveness Research (CER) on clinical impact of brain PET (FDG, Amyloid) evaluation of mild decline in cognition — $89,146

Huentelman, Matthew (co-PI)
Grant (Gro Amdam) — 01/01/2012 - 12/31/2015
The Research Council of Norway — 0.24 calendar mo.
A comparative screening-approach to identifying genes linked to successful cognitive aging — $28,582

Huentelman, Matthew (PI)
T32 (Catherine Barnes) — 06/01/2012 - 05/31/2018
NIH — 0 calendar mo.
Alzheimer's Consortium T32 (FY13-18) — $0

Huentelman, Matthew (co-PI)
R01(Amanda Myers) — 12/01/2012 - 11/30/2017
NIH — 1.2 calendar mo.
APOEomic: Searching for APOE interacting risk factors using omics data — $125,000

Huentelman, Matthew (co-PI)
P01 (Gene Alexandar) — 04/01/2013 - 03/31/2018
NIH — 2.4 calendar mo.
Successful Cognitive Aging: Genetics, Health Status & Neural Systems (3 projects) — $330,743

Huentelman, Matthew (PI)
R24 (Thomas Perls) 04/01/2013 - 03/31/2015
NIH 0.6 calendar mo.
The Centenarian Studies Network $8,137

Huentelman, Matthew (PI)
R01 (Eric Reiman) 07/01/2013 - 06/30/2018
NIH 0.6 calendar mo.
Brain Imaging APOE & Preclinical Course of Alzheimer's Disease $10,515

Huentelman, Matthew (PI)
UH2/UH 07/01/2013 - 06/30/2018
0.6 Yrs. 1&2; 1.2 Yr3
NIH/Trans-NIH Research 0.84 Yrs. 4&5 calendar mo.
exRNA signatures predict outcomes after brain injury $242,183

Huentelman, Matthew (PI)
UH2/UH3 07/01/2013 - 06/30/2018
NIH/Trans-NIH Research Support 0.6 Yrs. 1&2; 1.2 Yrs. 3-5
mos.
Profiling of exRNA for an Alzheimer's disease diagnostic marker $258,123

Huentelman, Matthew (co-PI)
UH2/UH3 (Michael Berens) 07/01/2013 - 06/30/2018
NIH/Trans-NIH Research 0.6 calendar mo.
Solid tumor behavior exposed by exRNA $179,238

Huentelman, Matthew (PI)
R01(Carol Barnes) 09/01/2013 - 08/31/2018
NIH 1.2 calendar mos.
Classification of immediate early genes as risk factors for neurological disease $291,958

Huentelman, Matthew (co-PI)
R21 (Jeanne Wilson-Rawls) 07/01/2013 - 06/31/2014
NIH 0.6 calendar mo.
Regenerative Potential of satellite cells $69,938

Dunckley, Travis (PI)
R01(Christopher Hulme) 04/01/2013 - 03/31/2018
National Institutes of Health 2.4 calendar mos.
Potent and selective DYRK1A inhibitors for the treatment of Alzheimer's disease $110,223

Dunckley, Travis (co-PI)
U01 (Michael Bittner) 07/01/2013 - 06/30/2018
NIH/NIGMS 1.2 calendar mos.
Center for Stochastic Systems Biology $975,466

Dunckley, Travis (co-PI)
UH2/UH3 (Matthew Huentelman) 07/01/2013 - 06/30/2018
NIH/Trans-NIH Research Support 0.6 calendar mo.
Profiling of exRNA for an Alzheimer's disease diagnostic marker $258,123

Dunckley, Travis ((PI)
R01 (Michael Sierks) 09/01/2013 - 08/31/2018
NIH 1.2 calendar mos.
Identification of novel druggable gene pathways for AD $303,959

Dunckley, Travis ((PI)
R21 (Deborah Santoro) 09/01/2013 - 06/30/2015 .
NIH 0.12 calendar mo.
Effects of genetic & lifestyle risk factors on Alzheimer's disease neuropathology $45,000

Dunckley, Travis ((PI)
U01 (Chris Hulme) 12/01/2013 - 11/30/2018
National Institues of Health/National Institute on Aging 2.4 calendar mos.
Development of DYRK1A Inhibitors: a Promising Avenue for Alzheimer's $110,223

Jensen, Kendall (co-PI)
UH2/UH3 07/01/2013 - 06/30/2018
NIH/Trans-NIH Research 0.6 calendar Yr. 1&2
1.2 Yr. 3&4 calendar mos.
exRNA signatures predict outcomes after brain injury $242,183

Jensen, Kendall (co-PI)
UH2/UH3 07/01/2013 - 06/30/2018
NIH/Trans-NIH Research Support 0.6 calendar mo.
Profiling of exRNA for an Alzheimer's disease diagnostic marker $258,123

Jensen, Kendall (co-PI)
UH2/UH3 07/01/2013 - 06/30/2018
NIH/Trans-NIH Research 0.6 calendar mo
Solid tumor behavior exposed by exRNA $179,238

Jensen, Kendall (PI)
R01(Hollis T. Cline) 08/01/2013 - 07/31/2018
NIH 4.2 calendar mos.
Exosomes: An Essential Intercellular Signaling Mechanism in Brain Development $200,000

Jensen, Kendall (PI)
Grant 08/01/2013 - 07/31/2016
MDA 1.8 calendar mos.
FGGY expression changes dramatically with ALS progression, what does FGGY do? $72,468

Alexander, Gene (PI; co-PIs: Glisky, Hishaw, Ryan, Trouard) 10/01/13 - 09/30/16
DOD W81XWH-12-MRPRA-CSRA, 13321001 $757,500 TC
Neuroimaging biomarkers of mild TBI-related risk for cognitive aging & dementia
(Pre-application approved with invited full proposal submission pending)

Alexander, Gene (PI; co-PIs: Glisky, Hishaw, Ryan, Trouard) 9/1/13 – 8/31/15
NIH R21 $416,624 TC
Multimodal imaging & cognitive measures for detection of mild TBI
in the elderly

Alexander, Gene (co-PI; PI: Madhavan) 04/01/13 – 03/31/18
NIH RO1 NS083670 $89,302 TC
Neural Stem Cells and the Aging Trajectory

Alexander, Gene (UA Subcontract PI; PI: Reiman) 07/01/13 – 06/30/18
2 RO1 MH57899 $89,290 TC (UA sub)
PET, APOE and he Preclinical Course of Alzheimer's Disease

Barnes, Carol and Huentelman, Matthew (PIs; co-PI: Billheimer) 09/01/13 – 08/31/18
1 RO1 AG046546 $4,273,913 TC
Classification of Immediate Early Genes as Risk Factors for
Neurological Disease

Barnes, Carol (co-PI; PI: Madhavan) 04/01/13 – 03/31/18
RO1 NS083670 $89,302 TC
Neural Stem Cells and the Aging Trajectory

Barnes, Carol (Sponsor; NRSA for James Engle) 07/01/13 – 06/30/16
1 F32 AG042240 $52,190/year TC
The Contribution of Degraded Sensory Systems on Memory
Function in the Aged

Barnes, Carol (co-PI; PI: Hay) 07/01/13 – 06/30/15
NIH R21 $35,717 TC
Central Renin Angiotensin Intervention in Age Related Cognitive Decline

Barnes, Carol (co-PI; PI: Hay) 09/01/13 – 08/31/18
NIH RO1 $75,750 TC
The Contribution of Degraded Sensory Systems on Memory Function
in the Aged

Billheimer, Dean (co-PI; PI: Gerald) 12/01/12 – 05/31/16
NHLBI – R18 $195,985 TC
The Cost Effectiveness of School-Based Supervised Asthma Therapy

Billheimer, Dean (co-PI; PI: Harber) 04/01/13 – 03/31/16
CDC $52,628 TC
Mining Exposure & Health Assessment

Billheimer, Dean (co-PI; PI: Funk) 09/01/13 – 08/31/16
NIH $70,079 TC
Curcuma longa L. in Rheumatoid Arthritis (CLaRA) Clinical Planning Study

Billheimer, Dean (co-PI; PI: Raison) 04/01/13 – 03/31/16
NIH $168,199 TC
Acute Antidepressant Effects of Whole Body Hyperthermia: Predictors, Pathways and Placebo-controlled Outcomes

Nadel, Lynn (co-PI: Edgin)
Expressive Language Sampling as an Outcome Measure 04/2014 – 03/2018
UC Davis (sub NIH) 4/14-3/18 $595,926 TC

Rapcsak, Steven (PI; co-PI: Verfaellie) 04/01/13 – 03/31/17
VA Merit Review $599,076 TC
Medial Temporal Lobe Contributions to Future Thinking: Evidence from Amnesia

Serio, Tricia (PI) 05/01/13 – 06/30/14
R13 NS084808 $33,808 TC
FASEB SRC on Molecular Mechanisms and Physiological Consequences of Protein Aggregation

Trouard, Ted (co-PI; PI: Madhavan) 04/01/13 – 03/31/18
RO1 NS083670 $72,493 TC
Neural Stem Cells and the Aging Trajectory

Trouard, Ted 07/01/13 – 01/31/18
R01 EB000343 $1,496,495 TC
Non-Invasive Monitoring of NP-C Progression and Therapy with MRS/MRI

Arizona Alzheimer's Consortium
15th Annual Scientific Conference
Friday, May 3, 2013

University of Arizona
College of Medicine
Phoenix, Arizona

Poster Abstracts

Poster 1

EVALUATION OF OLIGOMERIC ALPHA-SYNUCLEIN AGGREGATES IN ROTENONE AND MPP+ TREATED CELL MODELS AND IN MOUSE MODELS OF PARKINSON'S DISEASE.

Alam N, Emadi S, Sierks M, Chesselet M, Yacoubian T. Arizona State University; Brain Research Institute UCLA; University of Alabama; Arizona Alzheimer's Consortium.

Background: Misfolding and aggregation of alpha-synuclein (a-syn) has been strongly correlated with the pathogenesis of Parkinson's disease (PD). Reagents such as single chain antibody fragments (scFv) that can interact with specific aggregate forms of a-syn can be very useful to study how different aggregate forms affect cells and contribute to PD.

Methods: Here we utilize two scFvs, D5 and 10H, that recognize two distinct oligomeric forms of a-syn to characterize the presence of different a-syn aggregates in animal models of PD. Immunohistochemistry analysis was used to identify the differential presence of a-syn aggregates in 2 and 4.5 month old transgenic (Tg) and wild type (Wt) mouse brain slices. In addition, previous studies have indicated that rotenone can increase a-syn aggregation and accumulation in the same nervous system structures that are affected in PD. We used D5 and 10H to determine how rotenone altered a-syn aggregation in M17 cell models of PD using a sandwich ELISA.

Results: Increased oligomeric a-syn aggregates were observed in the 4.5 month Tg but not Wt mice. Treatment with rotenone results in rapid increases in the presence of oligomeric a-syn in cell models, although there was a time dependent difference in the occurrence of D5 and 10H reactive a-syn aggregates. Similar treatment of cells with MPP+ did not result in an increase in oligomeric a-syn.

Conclusions: The Thy-1 PD mouse model overexpresses a-syn through control of the Thy-1 promoter. This mouse model shows behavior deficits by 2 months. It is presented here that this mouse model shows increased presence of toxic oligomeric a-syn species at 2 months. The early presence of these a-syn species indicates that oligomeric a-syn has promise as an early biomarker for PD.

Poster 2

TDP-43 DEPOSITION IN PROSPECTIVELY FOLLOWED, COGNITIVELY NORMAL ELDERLY INDIVIDUALS: CORRELATION WITH CONCOMITANT PATHOLOGIES. Arnold SJ, Dugger BN, Beach TG. University of Arizona College of Medicine, Phoenix, Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Published/Journal Information: Acta Neuropathologica

Background: TAR DNA-binding protein 43 (TDP-43) has been heavily researched in recent years due to its involvement in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Several studies have also sought to investigate the frequency of TDP-43 deposition in other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, but there has been relatively little work focused on the prevalence, distribution and histopathological associations of abnormal TDP-43 deposits in the brains of cognitively normal elderly subjects.

Methods: We screened thick, free-floating coronal sections of mesial temporal lobe from 110 prospectively-followed and autopsied cognitively normal subjects (age range 71-100 years) using an immunohistochemical method for phosphorylated TDP-43.

Results: We found a 36.4% prevalence of pathologic TDP-43, mostly in the form of neurites with perikaryal cytoplasmic neuronal inclusions being uncommon, and intranuclear inclusions were rare. With respect to other concomitant pathologies commonly found in elderly individuals, cases with TDP-43 had a greater prevalence of argyrophilic grains (ARG) (40% vs. 18.6%). There were no additional associations with other concomitant pathologies, including cerebral white matter rarefaction, incidental Lewy bodies, neurofibrillary tangles or amyloid plaques.

Conclusions: These results indicate deposition of TDP-43 occurs in a substantial subset of cognitively normal elderly subjects and is more common in those with argyrophilic grains, supporting some previous studies that have shown evidence of occasional co-localization of pathological TDP-43 and pathological tau protein deposits.

Poster 3

VALIDATION OF THE ALZHEIMER'S PREVENTION INITIATIVE COMPOSITE COGNITIVE TEST SCORE. Ayutyanont N, Langbaum JBS, Hendrix SB, Fleisher AS, Caselli RJ, Monsell SE, Chen K, Kukull WA, Bennett DA, Tariot PN, Reiman EM. Banner Alzheimer's Institute; Pentara Corp; Mayo Clinic; U Washington; NACC; Arizona State U; Rush U Medical Center; U Arizona; TGen; Arizona Alzheimer's Consortium.

Published/Journal Information: Alzheimer's Association International Conference

Background: We previously used longitudinal datasets from cognitively unimpaired persons at risk for late-onset and autosomal dominant Alzheimer's disease (AD) to characterize the combination of cognitive test scores most sensitive to track preclinical AD and estimate sample sizes for preclinical treatment trials using the resulting Alzheimer's Prevention Initiative(API) Composite Cognitive Test Score. We now extend this approach to a larger multi-center dataset acquired September 2005-September 2012 from the 32 past and present Alzheimer's Disease Centers and provided by National Alzheimer's Coordinating Center (NACC) to demonstrate the generalizability of our initial findings, optimize the age range and provide sample size estimates for proposed preclinical apolipoprotein ε4 homozygote (HM) trial.

Method: 2-5 years of Uniform Data Set data from 4193 cognitively unimpaired subjects (3044 ε4 non-carriers, 1043 heterozygotes (HTs), and 106 HMs were used to compute longitudinal mean-to-standard-deviation ratios (MSDRs) to 1) confirm the power of the pre-specified composite cognitive score most closely resembling that derived from the Rush cohorts (despite differences in test batteries), 2) perform an exhaustive search of the combination of 1-8 UDS test scores most sensitive to distinguishing between persons who did or did not subsequently progress to clinical AD, providing an indicator of cognitive decline associated with preclinical AD after controlling for practice/aging effects, 3) identify the optimal age ranges for tracking composite score decline in the HMs and HTs, and 4) provide sample size estimates for preclinical trials within those age ranges.

Results: 1) The pre-specified composite cognitive score resulted in MSDRs similar to the Rush cohorts'. 2) The UDS-based composite score most sensitive to preclinical AD decline was similar to that identified using the Rush dataset. 3) Decline in this composite was greatest in 60-75 year-old HMs and in 65-80 year-old HTs. 4) 217 60-75 year-old HMs or 1717 65-80 year-old HTs per group are needed to detect 30% treatment effect with 80% power, p=0.05 for a 60-month trial.

Conclusions: The API Composite Cognitive Test Score for evaluation of preclinical late-onset AD treatments was confirmed to be sensitive to track preclinical AD in a large multi-center cohort and used to inform the design of API's proposed trial in ε4 HMs.
Funding: Arizona Alzheimer's Research Center Pilot Study, Alzheimer's Consortium Association(NA), National Institute on Aging (RF1 AG041705, R01 AG031581, P30 AG019610)(EMR), (P30 AG10161, R01 AG15819, R01 AG17917)(DAB), the State of Arizona, the Anonymous Foundation, the Nomis Foundation and the Banner Alzheimer's Foundation. The NACC database is funded by NIA (U01 AG016976).

Poster 4

NATURAL REDISTRIBUTION OF END-PROTECTION PROTEINS IN AGING CELLS AS TELOMERES SHORTEN. Baribault ME, Swanson MJ, Bae NS. Midwestern University; Mercer University School of Medicine.

Background: As human cells age, chromosomes shorten at telomeres. Normally proteins protect these ends to maintain genome stability. Our interest was to establish the fate of the protective proteins as telomeres shorten in older cells to determine if these proteins play a role in aging and age-related diseases.

Methods: Primary human dermal fibroblast cells were cultured, mimicking a natural aging process. At various population doublings, the cells' morphology was documented, telomere lengths were measured using Southern blotting, and the levels of telomeric proteins were measured by immunoblotting.

Results: As cells age, telomeres get shorter and the proteins involved in protecting telomeres decrease in quantity. However, one of the proteins, RAP1, does not decrease at the same rate as the others. Aging is a type of stress, and RAP1 translocates from nucleus to cytosol, eliciting a stress response.

Conclusions: Decreased expression and translocation of the telomeric proteins in aged cells may be linked to neurodegenerative diseases that have a late on-set, such as Alzheimer’s Disease. Further exploration of the change in levels and distribution of these proteins as cells age is underway.

Poster 5

ASSOCIATION BETWEEN HIGHER FASTING SERUM GLUCOSE LEVELS AND THE PATTERN OF LOWER REGIONAL GRAY MATTER VOLUMES IN COGNITIVELY NORMAL ADULTS. Bartell J, Burns C, Thiyyagura P, Li A, Parks S, Protas H, Lee W, Fleisher A, Kaszniak A, Chen K, Reiman EM. Banner Alzheimer's Institute; University of Arizona College of Medicine; University of Arizona; Arizona Alzheimer's Consortium.

Background: Insulin resistance, as seen in type 2 diabetes, has been shown to increase the risk of late onset Alzheimer's Disease (AD) by as much as two-fold. In AD patients, characteristic findings are seen with structural magnetic resonance imaging (MRI) including global atrophy as well as regional reductions in gray matter volume (GMV) in the hippocampus, precuneus, posterior cingulate gyrus, parietotemporal, prefrontal, and orbitofrontal cortices. Additionally, negative correlations between peripheral insulin levels and regional GMV are seen in insulin resistant subjects in the middle temporal gyrus, an area associated with verbal fluency and declarative memory.

Methods: The current study investigated whether elevated fasting glucose (FSG) levels were associated with lower GMV in brain areas that have been preferentially affected by AD. This association difference was further investigated between carrier and non-carrier (NC) groups of the apolipoprotein E (APOE) ε4 allele, a genetic risk factor for late onset AD.

Results: As predicted, significant correlations were seen between higher levels of FSG and lower GMV in AD-affected regions including the left inferior orbitofrontal cortex, parietal, and occipital lobes and the left and right frontal and temporal lobes. Negative correlations between FSG and regional GMV in the middle temporal gyri confirmed findings seen in insulin resistant subjects. Additionally, these associations in AD-related areas are seen in both carriers and NC.

Conclusions: Higher FSG levels in cognitively normal, non-diabetic older adults are associated with lower GMV in AD related brain areas, confirming that elevated FSG may be associated with AD risk, independent of APOE ε4 status. Lastly, this study encourages the consideration of elevated FSG and other indicators of glucose control as targets for AD prevention trials, complementing the findings previously established with fluorodeoxyglucose positron emission tomography neuroimaging.

Poster 6

AUTOPSY-BASED FEASIBILITY STUDY OF SUBMANDIBULAR GLAND BIOPSY FOR THE DIAGNOSIS OF DEMENTIA WITH LEWY BODIES. Beach TG, Adler CH, Shill HA, Sue LI, Serrano G, Dugger BN, Mariner M, Hidalgo J, Henry-Watson J, Chiarolanza G, Intorcia A, Saxon-LaBelle M, Carew J, Carter N, Jacobson S, Davis K, Akiyama H, Sabbagh MN. Banner Sun Health Research Institute; Mayo Clinic, Scottsdale; Tokyo Institute of Psychiatry; Arizona Alzheimer's Consortium.

Background: The clinical diagnosis of dementia with Lewy bodies (DLB) may be missed in up to 70% or more of subjects, critically impairing the recruitment of sufficient subjects for clinical trials and biomarker studies (1). We have previously shown that the submandibular gland is likely to be affected by Lewy-type α-synucleinopathy (LTS) in a high percentage of subjects with Parkinson's disease (2); a pilot clinical trial of needle biopsy in PD showed LTS in 9 of 12 subjects. Our preliminary studies (3) indicated that submandibular gland LTS is also present in autopsy-confirmed cases of DLB.

Methods: We extended these studies by performing immunohistochemical staining for LTS in sections of large segments (0.8 - 1.5 cm^2) of submandibular gland from 123 autopsied subjects with neuropathologically-confirmed diagnoses, including 23 with DLB, 7 with incidental Lewy body disease (ILBD), 28 Alzheimer disease with Lewy bodies (ADLB), 15 Alzheimer's disease without Lewy bodies (ADNLB) and 50 normal elderly. All cases had previously received an initial standardized neuropathological examination that included LTS evaluation on sections from multiple brain regions in order to classify their central nervous system Lewy body disease.

Results: In agreement with reports of low sensitivity for DLB in other studies (1), only 7 of the 23 neuropathologically-identified DLB cases had been clinically diagnosed as DLB. Submandibular gland LTS was found within 16/23 (69%) of DLB subjects and 4/28 (14%) of the ADLB subjects but none of the normal control, ILBD or ADNLB subjects. The DLB cases without submandibular gland LTS tended to have lower total brain LTS loads (mean LTS load 30.7 vs 23.0; $p = 0.06$).

Conclusions: These results suggest that *in vivo* needle biopsy of the submandibular gland may be a feasible means of improving DLB clinical diagnostic sensitivity. This would be particularly advantageous for identifying DLB subjects for clinical trials and for identifying, in AD clinical trials, those subjects with concurrent AD and DLB. Additionally, submandibular needle gland biopsy could be used as a gold standard in other biomarker studies. 1. Nelson PT et al. J Neurol. 2010 257:359-66. 2. Beach TG et al. J Neuropathol Exp Neurol 72:130-136, 2013. 3. Beach TG et al. Acta Neuropathol 119:689-702, 2010.

Poster 7

HIPPOCAMPAL VOLUMES AND AGE-RELATED MEMORY DECLINE OF POST-MENOPAUSAL WOMEN ARE MODULATED BY HORMONE THERAPY STATUS. Braden BB, Dassel KB, Connor DJ, O'Rourke HP, Sabbagh MN, Caselli RJ, Bimonte-Nelson HA, Baxter LC. Barrow Neurological Institute; Sun Health Research Institute; Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Menopause negatively affects the quality of life in many women in a variety of ways, including memory decline. There is evidence that estrogen-containing hormone therapy (HT) can prevent or improve memory decline in healthy, menopausal women. Women also experience an age-related decline in hippocampal volume, and under certain parameters estrogen-containing HT can protect against hippocampal volume loss. Findings for HT's positive effects on cognition and hippocampal volumes are debated, most notably due to the negative findings from the National Institutes of Health sponsored Women's Health Initiative Memory Study for combination HT-associated risk of dementia and regional brain volume loss.

Methods: In the current study we addressed discrepancies in the literature by further categorizing menopausal women as continuous HT users (CU; n = 16), discontinuous HT users (DU; n = 33), or never users (NU; n = 14) and measured verbal memory performance and hippocampal volumes via high resolution T1 MRI scans. We also evaluated HT's effect on entorhinal cortex (EC) volume loss due to the early emergence in EC volume loss in AD and few studies have examined the effect of HT on this brain region.

Results: The DU group had significantly larger hippocampal volumes than NU group (Left: $p = 0.024$; Right: $p = 0.0083$). The mean hippocampal volume of the CU group fell between the DU and NU group, but was not significantly different than either. The HT effect was specific for the hippocampus and was not observed for EC volumes. In contrast, the CU, and not the DU group showed an attenuation of the expected age-related decline in memory functioning.

Conclusions: We conclude that that HT treatment in menopausal women can have favorable outcomes on the preservation of hippocampal volumes and age-related memory decline, but benefits depend on parameters of use and the outcome measure being studied.

Poster 8

THE EFFECTS OF CAFFEINE AND EXERCISE ON IMPLICIT AND EXPLICIT MEMORY PERFORMANCE IN YOUNGER ADULTS: AN INVESTIGATION OF PHYSIOLOGICAL AROUSAL. Buckley T, Sherman S, Baena E, Ryan L. University of Arizona; University of Texas at Austin; Arizona Alzheimer's Consortium.

Published/Journal Information: Poster at the annual Cognitive Neuroscience Society meeting, San Francisco, CA, April 2013.

Background: Memory performance is best during an individual's optimal time-of-day, when physiological arousal is naturally highest, and decreases significantly during the non-optimal time-of-day when arousal declines. Previous research suggests that the time-of-day at which a memory task is completed may contribute to age-related disparities in memory performance. Ryan et al. (2002) found that this deficit could be eliminated in older adults by administering caffeine during their non-optimal time-of-day, the late afternoon. It remains unclear whether the same enhancement in memory would be seen in younger adults during their non-optimal time-of-day, early morning.

Methods: Experiment 1 examined whether caffeine enhanced memory in the early morning. Thirty minutes after consuming a cup of coffee (caffeinated or decaffeinated), participants completed implicit explicit versions of a word-stem completion task. Experiment 2 examined whether exercise would also ameliorate time-of-day deficits. Participants complete 15 minutes of either cardiovascular exercise or gentle stretching. Heart rates were taken throughout the experiment to measure physiological arousal.

Results: Experiment 1 showed that young adults who consumed caffeinated coffee demonstrated significant improvements in explicit memory, but not implicit memory. Experiment 2 showed that while exercise increased physiological arousal, exercise had no effect on either explicit or implicit memory.

Conclusions: Taken together, these results suggest a unique mechanism for caffeine-induced arousal that compensates for time-of-day memory deficits. These findings have real-world application for classroom settings where students are expected to perform optimally during early morning testing sessions.

Poster 9

EXTRACELLULAR MIRNAS ISOLATED FROM CSF AND BLOOD SERUM ARE POTENTIAL BIOMARKERS FOR ALZHEIMER'S AND PARKINSON'S DISEASES. Burgos K, Courtright A, Malenica I, Ghaffari L, Aldrich J, Rakela B, Metpally R, Tembe W, Beach T, Van Keuren-Jensen K. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Because of their small size, tissue specificity, and stability, miRNAs have the potential to be sensitive biomarkers for neurodegenerative diseases, including Alzheimer's disease. We profiled the miRNAs in cerebrospinal fluid (CSF) and serum of subjects with Alzheimer's disease (AD), Parkinson's disease (PD) and normal controls.

Methods: We used next generation sequencing to profile the full compliment of miRNAs in CSF and serum samples. This method allowed us to examine all miRNAs associated with disease as well as to identify novel miRNAs.

Results: We identified several miRNA markers that are differentially expressed between AD or PD subjects and control subjects, as well as between AD and PD. We also assessed miRNAs associated with Braak stage, tangle, and plaque density.

Conclusions: miRNAs show promise as diagnostic markers of Alzheimer's disease. CSF may have a stronger signal-to-noise ratio than serum.

Poster 10

ELEVATED FASTING SERUM GLUCOSE LEVELS AND BRAIN FUNCTION: AN FDG PET STUDY OF YOUNGER ADULTS. Burns CM, Kaszniak A, Chen K, Lee W, Caselli RC, Reiman EM. University of Arizona; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: Manuscript in preparation

Background: Elevated indicators of poor glucose control have been associated with lower scores on tests of cognitive functioning and decreased measurements of brain function and structure in older adults. For example, studies have shown that elevated fasting serum glucose (FSG) has been associated with reduced regional cerebral metabolic rate for glucose (rCMRgl) in Alzheimer's disease (AD) related areas in cognitively healthy older adults without diabetes. In order to investigate whether these associations occur earlier on in the lifespan, we investigated the association between elevated FSG and rCMRgl in a sample of younger adults.

Methods: This is a cross sectional study of 31 cognitively normal non-diabetic participants 31.1 ±5.4 years of age with an average FSG level of 81.6 mg/dl (±8.3) which ranged from 69-100 mg/dl. General linear model based voxel-wise analyses were performed to examine the overall negative correlation between fasting serum glucose and rCMRgl.

Results: Higher FSG levels were associated with reduced rCMRgl bilaterally in AD-related parietal and temporal areas. This association was also demonstrated in aging related frontal regions and the primary visual cortex.

Conclusions: Elevated FSG may have an impact on cerebral metabolism in early adulthood. These results underscore the importance of lifestyle or psychosocial interventions that address glucose control and brain health across the lifespan.

Poster 11

A METHODICAL EVALUATION OF ANDROSTENEDIONE'S COGNITIVE EFFECTS IN YOUNG SURGICALLY MENOPAUSAL RATS. Camp BW, Acosta JI, Mousa A, Alderete T, Mennenga SE, Koebele S, Demers L, Bimonte-Nelson HA. Department of Psychology, Arizona State University; Arizona Alzheimer's Consortium; Pennsylvania State University.

Background: It has been recently shown that androstenedione, the main circulating hormone present after menopause and follicle depletion, is positively correlated with poor spatial memory in chemically-induced follicular depleted rats (Acosta 2009a), and impairs spatial memory when administered as an exogenous treatment (Camp 2012). Androstenedione can be converted to either an estrogen (e.g., estrone) or to another androgen (e.g., testosterone).

Methods: We hypothesize that the impairment of spatial memory found previously after androstenedione administration is due to its conversion to either estrone or testosterone. The current study was conducted with the goal of elucidating the hormonal mechanism of the observed androstenedione effects on cognition by methodically blocking the conversion of androstenedione to estrone, or blocking androgen receptor activity, and evaluating changes in cognition.

Results: Measures of spatial working and reference memory performance were evaluated via the Water Radial Arm Maze and the Morris Water Maze. The previously found effects of androstenedione were supported. However, when decreasing the conversion of androstenedione to estrone, the impairing effects of andro were alleviated. When androgen receptor activity is blocked, there is negligible difference in comparison with the cognitive profile of andro given alone. The implications of this study are important in understanding andro's effects on cognition, especially in post-menopausal women.

Conclusions: Androstenedione's impairment seen on several spatial memory tasks in female rats appears to be mediated by its conversion to estrone. The implications of this study are important in understanding androstenedione's effects on cognition, especially in post-menopausal women.

Poster 12

ALZHEIMER'S DISEASE BIOMARKERS AS OUTCOME MEASURES FOR CLINICAL TRIALS. Caroli A, Prestia A, Wade S, Chen K, Ayutyanont N, Landau SM, Madison CM, Haense C, Herholz K, Reiman EM, Jagust WJ, Frisoni GB, the Alzheimer's Disease Neuroimaging Initiative. Laboratory of Epidemiology and Neuroimaging - IRCCS S. Giovanni di Dio-FBF, Brescia, Italy; Mario Negri Institute for Pharmacological Research, Bergamo, Italy; Bocconi University, Milan, Italy; Banner Alzheimer's Institute; Helen Wills Neuroscience Institute, University of California, Berkeley; Hannover Medical School, Clinic for Nuclear Medicine, Hannover, Germany; University of Manchester; Arizona Alzheimer's Consortium.

Background: There is a need to improve clinical trials in Alzheimer's disease (AD) by incorporating biomarkers of disease progression and patient selection in the mild cognitive impairment (MCI) and preclinical stages of the disease. The aim of this study was to investigate and compare the performance of the best-established diagnostic biological markers as outcome measures for clinical trials in MCI patients with CSF and MRI biomarker (qualified by medicines agencies as biomarkers for enrichment in clinical trials) evidence of AD.

Methods: We considered hippocampal volume automatically computed on MRI using Freesurfer software, three FDG-PET summary metrics of AD-like hypometabolism and CSF tau as markers of neurodegeneration, CSF A!1-42 as marker of amyloidosis, and ADAS-COG as clinical marker of AD progression, and we compared their effect size and statistical power over different followup periods (12 to 24 months, with 6-monthly or yearly biomarker assessment) in two MCI populations, selected from ADNI dataset based on baseline positivity to CSF A!1-42 (MCI ABETA+) or hippocampal volume (below fifth percentile in a cognitively normal population, MCI HIPPO+). Longitudinal biomarkers progression was modeled through mixed effect models. Scaled slope, defined as the average of the slopes (over all subjects) divided by its standard deviation, was chosen as the measure of effect size.

Results: Seventy-four ABETA+ MCI and 51 HIPPO+ MCI patients were included in the study. Most of the patients had biomarkers assessed every 6 months up to 24 months after baseline. Hippocampal volume showed highest effect size for all time lengths and both patient populations, followed by the other markers of neurodegeneration, ADASCOG, and, last, CSF Abeta42. Among FDG-PET biomarkers, HCI ranked first; metaROI ranked higher than logPALZ for shortest observation periods.

Conclusions: Imaging biomarkers of neurodegeneration outperformed markers of AD pathology and clinical markers of AD progression as outcome measures for clinical trials of MCI due to AD. Hippocampal volume measurements were associated with the highest effect sizes, even for short clinical trials with yearly observations. These findings provide information about the biomarker enrichment and outcome measurements that could be employed to reduce MCI patient samples and treatment duration in future clinical trials.

Poster 13

PHOSPHORYLATED A–SYNUCLEIN HISTOPATHOLOGY IN THE ESOPHAGUS OF A SUBJECT WITH DEMENTIA WITH LEWY BODIES AND SEVERE DYSPHAGIA. Carter N, Serrano G, Sue L, Mariner M, Hidalgo J, Intorcia A, Saxon-LaBelle M, Adler C, Akiyama H, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Tokyo Institute of Psychiatry; Arizona Alzheimer's Consortium.

Background: Abnormal accumulation of phosphorylated alpha-synuclein in brain, spinal cord and peripheral tissues is common in Lewy body disorders including Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Difficulty with swallowing, or dysphagia, is a common accompaniment of both PD and DLB and could be the result of deposits of phosphorylated α-synuclein in the autonomic peripheral nervous system. To our knowledge there are as yet no studies correlating esophageal α-synuclein pathology with dysphagia. This case report concerns an 82 year old man with a nine year history of cognitive dysfunction and parkinsonism accompanied by particularly severe dysphagia.

Methods: The subject received periodic standardized cognitive and neuromotor research assessments during life and was autopsied with a full neuropathological examination after death, according to standard protocols of the Brain and Body Donation Program at Banner Sun Health Research Institute, Sun City, AZ. Multiple brain and body regions were microscopically examined. For routine histological examination, 6 µm-thick, formalin fixed, paraffin-embedded (FFPE) sections were stained with hematoxylin and eosin. Additionally, FFPE sections from multiple brain and body regions including the olfactory bulb, amygdala, brainstem, cerebral cortex, esophagus, submandibular gland and spinal cord were used to screen for α-synucleinopathy using an immunohistochemical method for α-synuclein phosphorylated at serine 129. The same method was also used to study thick 80 µm sections of esophagus.

Results: The patient had first noticed symptoms of cognitive dysfunction about 9 years prior to death, at about age 73. In 2003 he had lost about 30 pounds and was having some difficulty swallowing. In 2005 he was continuing to lose weight and still having difficulty swallowing. Additionally, he began slurring his speech and having falls. In 2006 he had been treated with Botulinum toxin for esophageal strictures. In May 2008 a percutaneous endogastric feeding tube was placed due to continued dysphagia with antibiotic-refractory Candidal esophagitis. In the last year of life he was bed-bound and uncommunicative. FFPE sections stained immunohistochemically for phosphorylated α-synuclein showed immunoreactive neuronal inclusions and nerve fibers in the olfactory bulb, medulla, pons, amygdala, cingulate gyrus, spinal cord and esophagus. The clinicopathological diagnosis was dementia with Lewy bodies. Thick 80 µm sections of esophagus showed that the intermyenteric plexus contained very frequent immunoreactive fibers, many with multifocal greatly swollen and distorted segments.

Conclusions: This case may be instructive for the extreme degree of both dysphagia and esophageal densities of abnormal nerve fibers immunoreactive for phosphorylated α-synuclein. Further studies with sufficient numbers of subjects, employing standardized clinical measures of dysphagia, are needed to determine whether dysphagia in Lewy body disorders is correlated with the densities of such nerve fiber abnormalities.

Poster 14

AMYLOID PET IMAGING USING AZD2184 AND UNUSUALLY BRIEF RADIOTRACER UPTAKE AND SCANNING PERIODS. Chen K, Langbaum JB, Bandy D, Roontiva A, Liu X, Thiyyagura P, Luo J, Protas H, Ayutyanont N, Lee W, Richter NK, Goodwin S, Jakimovich L, Prouty A, Fleisher AS, Reiman EM. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of California San Diego, San Diego; Translational Genomics Research Institute; Univeristy of Arizona.

Background: AZD2184 is a [11C]-labeled amyloid PET ligand associated with relatively rapid uptake and equilibrium in brain and which appears to have relatively high specific-to-white matter binding. For common [11C] amyloid radiotracers a typical time length for PET acquisition ranges from 50-90 minutes. In this study, we examined the ability of AZD2184 to distinguish different stages of Alzheimer's disease (AD) with reduced emission scan acquisition times and short wait following radiotracer administration.

Methods: Dynamic 90-minute AZD2184 PET scans were performed in 7 patients with probable AD (71.0±4.5 years old), 9 patients with MCI (69.1±5.73 years old), 9 older healthy controls (oHC, 66.7±4.0 years old), and 7 cognitively normal APOE e4 young non-carriers (yNC, 28.3±6.2 years old). We examined scan frame data from 10-15 minutes after tracer administration for standard uptake value ratios (SUVR) computation. These times roughly correspond to the average peak specific gray matter binding time (i.e. maximal cerebral-to-cerebellar uptake difference). Six subjects were scanned twice within 65 days (28.5±20.1 days) for test-retesting variability (TRV). Preselected regions-of-interest (ROI) including mean-cortical ROI and an automated brain mapping algorithm were each used to characterize and compare the ability of AZD2184 SUVRs to distinguish the probable AD patients, MCI patients from the cognitively normal older and younger adults.

Results: AZD2184 SUVR values over 10-15 min scan interval had high test-retest reliability (TRV=1.81%±1.36%, intra-class correlation coefficient=0.99, p=3.87e-7). These mean cortical ROI SUVR values show increases from yNC, oHC, MCI to AD (yNC<oHC<MCI<AD, linear trend p=2.0e-7 and oHC<MCI<AD with p=5.9e-5). The AD and MCI groups were each significantly different from the older and younger controls groups using either mean cortical SUVRs ($p<0.0001$ for AD vs. yNC or vs. oHC, and $p<0.05$ for MCI vs. yNC) or voxel-wise comparisons ($p<0.005$ uncorrected for all comparisons). We also observed high variability of SUVR values for MCI patients. Voxel-wise analysis revealed a spatial pattern of amyloid deposition in AD and in MCI typically observed and reported in previous AD and MCI studies.

Conclusions: AZD2184 characterizes cerebral amyloid deposition with a radiotracer uptake period as brief as 10 min and an emission frame as brief as 5 min, a feature that may have practical advantages over other tracers. However, direct comparisons and larger studies are needed to compare the ability of different scanning time and emission intervals to distinguish subject groups with greater statistical power.

Poster 15

BASELINE FDG PET AND VOLUMETRIC MRI PREDICTS ALZHEIMER'S DISEASE CONVERSION FROM MILD COGNITIVE IMPAIRMENT: AN ADNI STUDY. 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. Banner Alzheimer's Institute; Banner Good Samaritan PET Center; Arizona State University; University of Arizona; University of California, San Diego; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: The feasibility of using imaging based biomarker data in the early stage of the AD (or preclinical phase of AD) such as Mild Cognitive Impairment (MCI) due to AD has been investigated in multiple studies recently. In this study, using data from Alzheimer's disease neuroimaging initiative (ADNI), we examine baseline measurement of FDG-PET, structural MRI each alone or in combination together also with cognitive test in distinguishing individuals with MCI who converted to AD and those who did not aiming to establish their usefulness in as predictors for progression to AD.

Methods: Total of 139 ADNI participants who were diagnosed as MCI were included in this study. Among them, 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. All subjects had baseline FDG-PET and MRI data. In addition to voxel-wise analysis for each of the two imaging modalities, FDG-PET hypometabolic convergence index (HCI) and MRI hippocampal (HCV) volume were used each separately or in combination together also with Alzheimer's Dementia Assessment Scale-modified (ADAS-mod) to examine the statistical power in distinguishing the two groups using Receiver Operating Curve (ROC).

Results: The two group did not differ in mean age, education and gender ratio. However, they differed significantly in APOE4 ratio ($p=0.02$) and cognitive tests (ADAS-11 $p=9.9e-8$, ADAS-mod $p=2.4e-8$, MMSE $p=0.001$). Voxel-based analysis for both baseline FDG PET and MRI VBM demonstrated reduced glucose uptake and regional gray matter volumes in converters compared to non-converters in the anterior cingulate, medial prefrontal cortex, posterior cingulate and precuneus regions. HCI, HCV and ADAS-mod each separately distinguished converters from non-converters (sensitivity/specificity =80%/64%, 78%/71% and 70%/64% for HCI, HCV and ADAS-mod). When combining these 3 indices together, the sensitivity and specificity were both increased and more balanced (sensitivity=82%, and specificity=80%).

Conclusions: FDG PET measured glucose uptake, MRI measured hippocampal volume and ADAS-mod at baseline can all distinguish MCI converters from non-converters and with increased statistical power when combined. Our findings validate several previous studies that demonstrated imaging based biomarkers as predictors of future clinical decline.

Poster 16

NEITHER ALZHEIMER'S DISEASE NOR THE APOLIPOPROTEIN E ALLELE IS ASSOCIATED WITH A LOWER GLOMERULAR FILTRATION RATE. Chiarolanza G, Sue L, Mariner M, Hidalgo J, Henry-Watson J, Davis K, Jacobson S, Sabbagh M, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Published/Journal Information: manuscript in preparation

Background: Numerous reports have been suggestive of associations between renal and brain microvascular disease, and between renal function, cardiovascular function, cognitive function and Alzheimer's disease (AD). Most of these studies have been hampered by not having had autopsy assessment of the brain, heart and kidneys. These associations were investigated using brain, heart and kidney tissue as well as clinical data derived from the Arizona Alzheimer's Disease Core Center and the Arizona Alzheimer's Consortium, which are overlapping longitudinal clinicopathological studies based in Sun City, Arizona. Subjects are autopsied by the Brain and Body Donation Program at Banner Sun Health Research Institute.

Methods: Consecutive cases with whole-body autopsy were selected (N = 59). Cases were excluded if they had renal infarcts, neoplasms or significant renal inflammation. Apolipoprotein E genotyping was performed. History of hypertension (HT), congestive heart failure (CHF), coronary artery disease (CAD) and myocardial infarction (MI) was determined from review of subjects' private medical records as was estimated glomerular filtration rate (eGFR): the eGFR closest to death was used. Sections of renal cortex were assessed for densities of sclerotic glomeruli. Heart weight, left ventricular thickness and presence or absence of left ventricular myocardial infarction were utilized from autopsy data while autopsy brain measures included circle of Willis atherosclerosis score (CW), white matter rarefaction score (WMR), numbers of lacunar and microscopic infarcts and presence or absence of histopathological diagnostic criteria for AD-type dementia.

Results: Subjects were 68% male and 32% female with a mean age of 81 (SE 12.9). Neuropathologically, subjects included 28 with AD, 21 cognitively normal elderly controls, 8 with Parkinson's disease, 6 with dementia with Lewy bodies, 6 with vascular dementia, 2 with progressive supranuclear palsy, 2 with motor neuron disease, 2 with frontotemporal lobar degeneration with TDP-43-positive inclusions and 1 with hippocampal sclerosis dementia. Diagnoses are not mutually exclusive as many cases had more than one diagnosis. Univariable logistic regression analysis found only a history of HT to be significantly associated with a lower eGFR while only AD and possession of the apoE-4 allele were associated with a significantly lower MMSE score. Increased heart weight and increased CW atherosclerosis score had trends to having a significant association (p values 0.09 and 0.07) with a lower MMSE score.

Conclusions: Measures of cardiovascular disease are associated with lower eGFR and, with a larger sample, would probably be associated with a lower MMSE score. Renal and brain function appear to be jointly affected by atherosclerotic and microvascular changes induced by aging and hypertension. Neither AD nor the apolipoprotein E-E4 allele are associated with a lower eGFR.

Poster 17

EPIC (EARLY-STAGE PARTNERS IN CARE): A SUCCESSFUL PILOT INTERVENTION FOR EARLY-STAGE DYADS. Coon DW, Whitlatch C, Felix V, Walker T, Contreras V, Allen A, Schaus D, Besst D. Arizona State University; Benjamin Rose Institute; Desert Southwest Chapter of the Alzheimer's Association; Arizona Department of Economic Security; Arizona Alzheimer's Consortium.

Published/Journal Information: Under review.

Background: Roughly 5.4 million Americans live with Alzheimer's disease and related disorders (AD), and this number is expected to grow 30% by 2025. Identification of AD in the early stages creates advantages for early-stage people (EPs) and their care partners (CPs). For example, earlier intervention affords EPs the opportunity to more fully participate in care decision-making; it permits EPs and CPs to work together to more effectively mobilize support and develop future plans; and, as a result, it helps to enhance positive EP/CP outcomes. While the emphasis on early detection and treatment is growing, there has not been a corresponding emphasis on psychosocial interventions that would address the CP's or EP's mental health and well-being at the early stage of the disease. Although evidence-based, nonpharmacological multimodal treatment protocols for EPs have produced some positive outcomes, these interventions have usually focused solely on EPs, ignoring CPs and the opportunity for the EPs' voices to be heard by CPs regarding future treatment decisions and care options.

Methods: Funded by a U.S. Administration on Aging grant, 42 dyads of EPs and their current or future CPs (N=84) across the state of Arizona participated in EPIC, a seven session group dyadic intervention. EPIC was embedded into the community through the local Alzheimer's Association from its inception. Trained and supervised chapter staff delivered EPIC which focuses on EP care preference and values clarification, skill building, and social support. This pilot project used a basic pre-post quasi-experimental design. Key outcomes included measures of positive and negative affect and care preparedness for both EPs and CPs; EP self-esteem and quality of life; and, CP self-efficacy, and knowledge of EP future care preferences.

Results: EPIC yielded a variety of significant outcomes (*ps*<.05) including improved care preparedness and partner interactions, and reductions in depressive symptoms for both EPs and CPs. EPs also reported increased quality of life, self-esteem, and positive affect, and reduced anger/hostility. Additional outcomes for CPs included increased problem solving self-efficacy, and knowledge of EP's daily care preferences and long-term care wishes. Over 94% of participants said EPIC improved their understanding of memory loss, increased their confidence in dealing with memory problems, made their lives easier, and enhanced their ability to care for each other. Effect sizes ranged from .28 to 1.49.

Conclusions: EPIC is a feasible and acceptable intervention for early-stage individuals and their care partners, and it is the first of its kind embedded into a community based organization from its inception that yielded significant outcomes for both EPs and CPs. In addition, its group based, manualized format holds promise for delivery in a cost effective manner when compared to more intensive individualized treatments. Findings warrant a future EPIC RCT with longitudinal follow-up.

Poster 18

LENALIDOMIDE AS ANTI-NEUROINFLAMMATORY AND BACE1 INHIBITOR: PILOT STUDY ON APP23 MICE. Decourt B, Walker A, Macias MP, Gonzales A, Sabbagh MN. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Preliminary results indicated that chronic administration of the very potent TNFa inhibitor thalidomide significantly reduces brain inflammation and amyloid pathology in APP23 transgenic mice. We hypothesized that lenalidomide, a less toxic analog of thalidomide, might represent a safer alternative to treat Alzheimer's disease (AD) in humans. Here, we are presenting new data from our pre-clinical proof of concept study collected in the past months.

Methods: The effects of two doses of lenalidomide were evaluated: 0 and 100 mg/kg administered intraperitoneally for four weeks to APP23 mice (n=4 and 5, respectively). Non-transgenic (WT) littermates were used as controls (n=5 per dose). After sacrifice, brains were hemisected and used in histological and biochemical experiments. Brain sections were immunostained with an anti-amyloid beta antibody (6E10) and counterstained with thioflavin S. Quantitative PCR and Western blotting for TNFa precursor and BACE1 were conducted on the cortex from the same animals (n=2 APP23 and 4 WT mice per drug group). In addition, Western blots were conducted on whole half-brain lysates.

Results: APP23 mice treated with 100 mg/kg lenalidomide showed ~70% decrease in total (dense + diffuse plaques) and dense cortical amyloid plaques compared to vehicle-treated animals. The immunomodulatory efficacy of lenalidomide treatment was confirmed by a 50% decrease in cortical TNFa mRNA levels measured by qPCR. In addition, both qPCR and Western blotting also revealed a 50% and 20% decrease, respectively, in cortical and whole brain BACE1 signals after lenalidomide treatment. No change in TNFa and BACE1 levels were detected in WT mice after drug treatment.

Conclusions: The data presented here warrant further examination of lenalidomide as both anti-inflammatory and anti-amyloid treatment for AD. Additional experiments using larger sample sizes and including cognitive/behavioral tests are in progress. If confirmed, our data will provide grounds for the rapid translation of lenalidomide for clinical application and therapeutic trials This project was supported by NIA grants R01AG034155, P30AG019610-09, and 5P30AG019610-12, and by an Alzheimer's Association grant (NIRG-12-237512).

Poster 19

APOE AND QUALITY OF LIFE IN THE ARIZONA APOE COHORT. Dueck AC, Locke DEC, Caselli RJ. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: ApoE e4 has previously been shown to be associated with Alzheimer's disease and other adverse health outcomes which may impact perceived quality of life (QOL). Previous studies employed general QOL measures and have not shown a relationship between ApoE status and QOL. This cross-sectional analysis examined the association between QOL and ApoE status, and between QOL and measures of depression and cognitive function in the Arizona ApoE Cohort using a tool appropriate for subjects at risk for cognitive impairment.

Methods: Cognitively normal residents of Maricopa County age 21 years and older (the Arizona ApoE Cohort) had neuropsychological testing every two years that included the long term memory score of the Auditory Verbal Learning Test (AVLT-LTM), Folstein Mini-Mental State Examination (MMSE), Controlled Oral Word Association Test (COWAT), Judgment of Line Orientation (JLO), and the Mattis Dementia Rating Scale (DRS). Subjects also completed the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HAM-D) at each visit. In 2011, a QOL assessment (Quality of Life-Alzheimer's Disease Scale, QOL-AD, Logsdon et al, 2002) was added to the battery. First administration of the QOL assessment was available in 186 subjects for a cross-sectional analysis. Categorical and continuous variables were compared between groups using chi-squared tests and t-tests, respectively. A general linear model was used to compare QOL between groups while adjusting for subject characteristics. Pearson correlations were computed between QOL-AD and measures of depression and cognitive function.

Results: 18 e4 homozygotes (HMZ), 58 e4 heterozygotes (HTZ), and 110 e4 noncarriers (NC) did not differ significantly in age (median 67yrs, range 41-86), gender (67% women), race (95% Caucasian), ethnicity (12% Hispanic), years of education (median 16 yrs, range 8-22), family history of dementia (74%), history of depression (40%), and time since study enrollment (median 8.6 yrs, range 0-18.3). Groups differed by body mass index (16% obese in carriers vs 30% in NC, $p=0.02$). There was a trend for lower QOL-AD scores in carriers vs NC (mean 41.8 vs 43.1, pooled SD=5.1, $p=0.07$) which persisted when adjusting for subject characteristics ($p=0.02$). However, the relationship between QOL-AD scores andApoE status did not appear to be gene-dose dependent (linear trend $p=0.15$; mean 42.3 [HMZ] vs 41.6 [HTZ] vs 43.1 [NC]). QOL-AD was significantly correlated with BDI ($r=-.44$, $p<0.001$), HAM-D ($r=-.49$, $p<0.001$), DRS ($r=.15$, $p=0.045$), and COWAT ($r=.20$, $p=0.005$) with a trend towards significance with the MMSE ($r=.14$, $p=0.06$) in the unstratified cohort. Magnitude of correlations with the depression measures were considered moderate (>.4 in absolute value), whereas for cognitive function wereweak (</=.20 in absolute value). QOL-AD did not appear to correlate with AVLT-LTM nor JLO.

Conclusions: Cross-sectional analysis suggested a trend towards decreased QOL in ApoE e4 carriers though not in a gene-dose fashion. Longitudinal assessment of QOL in the Arizona ApoE Cohort is ongoing.

Poster 20

NEUROPATHOLOGICAL OUTCOME OF PROSPECTIVELY FOLLOWED NORMAL ELDERLY BRAIN BANK VOLUNTEERS. Dugger BN, Hentz J, Adler C, Sabbagh M, Shill H, Jacobson S, Caviness J, Belden C, Driver-Dunckley E, Davis K, Sue L, Beach TG, APDC. Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: Submitted AAIC abstract

Background: Existing reports on incidence rates of neurodegenerative disease are entirely based on clinical diagnosis and thus subject to considerable diagnostic error. To our knowledge, there have been no studies of incidences of neuropathologically-defined neurodegenerative disease in elderly subjects. This study reports neuropathological outcome of elderly subjects prospectively followed and originally established, with standardized research assessments, as cognitively normal and without a major movement disorder at the beginning of the study.

Methods: The Banner Sun Health Research Institute Brain and Body Donation Program database was queried for autopsied cases that were normal at the time of study entry. Study entry was defined as the first epoch with both cognitive and movement examinations and diagnoses not being more than 1 year apart. Normal was defined as subjects, who at initial cognitive and motor examinations, were cognitively normal (lacking diagnosis of dementia or mild cognitive impairment), lacked a diagnosis of any form of parkinsonism, Huntington's disease, amyotrophic lateral sclerosis, and/or primary lateral sclerosis, as well as normal pressure hydrocephalus.

Results: One hundred and nineteen cases fit inclusion and exclusion criteria, 52% were female, mean age of entry was 83.7 years (range 67 to 99), and with a mean duration until death was 4.3 years (range 0-10). Of these 119 cases, 84 (71%) remained normal lacking a defined neuro-clinicopathologic diagnosis at autopsy. Within these, 17/84 (20%) had incidental Lewy bodies and 4 (5%) had incidental progressive supranuclear palsy (PSP). Of the total series, by the time of death 21/119 (18%) were diagnosed with Alzheimer's disease, 4 (3%) with PSP, 7 (6%) with vascular dementia, 3 (3%) with Parkinson's disease, 2 (2%) with dementia with Lewy bodies, 1 with corticobasal degeneration and 1 with multiple system atrophy. These diagnoses are not mutually exclusive.

Conclusions: The neuropathological outcome of these initially-normal elderly subjects represents an estimate of incidence of several neurodegenerative conditions over a defined time period. As the only other comparable data is derived from epidemiological studies based on clinical diagnoses, the data presented is likely to be considerably more accurate than earlier reports.

Poster 21

THE DISTRIBUTION OF PHOSPHORYLATED TAU IN SPINAL CORDS OF ALZHEIMER'S DISEASE AND NON-DEMENTED INDIVIDUALS. Dugger BN, Hidalgo JA, Chiarolanza G, Mariner M, Henry-Watson J, Sue LI, Beach TG. Civin Laboratory for Neuropathology, Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
Published/Journal Information: Journal of Alzheimer's Disease

Background: Abnormal phosphorylation of the microtubule-associated protein tau develops in selected brain regions in normal aging and becomes widespread throghout the brain in Alzheimer's disease (AD). Braak and others have described the distribution of neurofibrillary tangles and deposition of abnormally phosphorylated tau (p-tau) and correlated this with the progressive cognitive dysfunction in AD. However, to date there have been no comprehensive studies examining abnormally phosphorylated tau deposition in the spinal cord as part of normal aging or AD.

Methods: We investigated, using immunohistochemical methods, the presence of p-tau in the spinal cord of 46 cases with a clinicopathological diagnosis of AD as well as 37 non-demented(ND) individuals lacking any defined central nervous system-related clinicopathological diagnosis.

Results: We found the cervical cord segments to be the most frequently affected subdivision (96% AD versus 43% ND), followed by thoracic (69% AD versus 37%ND), lumbar (65% AD versus 27% ND), and sacral (53% AD versus 13% ND). The spinal cord was often affected at early-stage brain disease, with p-tau spinal cord immunoreactivity in 40% of subjects at Braak neurofibrillary stage I; however, there were no cases having spinal cord p-tau that did not have p-tau within the brain.

Conclusions: As p-tau immunoreactivity is present within the spinal cords of ND as well as AD subjects, it is likely that the phosphorylation of spinal cord tau occurs in the preclinical stage of AD, prior to dementia. The presence of significant spinal cord p-tau-immunoreactive pathology has important implications for both the pathogenesis and clinical manifestations of AD.

Poster 22

EXAMINATION OF BODY MASS INDEX, ORGAN WEIGHTS, AND DIAGNOSED MEDICAL CONDITIONS IN AN AUTOPSY SERIES OF ALZHEIMER'S DISEASE AND NON-DEMENTED INDIVIDUALS. Dugger BN, Saxon-LaBelle M, Chiarolanza G, Hidalgo JA, Maarouf C, Malek-Ahmadi MH, Wilson J, Roher AE, Beach TG. Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Published/Journal Information: AAIC submitted abstract

Background: Some studies suggest body weight decreases in Alzheimer's disease (AD) and this may even precede dementia. However, weight loss occurs at differing rates in organs and no studies to date have examined weights of peripheral organs in AD. Furthermore, many medical conditions are known to have certain associations with AD, and whether these associations may be due to decreases in weight and/or AD is unclear.

Methods: The purpose of this study was to compare the last recorded body mass index (BMI) during life, autopsy weights of major organs including brain, heart, liver, lungs, kidney, and spleen, and commonly diagnosed medical conditions between clinicopathologically confirmed AD (N= 87), and non-demented individuals lacking a defined clinicopathological neurodegenerative disease (NC, N= 68). Multiple linear and logistic regression models adjusted for age at death, postmortem interval, gender, and last BMI were used.

Results: BMI was significantly less in AD compared to NC at autopsy (23 vs.25), confirming previous reports. When examining individual organ weights, only the liver and brain in AD cases had significantly lower weights when compared to NC. There were no correlations between dementia duration or disease stage (Braak) and BMI to any organ weight. Furthermore, upon retrospective medical chart reviews of commonly diagnosed medical conditions in our database, AD cases had significantly lower incidences of arthritis(53 vs.75%), cataracts(39 vs.56%), gastroesophageal reflux disease(29 vs.47%), diverticular disease(22 vs.37%) renal(17 vs.43%), and congestive heart failure(15 vs.40%), but an increased incidence of incontinence (19 vs.55%) when compared to NC.

Conclusions: The central nervous system is the integrating and command center of the body; interpreting sensory input and dictating responses which are sent to the peripheral organs. These data further support AD can cause changes outside the realm of the central nervous system.

Poster 23

COMPREHENSIVE PROFILING OF DNA METHYLATION DIFFERENCES IN PATIENTS WITH ALZHEIMER'S AND PARKINSON'S DISEASE. Dunckley T, Meechoovet B, Caselli RJ, 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.

Poster 24

MAPPING THE SPATIAL NAVIGATION NETWORK OF YOUNG AND AGED RHESUS MACAQUE MONKEYS: A POSITRON EMISSION TOMOGRAPHY STUDY. Engle JR, Machado CJ, Maurer AP, Permenter M, Vogt J, Barnes CA. Evelyn F. McKnight Brain Institute; University of Arizona; California National Primate Research Center, Davis CA; ARL Div Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: 2012 Society for Neuroscience, New Orleans, LA

Background: Activation of the neural substrates devoted to spatial navigation is largely dependent upon behavioral and environmental cues. Much of our current understanding of how such cues engage these neural substrates comes from studies of freely moving rodents, as it is technically more difficult to study this problem in the nonhuman primate brain.

Methods: To gain a better understanding of nonhuman primate spatial navigation networks and how they change with age, four rhesus monkeys were trained to freely or passively traverse a long enclosure, and to walk on a treadmill. We measured cerebral glucose metabolism with the radiotracer 2-deoxy-2[18F]-fluoro-D-glucose (FDG) and high-resolution positron emission tomography (microPET). Two of the four monkeys have been successfully scanned after the four conditions given in pseudorandom order: 1) freely traversing the enclosure, 2) passive traversals in the same enclosure not excluding optic flow, 3) walking on a treadmill without optic flow, 4) sitting in a cage (control condition).

Results: We used ROI analysis to assess the contributions of behavioral state and age on spatial navigation network activity. Our preliminary results from two monkeys (12 and 27 years old) suggest that ROIs in the right hemisphere overall had a significantly greater uptake of FDG than ROIs in the left hemisphere (t-test, $p < .001$). The magnitude of the percent change across the behavior conditions, however, interacted with age. The difference in FDG uptake compared to the control condition was more pronounced when the young monkey was considered separately, although movement behavior was matched across age. This interaction was found in the right medial temporal lobe, area TE, anterior cingulate, retrosplenial and medial occipitoparietal area ROIs.

Conclusions: These preliminary results suggest that the right hemisphere of the rhesus monkey may contribute to spatial navigation, and may undergo similar age-related changes in the spatial navigation network that has been reported in aged rodents. Support: NIH Grant AG003376, NIH Grant NS070464, California National Primate Research Center Grant P51 RR00169, McKnight Brain Research Foundation.

Poster 25

REGIONAL BRAIN NETWORK OF MRI GRAY MATTER WITH GRADUAL INDUCTION OF HYPERTENSION IN THE CYP1A1-REN2 TRANSGENIC RAT. Fitzhugh MC, Totenhagen JW, Yoshimaru ES, Richards A, Hoang LT, Allen AN, Turk M, Krate J, Biwer LA, Hale TM, Chen K, Moeller JR, Coleman PD, Mitchell KD, Huentelman MJ, Barnes CA,Trouard TP, Alexander GE. University of Arizona and McKnight Brain Institute; TGen; Banner Alzheimer's Institute; Columbia University; Banner SHRI; Tulane University; Arizona Alzheimer's Consortium.
Published/Journal Information: presented at: SfN 2012, Society for Neuroscience 42nd Annual Meeting: 2012 Oct 13-17; New Orleans, LA

Background: It is well established that hypertension (HTN) in humans can lead to regional brain atrophy and cognitive decline. With a high prevalence in the community-dwelling elderly population, HTN may be an important factor influencing the development and progression of cognitive aging. We sought to investigate the effects of HTN on gray matter volume from magnetic resonance imaging (MRI) scans of the brain obtained in a rodent model of HTN. Since the onset and progression of HTN in humans often occurs gradually after middle-age, we used transgenic rats that allow for the gradual induction of HTN in middle-aged animals (Mitchell et al., 2006).

Methods: The inbred male rats, with a Fischer 344 background, have the cytochrome P450 promoter (Cyp1a1) inserted to up-regulate the expression of the mouse renin (Ren2) gene. Administration of 0.15% indole-3-carbinol (I3C) activates the Cyp1a1 promoter to induce a gradual onset of HTN. We administered an I3C augmented diet at 16 months of age over a 6-week interval to produce a HTN group of Cyp1a1-Ren2 rats (N = 5), whereas the control group of transgenic rats (N = 5) received normal food pellets. Volumetric T2-weighted MRI scans were acquired at 7.0 T with 150-micron isotropic voxel resolution for both the HTN and control groups. Multivariate network analysis with voxel-based morphometry (VBM) and the Scaled Subprofile Model (SSM; Alexander and Moeller, 1994) was used to identify a regional network pattern of MRI gray matter that differed between the groups.

Results: The HTN group had higher mean systolic ($p < 0.009$) and diastolic ($p < 0.016$) blood pressures during the 6-week interval than controls. Additionally, when analyzed as a proportion of body weight, heart and kidney weights were increased for the HTN group compared to controls ($p < 0.009$). SSM analysis of MRI VBM with bootstrap re-sampling of the HTN and control groups combined identified two regional network patterns of gray matter that distinguished the hypertensive rats from controls ($p < 0.009$). This linearly combined pattern was characterized by gray matter reductions in the vicinity of the thalamus, basal ganglia, cerebellum, and a region of the hippocampus with relative increases observed in selective frontal and temporal areas.

Conclusions: Together, these findings provide preliminary support for the use of the Cyp1a1-Ren2 rat to help advance translational research on the cerebrovascular effects of HTN during aging. The use of such transgenic rodent models combined with high resolution MRI and network analyses may aid efforts in the evaluation of new treatments and prevention therapies for the brain changes associated with healthy and pathological aging.

Poster 26

PRE-SYMPTOMATIC FUNCTIONAL BRAIN CHANGES IN PS1 E280A MUTATION CARRIERS COMPARED TO OTHER BIOMARKERS: PILOT DATA FROM THE ALZHEIMER'S PREVENTION INITIATIVE BIOMARKER PROJECT. Fleisher AS, Chen K, Quiroz YT, Jakimovich LJ, Gomez MG, Langbaum JBS, Roontiva A, Thiyyagura P, Liu X, Lee W, Ayutyanont N, Parks SA, Ruiz A, Tariot PN, Lopera F, Reiman EM. Banner Alzheimer's Institute; Banner Good Samaritan PET Center; Arizona State University; University of Arizona; University of California, San Diego; Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Boston University; Universidad de Antioquia.

Background: The Alzheimer's Prevention Initiative (API) has conducted pilot biomarker studies to characterize and compare age-related changes in the preclinical course of autosomal dominant Alzheimer's disease (AD) in the PS1 E280A mutation kindred from Antioquia, Colombia. We previously presented evidence of changes in florbetapir positron emission tomography (PET) 17 years before, cerebrospinal fluid AB42 and Tau 14 years before, and hippocampal volume reductions 7 years prior to the median age of MCI onset. We have now completed FDG PET and functional MRI (fMRI) assessments for comparison.

Methods: Fifty family members from Colombia received FDG PET measurements on a Siemens Biograph mCT 64 PET CT scanner with 30-min dynamic emission scan acquired 30-min after the IV administration of 5mCi of FDG. The cohort included 11 symptomatic carriers (7 with MCI (46 years +/- 4.5), 4 with AD dementia (51 years +/- 1.9)), 19 cognitively normal mutation carriers (33 years +/- 8.0) and 20 non-carriers (NC, 34 years +/- 8.5) between ages 20 to 56 years old.. Regional-to-whole brain cerebral metabolic rates of glucose (CMRgl) were compared between PS1 E280A mutation carriers and NC, accounting for age effects. A nonlinear model was used to characterize CMRgl decline and to estimate the age at which its reductions in mutation carriers became apparent as compared to NC. Voxel-wise comparisons of resting state fMRI default mode network (DMN) was compared between carriers and NC using a 10mm spherical posterior cingulate seed region.

Results: Compared to non-carriers, symptomatic and pre-symptomatic mutation carriers had significantly lower CMRgl in posterior cingulate, precuneus, parietal and temporal regions known to be preferentially affected by AD. And mutation carriers had significantly greater associations between these CMRgl reductions and age. Precuneous CMRgl reductions appear to begin approximately 18 years prior to the typical median age of MCI onset, roughly similar to the age at fibrillar amyloid accumulation and CSF Aβ and Tau changes. Compared to non-carriers, symptomatic and pre-symptomatic mutation carriers also had significantly reduced resting state functional connectivity in the DMN.

Conclusions: Functional PET and MRI imaging identifies pre-symptomatic brain changes in PS1 E280A carriers. FDG PET reductions are seen near the time of fibrillar amyloid accumulation. Estimates of ages of AD biomarkers are partly based on the biomarker modality, as well as on analysis methodology. These biomarkers provide additional tools for evaluating pre-symptomatic Alzheimer's disease.

Poster 27

A STUDY OF THE COMMUNITY-BASED ELDERVENTION® SUICIDE PREVENTION PROGRAM ON THE RISK FACTOR OF SOCIAL ISOLATION IN OLDER ADULTS. Flint M, Virden T, McDermott B. Midwestern University, Area Agency on Aging, Region One.

Background: The impact of older adult suicide is pervasive. With increasing numbers of older adults dying by suicide, focus on a primary prevention level program to reduce the risk of developing suicidal ideation/ suicidal actions is warranted. Although much research has been done assessing postvention strategies, few have reflected solely on primary prevention strategies delivered within community environments. Through the use of the community based ElderVention® Suicide Prevention Program, this study aims to evaluate the effectiveness of the Program on identifying persons at risk for suicidal behavior based on their social isolation (lack of connectedness/ belongingness).

Methods: Existing curriculum-based "Transition Workshops" offered at senior centers through the ElderVention® program will be evaluated for their impact on the suicide risk factor of isolation using the Coping Resources Inventory (CRI) and the Beck Scale for Suicidal Ideation (BSI). Study results will provide information about the Program's effectiveness, the impact of decreasing social isolation in this vulnerable population as well as provide strong empirical basis to support the need for community based interventions to decrease social isolation for older adults.

Approximately 400 new participants of the ElderVention® program will be invited from among 17 sites already receiving ElderVention® services through the Area Agency on Aging, Region One to participate in this study via on-site advertisements and direct invitation from staff. These sites range from those located in the metropolitan Phoenix area to rural locations in Maricopa County. Based on current demographics of ElderVention® participants, it is anticipated that 77% (n = 208) participants will be female, 60% (n = 240) will be Caucasian, 2% (n = 8) will be Hispanic, 2% (n = 8) will be African American, and 1% (n = 4) will be Asian. Participants will be randomly assigned to either the immediate treatment (IT) or the wait-list control (WLC) groups.

The present study is designed to assess the efficacy of the ElderVention® program in decreasing suicidal ideation and increasing a sense of belonging in elder participants relative to those who are not participating in the program. In addition, this study will establish the maintenance of gains for 4 months after program completion. To that end, the proposed study will utilize a 2 X 4 mixed factorial design with treatment condition as the between groups factor at two levels (IT vs. WLC) and testing interval (0, 8, 16, and 24 weeks) as the repeated measure. Participants will be asked to appear at their ElderVention® site on four occasions at 8-week intervals for testing during a 24-week cycle. At each test session, participants will be administered the BSI and CRI at their ElderVention® site by trained staff who are supervised by licensed psychologists. Participants randomly assigned to the IT group will participate in the 8-week ElderVention® program as described in this document immediately after testing at week 0 of the testing cycle. Those assigned to the WLC group will be enrolled to begin the ElderVention® program at week 8 of the testing cycle.

To determine changes in BSI and CRI scores at each time point for each group, a repeated measures analysis of variance (ANOVA) will be utilized for both the IT and WLC groups. Effectiveness of the ElderVention® program will be assessed via a multivariate analysis of covariance (MANCOVA) utilizing BSI and CRI scores week 0 as a covariate. Treatment group (WLC or IT) will be utilized as a grouping variable and test scores at the 8, 16, and 24-week time intervals as dependent variables. It is anticipated that ANOVA results will indicate that test scores at 8, 16, and 24 weeks will show significant improvement relative to week 0 scores for the IT group and test scores at 16 and 24 weeks will demonstrate significant improvement relative to scores yielded at weeks 0 and 8 among participants in the WLC group. Similarly, it is anticipated that MANCOVA results will demonstrate that participants in the

IT group will yield greater changes in test scores at 8 weeks relative to 0 weeks than will participants in the WLC group. No differences between groups in this analysis will be expected at 16 or 24 weeks.

Poster 28

PITUITARY ADENYLATE CYCLASE ACTIVATING POLYPEPTIDE PROTECTS AGAINST BETA-AMYLOID TOXICITY BY ENHANCING MITOCHONDRIAL FUNCTION. Han P, Tang Z, Yin J, Maalouf M, Beach TG, Reiman EM, Shi J. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Published/Journal Information: submitted

Background: The prevention and treatment of Alzheimer's disease and other neurodegenerative conditions remain a challenge for medical research. One of the primary goals is to find a highly efficient neuroprotective agent with insignificant adverse effects. Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) is intrinsically expressed in mammals and is considered to be a potent neurotrophic and neuroprotective peptide.

Methods: Post mortem human brain samples from AD and Non-AD patients were provided by Sun Health Research Institute Body and Brain Donation program. Cortical neurons from P0-P3 pups were obtained to establish primary neuronal cell culture. A short sequence of 19 nucleotides targeting Sirtuin3 location 764 was constructed into OmicsLink shRNA expression clone to knock down the expression of Sirt3. This vector and control vector were packaged in Lentiviruses to transfect the cultured neurons. Mitochondrial respiratory function was measured by metal-porphyrin based oxygen probe. Western blot and immunochemistry were used to detect and quantify PACAP and Sirt3 protein expression.

Results: PACAP level was reduced in both human AD brain and the 3×Tg-AD mouse brain. This reduction of PACAP correlated with the lower expression of SIRT3, a modulator for mitochondrial respiratory chain. PACAP protected neurons from beta-amyloid induced toxicity in vitro by potentiating mitochondrial respiratory function, as knocking down intrinsic SIRT3 expression abolished this protective effect.

Conclusions: PACAP is neuroprotective in Alzheimer's disease by enhancing mitochondrial respiratory function.

Poster 29

THE EFFECTS OF CONJUGATED EQUINE ESTROGEN ON COGNITION AND ANXIETY-LIKE BEHAVIOR. Hiroi R, Mennenga S, Koebele S, Hewitt L, Mendoza P, Lavery C, Weyrich G, Kolodziej A, Karber L, Atchison H, Patel S, Poisson M, Bimonte-Nelson H. Department of Psychology, Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging and the menopausal transition are each associated with cognitive impairment, which is often co-morbid with affective disorders such as depression and anxiety. Low or changing levels of estrogen in women, such as during post- and peri- menopause, are associated with cognitive and affective disorders, which are often effectively treated by estrogen therapy. Benefits of 17 beta-estradiol (E2), the most potent naturally circulating estrogen, on cognitive, anxiety-like, and depressive-like behaviors have been shown. Although conjugated equine estrogen (CEE) is the most commonly prescribed estrogen in hormone therapy in menopausal women, there is a marked gap in knowledge regarding whether CEE affects cognition, anxiety-like, and depressive-like behaviors. We previously found that CEE has beneficial effects on cognition in adult and middle-aged rats. Previous studies have also shown anti-anxiety effects of CEE in middle-aged rats. However, none of these studies tested all measures in one study precluding evaluation of relationships between these behaviors. In the present study, we investigated the effects CEE treatment on a battery of cognitive, anxiety-like, and depressive-like behaviors, and compared these effects to those seen after E2 treatment.

Methods: Female Sprague-Dawley rats were ovariectomized at 3 months of age, and were administered either E2 (3 micrograms), CEE (30 micrograms), or vehicle (sesame oil). Rats were tested in a battery of behaviors in the following order: Water Radial Arm Maze (WRAM, spatial working and reference memory), Morris Water Maze (MWM, spatial reference memory), Delayed Match-to-Sample (DMS, spatial working memory), Visible Platform (VP, overall motor and visual ability), Open Field Test (OFT, anxiety-like behavior and overall locomotion), Elevated Plus Maze (EPM, anxiety-like behavior) and the Forced Swim Test (FST, despair-like behavior).

Results: Preliminary results showed that CEE enhanced spatial working memory in both the WRAM and DMS tasks, and that E2 decreased total errors in the DMS task, which was only a transient enhancement. CEE had no significant effects on the anxiety-like behaviors in the OFT or EPM. Replicating prior effects of others, E2 decreased anxiety-like behavior, as measured by increased time spent in the center and decreased time spent in the corner of the OFT, and by increased time spent in the open arms of the EPM. Correlations showed evidence of a relationship between poorer DMS performance and more anxiety-like behavior. This relationship was seen for both open field and elevated plus maze measures. Data are currently being scored to evaluate the effects of CEE on depressive-like behaviors.

Conclusions: The current study found that in young adult rats, CEE enhanced spatial maze performance in the WRAM and DMS. This result is consistent with previous reports in adult and middle-aged rats showing beneficial effects of CEE in these measures. In contrast, CEE had no significant effect on anxiety-like behaviors in either task testing these, including the OFT or the EPM. Further, we found that the beneficial cognitive effects of E2 were not as pronounced as those of CEE; E2 only transiently enhanced performance during learning of the DMS. Given prior evidence from our laboratory that in young animals the benefits of E2 treatment becomes evident only with a high working memory load, the cognitive tasks investigated herein may not have sufficiently taxed the working memory system to reveal beneficial E2 effects in young adults. This hypothesis is currently being tested in our laboratory. Moreover, as expected, E2 decreased anxiety-like behavior in both the OFT and EPM. This decrease in anxiety-like behaviors tended to be associated with enhanced performance in the DMS. Taken together,

these preliminary results suggest that a negative anxiety state might interfere with performance on some spatial memory tasks. Further studies are warranted to confirm and extend these findings, as well as investigate the mechanisms underlying these potential associations.

Poster 30

INVESTIGATING KIBRA/WWC1 DNA-BINDING ACTIVITY (CHIP-SEQ) DURING IN VITRO NEURAL DEVELOPMENT. Hjelm BE, Corneveaux JJ, Nguyen C, Beach TG, Huentelman MJ, Craig DW. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Published/Journal Information: Induction of Pluripotent Stem Cells from Autopsy Donor-Derived Somatic Cells. Hjelm et al. Neuroscience Letters (2011), 502(3): 219-224. Evidence for an association between KIBRA and late-onset Alzheimer's disease. Corneveaux et al. Neurobiol Aging (2010), 31(6):901-9.

Background: Induced pluripotent stem cells (iPSCs) are particularly intriguing tools for investigating the function of genes associated with neurological disease, because neural lineage-specific cell types (e.g., neurons and glia) that retain the donor's complex genetics can be generated in vitro. We observed an increase in expression and nuclear localization of KIBRA/WWC1 as our in vitro cells were reprogrammed from fibroblasts to iPSCs and were subsequently differentiated into neurons/glia. We are exploring the potential DNA-binding activity of KIBRA/WWC1 in cell-type specific contexts using chromatin immunoprecipitation and sequencing (ChIP-Seq).

Methods: In this study, we generated iPSCs from dermal fibroblast cells obtained during autopsy. This particular autopsy donor was a 75-year-old male, defined by both clinical criteria and postmortem neuropathological observations as a neurological control. The neural differentiation protocol used in these studies was specific to the development of forebrain, cortical neurons (and glia), or what is commonly referred to as the "default" neural differentiation pathway when no additional morphogens are included in culture. KIBRA/WWC1, a gene previously identified in genome-wide association studies of episodic memory and late-onset Alzheimer's Disease, was investigated across multiple in vitro cell types (i.e. fibroblasts, iPSCs, neural precursors, and cortical neurons). Localization of KIBRA/WWC1 protein was performed using immunocytochemistry. Chromatin immunoprecipitation was performed in replicate samples of all cell types described using an anti-KIBRA polyclonal antibody. DNA was isolated from enriched chromatin and was subsequently sequenced using next-generation sequencing technologies. ChIP-Seq "peaks" or enriched regions were identified using the MACS and PeakAnnotator programs, and genes identified were evaluated for possible roles in biological processes using the GO processes network using the MetaCore search engine from GeneGo Inc.

Results: KIBRA/WWC1 protein was localized primarily to the nucleus in iPSCs, neural precursors (NPCs) and in vitro neurons. ChIP-Seq studies revealed enriched genes identified from multiple cell types. Analysis of GO processes suggested KIBRA/WWC1 DNA-binding activity might have functional roles in human synaptic activity, neuron apoptosis, actin polymerization, ER-localization, and/or oogenesis. Additional studies are underway in order to validate the DNA-binding activity of KIBRA/WWC1 protein, and to understand if the binding sites identified are the result of direct KIBRA/WWC1-DNA binding or are due to binding effects of another protein or protein complex to which KIBRA/WWC1 is bound.

Conclusions: KIBRA/WWC1 was expressed in multiple cell types, and primarily localized to the nucleus in iPSCs, NPCs, and cortical neurons. ChIP-Seq studies suggest KIBRA/WWC1 may possess DNA-binding activity important to multiple biological processes, including synaptic activity and neuronal cell death. This study may provide important biological insights about the roles of KIBRA/WWC1 protein in neural cells, potentially increasing our understanding of this gene's association with memory and Alzheimer's Disease.

Poster 31

GLIAL FIBRILLARY ACIDIC PROTEIN INTERACTS WITH A HUMAN TELOMERIC PROTEIN THAT STABILIZES GENOME INTEGRITY. Israel JN, Swanson MJ, Bae NS. Midwestern University; Mercer University School of Medicine.

Background: As human cells age, chromosomes shorten at their telomeres. Normally, proteins protect these ends to maintain genome stability. One protein, RAP1, is crucial in preventing chromosomal end-fusion, a characteristic of diseased cells. Our interest was to identify proteins interacting with RAP1 to prevent diseased state.

Methods: A yeast two-hybrid screen was conducted using RAP1 as bait and a human fetal brain cDNA library as the prey. Positive candidates were expressed in bacteria then affinity purified to test direct interactions. Deletions constructs were used to map the interacting region of RAP1.

Results: Glial fibrillary acidic protein (GFAP) was identified as an interacting protein of RAP1. The interaction was verified using His6-GFAP and GST-RAP1 precipitated with Ni-agarose or glutathione sepharose beads. The interaction was mapped to the conserved myb-domain and a coiled domain of RAP1.

Conclusions: Mutation and misregulation of GFAP are involved in several neurodegenerative diseases, such as Alexander's Disease. Based on our data, it is possible that part of the effect is through RAP1 and telomere dysfunction. Further exploration of the interaction in normal and diseased states is needed.

Poster 32

CHANGES IN DENDRITIC BRANCHING, BRAIN CELL PACKING DENSITY, AND GENE EXPRESSION IN A MOUSE MODEL OF NEURODEVELOPMENTAL DISEASE. Jentarra G, Olfers S, Rice G, Naidu SB, Narayanan V. Midwestern University; Barrow Neurological Institute; Kennedy Krieger Institute.

Published/Journal Information: BMC Neuroscience 2010 Feb 17;11:19.

Background: Rett syndrome (RTT) is a neurodevelopmental disorder caused by MeCP2 mutations. We are studying the MeCP2 A140 mouse model to understand how MeCP2 mutations disrupt brain function. Patients initially develop normally, but then undergo rapid developmental regression. RTT results in a small brain, increased cell density and simplified dendrites.

Methods: Dendritic complexity was measured by Scholl analysis of Golgi-Cox stained cortical pyramidal neurons. Cell packing density was analyzed in cresyl violet stained brain tissue slices. Quantitative neurotransmitter receptor gene expression analysis of extracted brain RNA (qPCR) was done using SA Biosciences qPCR array plates.

Results: MeCP2 A140V mice showed simplified branching complexity of apical and basal dendrites of cortical pyramidal neurons. Brain cell packing density in A140V mice was visibly increased and shown to be significant in the cerebellum. Gene expression arrays showed differences between expression in the cortex and cerebellum and between 2 and 4 week old mice.

Conclusions: MeCP2 A140V mutant mice show brain structure abnormalities similar to those in RTT patients and in other MeCP2 mutant mouse models. In addition, we have identified dysregulation of neurotransmitter receptor and regulator genes essential for normal brain function. The identified genes may be potential therapeutic targets for the treatment of RTT.

Poster 33

THE EFFECTS OF KIBRA, APOE, AND HYPERTENSION STATUS ON A COMPOSITE MEASURE OF MEMORY FUNCTIONING IN OLDER ADULTS. Kawa K, Ryan L, Stickel A, Walther K, Glisky E, Hackett N, Huentelman MJ. Evelyn F. McKnight Brain Institute, University of Arizona; Ludwig Maximilians University, Munich, Germany; 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, the combined effects of KIBRA and APOE have not been investigated. Furthermore, the effects of KIBRA in older adult samples has been inconsistent, with some studies demonstrating better performance on measures of episodic memory in T allele carriers than non-carriers (Almeida et al., 2008; Papassotiropoulos et al., 2006; Schaper et al., 2008) and others showing no differences in performance between T allele carriers and non-carriers (Nacmias et al., 2008; Need et al., 2008; Sedille-Mostafaie et al., 2012). The purpose of the present study was to investigate whether interactions between KIBRA and APOE as well as pre-existing health conditions such as hypertension may account for the differences in results in the KIBRA literature.

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. Given that previous research has shown worse performance on measures of episodic memory in KIBRA CC homozygotes (Almeida et al., 2008; 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 (n = 104) and APOE ε4 carriers (n = 47) in our sample would likewise perform worse than KIBRA T-carriers (n = 109) and APOE ε4 non-carriers (n = 166). 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.

Results: As expected, APOE ε4 carriers had lower scores on the Wechsler Memory Scale III (WMS-III) General Memory Index, $F(1, 207) = 5.02$, $p < .05$. Surprisingly, the effects of KIBRA were not significant, $F(1, 207) = 1.93$, $p = .16$. With regard to hypertension status, hypertensive individuals had lower scores on the WMS-III General Memory Index than normotensive individuals, $F(1, 207) = 4.47$, $p < .05$. The interactions between hypertension status, APOE, and KIBRA, however, were not significant, all p's > .10.

Conclusions: While APOE and hypertension status each predicted performance on this composite measure of memory functioning, KIBRA did not, suggesting that other genetic and pre-existing health conditions have a greater influence on memory than KIBRA, at least in our sample of older adults. APOE, on the other hand, appears to be more resilient to the masking effects of hypertension and continues to exert its effects on memory. It is important to note that the pattern of results we observed may not apply to younger adults. In younger adult samples, the effects of KIBRA may not be overshadowed by the effects of other genes and pre-existing health conditions. As a result, the benefits of the T allele on memory performance may be more likely to be detected. Future studies investigating KIBRA and APOE in younger and older adults may help reveal the conditions under which each gene exerts its effects on memory performance.

Poster 34

EFFECTS OF CYTOPROTECTIVE MULTIFUNCTIONAL RADICAL QUENCHERS ON LYMPHOCYTES FROM REPRESENTATIVE MITOCHONDRIAL AND NEURODEGENERATIVE DISEASES. Khdour OM, Arce PM, Goldschmidt R, Dey S, Jaruvangsanti J, Hecht SM. Arizona State University; Arizona Alzheimer's Consortium.

Published/Journal Information: Bioorg. Med. Chem. 2013, 21 (4), 969-978.

Background: Mitochondrial dysfunction is a hallmark of amyloid beta induced neuronal toxicity in Alzheimer's disease (AD), and considered to be an early event in AD pathology. While oxidative stress is not the cause of AD, it is likely to contribute importantly to the progression of the disease. 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).

Methods: A number of coenzyme Q10 analogues (MRQs) were prepared and tested for their ability to supress ROS formation, restore ATP production and confer protection in several different cell lines from a wide spectrum of mitochondrial and neurological disease patients.

Results: The coenzyme Q10 analogues were found to be excellent ROS scavengers, and to protect the cells from oxidative stress induced by glutathione depletion.These MRQs were more effective than idebenone. Some of these optimal MRQs were also shown to augment ATP levels in a number of these disease cell lines.

Conclusions: We have succeeded in preparing coenzyme Q10 analogues that protect against oxidative stress and preserving mitochondrial function. These agents may be broadly applicable to the treatment of additional neurological diseases, and diseases having a component of energetic dysfunction involving mitochondrial respiration.

Poster 35

COMPARISON OF TWO ESTROGENS THAT CIRCULATE ENDOGENOUSLY AND ARE GIVEN AS COMPONENTS OF HORMONE THERAPY ON PLACE VERSUS VISUAL OBJECT RECOGNITION IN MIDDLE-AGED SURGICALLY MENOPAUSAL RATS. Koebele S, Engler-Chiurazzi E, Jordan A, Hiroi R, Bimonte-Nelson H. Department of Psychology, Arizona State University; Arizona Alzheimer's Consortium.

Published/Journal Information: In Preparation

Background: Conjugated equine estrogen (CEE; tradename Premarin) is the most widely used estrogen component of hormone therapy (HT) in the United States (Hersh et al., 2005). Clinical studies assessing the cognitive effects of CEE have been inconclusive, with some studies showing positive effects, and some studies showing negative effects (Sherwin, 2008). CEE is a complex estrogen formulation composed of over 50% estrone sulfate, which gets converted to estrone (E1), and then to 17β-estradiol (17β-E2). Of note, both E1 and 17β-E2 are endogenous to women and rats, and have been identified as possibilities for "bioidentical"-type HT regimens. We previously found that exogenously administered E1, known to increase in circulation following Premarin treatment, impaired spatial working memory performance in middle-aged, ovariectomized (Ovx) rats (Engler-Chiurazzi et al., 2012). These findings are in accordance with recent findings of others showing that exogenously given E1 negatively impacts hippocampal-dependent fear conditioning in young adult rats (Barha et al., 2009).

Methods: Given the prior focus of animal work testing estrogen-related changes on spatial tasks, and the work in women showing estrogen-related changes on non-spatial tasks, we now question whether impairments of E1 extend to non-spatial tasks. As a first step toward addressing this question of spatial or non-spatial specificity of effects, we performed a pilot study to assess the impact of E1 administration in middle-aged Ovx rats on object memory using the visual and place recognition tasks. The visual object recognition task assesses non-spatial memory, and the place object recognition task assesses spatial memory. In addition, given that 17β-E2 has been shown previously to improve object recognition memory, we included a group of rats treated with 17β-E2 as a positive control. Rats were first tested on the visual object recognition task. On the sample trial of each testing day, animals were exposed to two identical objects. On the test trial, one of the identical objects was replaced with a novel object. Animals were first tested with a minimal delay between sample and test trials (the approximate two minutes to clean the maze was the delay interval in this case). To test delayed memory retention, on subsequent days, a 4-hour delay and a 24-hour delay were instilled between sample and test trials. For place object recognition, procedures were identical to the visual object recognition protocol, with the exception that for the place object recognition test trial, one of the identical objects was moved to a new location in space.

Results: For visual object recognition, the pattern of discrimination for the novel versus familiar objects did not differ by hormone manipulation for any test day (minimal delay, 4-hour delay, and 24-hour delay). For place object recognition with the minimal delay, Vehicle- and 17β-E2- treated animals spent significantly more time exploring the object in the novel location versus the object in the old location, indicating that these animals were able to show place discrimination after a minimal delay. This effect was not seen in E1-treated animals, indicating a lack of place discrimination after a minimal delay. Further, there were no differences in time spent exploring the object in the novel versus familiar location for the 4- and 24-hour delay days for any treatment group.

Conclusions: These preliminary data suggest that in middle-aged Ovx rats, unlike with Vehicle treatment or 17β-E2 treatment, E1 treatment resulted in an inability to discriminate a novel object placement after

even a minimal delay, indicating memory impairments that could be specific to spatial memory. While further studies are necessary to confirm and extend these findings of spatial specificity, the approach to these evaluations allows a template by which to guide choice of specific estrogenic assessments to build an optimal “bioidentical” HT regimen.

Poster 36

BIOCHEMICAL CONSEQUENCES OF TRAUMATIC BRAIN INJURY IN DEMENTIA PUGILISTICA. Kokjohn TA, Daugs ID, Maarouf CL, McKee AC, Sabbagh MN, Beach TG, Roher AE. Banner Sun Health Research Institute; Midwestern University; Boston University School of Medicine; Arizona Alzheimer's Consortium.

Published/Journal Information: 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. Neurochemical profile of dementia pugilistica. J Neurotrauma. 2012 Dec 26.

Background: Dementia pugilistica (DP) is a condition that occurs in boxers resulting from repetitive blows to the head and consists of an array of deleterious anatomical, biochemical and functional cognitive dysfunctions. Ten to 20% of DP cases exhibit more serious neuropsychiatric consequences that end in Alzheimer's disease (AD) or Parkinson's disease (PD).

Methods: We employed 1D and 2D Western blots and ELISA to quantify 18 proteins present in the gray matter (GM) and white matter (WM) of 3 individuals (mean: 77 years) who died with DP. Case #1 (ApoE ε3/3) was neuropathologically uncomplicated, case #2 had the additional diagnosis of AD (ApoE ε3/4) and case #3 was complicated with PD (ApoE ε3/3). For comparison we utilized a group of 3 age-matched (mean: 75 years) non-demented control (NDC) cases with ApoE ε3/3 genotypes.

Results: There were no differences in the Aβ levels between DP and NDC cases with the expected exception of DP case #2. Tau was 60% reduced in the DP vs NDC. Alpha-synuclein was significantly reduced in the DP vs NDC cases. There were qualitative and quantitative differences in the 2D Western blots of tau, α-synuclein and GFAP among the DP cases and between DP and NDC. Scanning densitometry demonstrated statistically differences between DP and NDC in neprilysin, BDNF, GFAP, APP, α-synuclein, tau in GM and neprilysin, GFAP and MBP in WM.

Conclusions: Major biochemical differences persisted in the brains of boxers with DP which included alterations in cytostructural proteins and reduced BDNF levels. DP is also characterized by a modified biochemical profile of GFAP. The damage is also manifested in the WM as dysmyelination/defective re-myelination that may result in faulty transmission of action potentials. Our studies indicate that biochemical responses associated with DP during life are long-lasting and permanent.

Poster 37

METHYLATION AND EXPRESSION PROFILING OF MEDIAL TEMPORAL GYRUS IN ALZHEIMER'S DISEASE PATIENTS REVEALS AN ENRICHMENT IN NEURO-TRANSMISSION SIGNALING PATHWAYS. Krate J*, Piras IS*, Delvaux ER, Nolz JD, Persico AM, Beach TG, Huentelman MJ, Coleman PD. TGen; Univ. Campus Bio-Medico; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
*Equal contribution

Background: Gene Expression Profiling (GEP) studies of AD across mixed cell samples in various brain regions have identified different patterns of altered expression. In the mild to moderate dementia progression, temporal lobe-hippocampus and frontal-prefrontal cortex showed the greatest number of DEGs in AD. Additionally, genes detected in such studies are involved in intracellular signaling pathways such as calcium signaling and neuroinflammation. Downregulation of synaptic genes in AD across different areas has been reported. Out of the four brain regions studied, (superior frontal gyrus, postcentral gyrus, hippocampus, and entorhinal cortex), mostly the hippocampus showed significant changes in gene expression. One cellular mechanism utilized to regulate gene expression is DNA methylation. Our goals for this study included the extension of the gene expression profiling results in AD to the medial temporal gyrus and the investigation of methylation differences within the same brain region and same subjects.

Methods: We performed whole genome differential expression and methylation analysis on medial temporal gyrus (MTG) tissue from clinically characterized and neuropathologically verified Alzheimer's disease (AD) cases and controls (ND, n=100 in each group) using array technology from Illumina.

Results: GENE EXPRESSION: Quantile normalization followed by moderated t-statistic for differential analysis on data from Illumina HumanHT-12 BeadChip was performed. After P-value (FDR|0.8|) filtering, we identified 143 DEGs in the AD/ND comparison. The DEGs were enriched for two groups of genes (both underexpressed in AD) belonging to pathways labeled "Synaptic Vesicle Trafficking" (SVT) and "Muscarinic Acetylcholine Receptor Signaling" (MARS). The AD/ND comparison when analyzed by gender showed 45 and 328 DEGs for males and females, respectively. SVT was significantly enriched in both gender groups while MARS was only significant in the female group suggesting a potential gender difference in the pathways affected by AD. METHYLATION: After correction with the FDR method, we obtained a total list of 59,602 CpGs differentiated loci (26,228 hypermethylated and 33,374 hypomethylated in AD). A pathway analysis on both hypermethylated and hypomethylated probes suggest the presence of some enriched pathways. Some pathways are significant in both groups (Integrin Signaling, Inflammation mediated by chemokine and cytokine signaling, Angiogenesis and Gonadotropin releasing hormone receptor pathway), whereas other pathways are specific for only one group, such as Metabotropic glutamate receptor group III pathway in the hypermethylated group and Alzheimer disease presenilin pathway in the hypomethylated group. COMBINED: Since methylation has been described as having an inverse correlation to gene expression, we analyzed for genes showing hypermethylation/underexpression and hypomethylation/overexpression patterns, finding 73 genes (62.9% of total underexpressed genes) and 19 common genes (70.3% of total overexpressed genes), respectively.

Conclusions: Our expression analysis concludes that in the MTG of AD patients there is a decreased expression of SNARE complex members involved in synaptic vesicle docking at the presynaptic membrane and highlight that MARS gene expression changes are only found in females. Our data replicates prior findings in AD that include a decreased expression of SVT genes in frontal cortex and a demonstrable SNARE complex protein expression loss in the hippocampus and entorhinal cortex. The methylation/expression analysis of the hypermethylation/underexpression comparison resulted in the same

finding as above; highly significant MARS and SVT values for these two pathways. The hypomethylated/overexpressed comparison resulted in no significant pathway findings. In conclusion, the combination of expression and methylation results confirm the findings of SVT and MARS pathways since the methylation patterns of most genes is complimentary to the expression levels.

Poster 38

BEHAVIOR OF THE STATISTICAL DISTRIBUTION AND DIFFUSION KURTOSIS MODELS IN HUMAN ISCHEMIC STROKE. Lee C, Bennett KM, Debbins JP. Barrow Neurological Institute; Arizona State University.

Published/Journal Information: 21st Annual Meeting of the International Society for Magnetic Resonance in Medicine, 2013.

Background: The apparent diffusion coefficient (ADC) of the monoexponential model has been shown to decrease following ischemic stroke [1,2]. The underlying mechanisms of the reduction in the ADC remain unclear. The increased cell volume fraction is suggested to be one mechanism that results in more hindered extracellular diffusion [3,4]. However, intracellular diffusion was found to decrease [5] or increase [6] in separate studies. Reduced membrane permeability was shown to have a minor impact on reduced ADC [7]. Recently, with a b-value of up to 2500 s/mm2, the statistical distribution model [8] and diffusion kurtosis model (DKI) [9] have been used to study biophysical and pathological changes, potentially exhibiting higher sensitivity compared to the ADC [10-13]. The aim of this study was to investigate the relationship between the non-monoexponential models and microstructural changes in ischemic stroke. For this purpose, we studied the fitted parameters: σstat of the statistical distribution model (width of the distribution of diffusion rates) and Kapp of the DKI model (measure of non-Gaussian diffusion) in response to simulated microstructural changes. We compared our simulation results to the in vivo measurements of human ischemic stroke (n = 6). The results suggest that the non-monoexponential models may be useful in identifying the biophysical mechanisms in ischemic stroke.

Methods: Simulation: We performed a Monte Carlo simulation of 2-D water diffusion inside simulated tissue consisting of semi-permeable cells and a variable cell size and inter-cell distance [14,15]; mean cell size: 10 μm, cell volume fraction: 0.65, and membrane permeability: 0.01 mm/s. We generated DWI signals using a simulated PGSE sequence [15], and fitted the models to the simulated DWI signals with b = 2500 s/mm2 in increment of 500 s/mm2. For comparison, we calculated the ADC of the monoexponential model (b-value = 1000 s/mm2). To simulate possible microstructural changes in ischemic stroke, we decreased or increased intracellular diffusion by varying cell size (5-10-15 μm) [7]. In addition, we increased cell volume fraction (0.65-0.80) [4], and decreased membrane permeability (0.01-0.001 mm/s) [7] in separate experiments to study how the fitted parameters varied with these changes. In vivo experiments: We collected DWI images from six patients with ischemic stroke within 48 hours after the onset of neurological deficits. No patients had hemorrhages. The maximum b-value was 2500 s/mm2 in increment of 500 s/mm2 with diffusion gradients applied respectively on x, y, and z axes. Other imaging parameters were: SENSE: 2, TR/TE = 4000/104 ms, NEX = 4, slice thickness = 4.5 mm, FOV = 240 × 240 mm2, and matrix = 128 × 128. We defined two ROIs (Fig. 2): lesion ROI on DWI images with hyper-intensity, and contralateral white matter ROI on T2-weighted images segmented using SPM (University College London, UK). We compared the differences between these two ROIs using the paired Student's t-test with significance level: $p < 0.05$.

Results: Simulation: The ADC was sensitive to all microstructural changes except to the decrease in membrane permeability (Fig. 1). The ADC increased with larger cell size, and decreased with smaller cell size, larger cell volume fraction, and smaller membrane permeability. The σstat of the statistical distribution model decreased specifically with the increase in cell volume fraction (Fig. 1). The Kapp of the DKI model increased specifically with the decrease in cell size. In vivo experiments: All the fitted parameters showed significant differences between white matter and lesion ROIs (Fig. 3). Compared with

white matter ROI, the stroke lesion showed a decrease in the ADC by 37 % and a decrease in the σstat by 26 % (Fig. 3). However, the stroke lesion showed an increase in the Kapp by 53 %.

Conclusions: We simulated the three important microstructural changes in ischemic stroke and have demonstrated that the non-monoexponential models of water diffusion have different, specific microstructural sensitivities. Our simulated microstructure is a simplistic physical system. Nonetheless, we suggest that these different sensitivities of the diffusion models may contribute to the observed differences in the in vivo experiments. More importantly, a combination of these models may give insights into the microstructural underpinning of ischemic stroke.

Poster 39

AGING DOES NOT AFFECT THE PROPORTION OF DORSAL MEDIAL ENTORHINAL CORTEX CELLS ACTIVE DURING TRACK RUNNING BEHAVIOR. Liang J, Lister JP, Barnes CA. Evelyn F. McKnight Brain Institute and ARL Division of Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: 2012 Society for Neuroscience, New Orleans, LA

Background: Previous work has shown that hippocampal place cells in aged rats show changes in their population dynamics: in CA1 there are errors in retrieving the correct map for a known location (e.g., Barnes et al., 1997), and in CA3 they exhibit difficulty in establishing a new map for a novel location (Wilson et al., 2005). The entorhinal cortex provides input to the hippocampus and could contribute to these observed age-related changes in the population code for space. The medial entorhinal cortex (MEC) contains "grid cells" that fire in a highly spatially regular fashion (e.g., Hafting et al., 2005). These cells fire in repeating patterns across an entire environment and are believed to contribute significantly to the spatial signal within downstream hippocampal regions.

Methods: The current experiment investigated whether aging affects population activity in MEC during track running, by quantifying expression of the immediate early gene Arc using the "catFISH" method (Guzowski et al., 1999). The rigid kinetics of Arc localization to distinct cellular compartments allows this gene to mark neuronal activity during discrete behavioral epochs. Young (9 months) and old (24 months) Fischer 344 male rats (N = 24 at each age) were divided into three groups: caged control (CC), maximal electroconvulsive shock control (MECS), and track running behavior. Rats learned to run alternating clockwise and counterclockwise laps on a circular track (48 inch diameter) for food reward. For the experiment, CC rats were sacrificed immediately from home cages, and the MECS group was sacrificed following a shock that activates Arc expression in all neurons capable of expressing the gene. Rats in the running group performed two 5 min sessions of track running, separated by a 20 min rest period in their home cage. Immediately after the second session, animals were sacrificed. After sacrifice, brains were flash-frozen to preserve mRNA, sectioned on a cryostat, stained for Arc expression with fluorescence in situ hybridization, and the dorsal MEC was examined in each rat (3 sections per brain).

Results: Neurons were quantified as nuclear positive (Nuc+), cytoplasmic positive (Cyto+), or double-labeled (Dbl+). Repeated measures ANOVA revealed a significant ($p<0.01$) effect of the Arc-compartment factor - there was a significantly higher proportion of Dbl+ neurons than Nuc+ or Cyto+ in both age groups.

Conclusions: The age factor was not significant, indicating that the ability of MEC to reactivate the same populations during the two sessions of track running in the same environment is not affected by age. This suggests that at least the cellular composition of the path integration input to the hippocampus is preserved during aging. Supported by: McKnight Brain Research Foundation; NIH Grant AG033460; NIA Grant AG036053; NIA Grant AG003376

Poster 40

IMPACT OF ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTORS IN AMYLOID TOXICITY. Liu Q, Gao M, Lukas RJ, Wu J. St. Joseph's Hospital and Medical Center; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Published/Journal Information: Journal of Neuroscience (pending)

Background: Alzheimer's disease (AD) pathogenesis and to find an effective strategy to treat AD. AD is a neuron-degenerative dementia characterized by increased accumulation of Aβ, degeneration of neurons of basal forebrain, hippocampus and neocortex, and a gradually-developing learning and memory deficit. It has been postulated that an aberrant high-level of Aβ may contribute to the pathogenesis in AD, but the mechanism of Aβ-induced neurodegeneration remains unclear. Nicotinic acetylcholine receptors (nAChRs) are important mediators of cholinergic signaling in basal forebrain, hippocampus and neocortex. One of the earliest events in the pathogenesis in AD patients or AD model animals is a significant increase of mRNA and protein expressions of α7 nAChRs. However, a consensus is yet to emerge as to how these enhanced α7 nAChRs play a role in the mediation of Aβ-induced neuronal degeneration and death.

Methods: Relevant nAChR function and structure were characterized using electrophysiological, cell and molecular biological approaches in primary cultured hippocampal neurons prepared from wide-type and nAChR α7 knockout mice. Neurotoxicity will be evaluated by measuring lactate dehydrogenase (LDH) release.

Results: 1. Chronic exposure with 100 nM Aβ1-42 fibrils for 7-10 days significantly increased LDH release, suggesting a neurotoxicity. 2. Similar treatment of Aβ1-42 fibrils up-regulated α7 nAChR expression and function, but this up-regulation occurred (at day 4) early than the increased LDH level (after 7 days). 3. Pharmacological block or genetic deletion of α7 nAChR significantly prevented Aβ toxicity. 4) Pharmacological block or genetic deletion of β2 nAChR did not prevent Aβ toxicity.

Conclusions: Chronic exposure of nanomolar concentrations of Aβ1-42 fibrils up-regulates α7 nAChR and then, results in neurotoxicity in primary hippocampal cultured neurons. Pharmacological block or genetic deletion of α7, but not β2 nAChR significantly prevented Aβ toxicity. These results suggest an important role played by α7 nAChRs in the mediation of Aβ toxicity.

Poster 41

DEPRESSIVE SYMPTOMS IN HEALTHY APOE E4 CARRIERS AND NONCARRIERS: A LONGITUDINAL STUDY. Locke DEC, Dueck A, Stonnington CM, Caselli RJ. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: [Abstract]. Alzheimer's & Dementia. 2012;8(Suppl 2):622].

Background: Studies evaluating the possible impact of depression on the risk of transitioning from normal cognitive aging to Mild Cognitive Impairment (MCI) due to Alzheimer's disease have been mixed. Researchers have hypothesized that depressive symptoms may be an early manifestation of rather than a risk factor for Alzheimer's disease. Apolipoprotein E (APOE) e4 is the most prevalent known genetic risk factor for Alzheimer's disease. We have previously shown that age-related memory decline accelerates preclinically in APOE e4 carriers who remain cognitively normal. If depression is intrinsic to the AD syndrome then a similar increase in depressive symptoms could be expected preclinically in those at genetic risk for AD. The primary aim of this longitudinal investigation is to evaluate whether depressive symptomatology increases preclinically cognitively normal APOE e4 carriers as compared to noncarriers.

Methods: 633 cognitively and functionally normal members of the Arizona APOE Cohort aged 21-86 years underwent neuropsychological testing every 1-2 years that included the Hamilton Depression Scale (Ham-D), the Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS), and the Personality Assessment Inventory (PAI). We estimated the longitudinal change on these measures using mixed models that simultaneously modeled cross-sectional and longitudinal effects of age on depression scores by APOE status and the interaction between the two. We also estimated incident depression using accepted clinical cut-scores on depression measures and use of depression medications.

Results: Comparing APOE e4 carriers with noncarriers, there was no significant longitudinal difference in the rate of change or slope of change on any depression scale or subscale. There was also no difference in incident depression or antidepressant drug use between the carrier and noncarrier groups.

Conclusions: These data fail to support a relationship between APOE genotype and longitudinal change in depression symptoms, suggesting that depression symptoms may not be intrinsic to the early pre-clinical phase of AD.

Poster 42

ENROLLMENT AND RETENTION DATA FROM A MULTI-SITE RANDOMIZED REHABILITATION INTERVENTION TRIAL FOR INDIVIDUALS WITH AMNESTIC MILD COGNITIVE IMPAIRMENT. Locke DEC, Hoffman Snyder C, Cuc AV, Fields JA, Smith GE, Chandler Greenaway M. Mayo Clinic Arizona; Mayo Clinic Rochester; Mayo Clinic Florida; Arizona Alzheimer's Consortium.

Background: To date, there are no FDA approved medications options for MCI. Moreover, patients with MCI want to engage active strategies to improve or maintain their memory functioning and prevent or delay further neurodegeneration. This is why non-pharmacologic or behavioral interventions are growing in popularity with patients with MCI. Memory compensation techniques and cognitive activity are two such activities and were studied here.

Methods: Two hundred and one people with MCI were approached to participate in a four-armed (2 by 2) trial of Memory Support System (MSS) versus Posit Brain fitness (Posit) training delivered in either a 6-week or 10-day format. Ultimately 64 participants with MCI were randomized. Individuals in the Posit group were given the MSS materials and encouraged to use them, but given no formal training. Primary aims of this pilot trial were (1) to generate a reliable estimation of expected enrollment in this type of time-intensive training program, (2) to assess retention rates for this type of behavioral program, and (3) to assess adherence with the MSS program with and without training. Secondary aims included comparing delivery of the MSS training in a condensed 2 week program to an extended 6 week program. Finally, an exploratory aim focused on preliminary efficacy comparison data for the MSS and Posit. Because follow-up data collection is ongoing, those efficacy data receive only cursory presentation here.

Results: Enrollment data show that 37% of those approached about the study expressed interest and completed an eligibility visit (75/201). In Arizona, specifically, 41% of those approached for the study completed an eligibility visit. Eleven individuals across sites were ineligible after the screening visit. The remaining 63% (126/201) were not interested in the program with the primary reasons for decline being (1) time commitment and (2) distance to travel. Only 4 individuals declined to participate because they did not think such an intervention would be helpful and 11 declined due to concerns about the randomization process and which group they would be assigned. Retention was high with 86% (55/64) of those enrolling in the study completing their training program. End of program MSS adherence was greater in the MSS-trained participants compared to Posit participants despite the later group also being encouraged to use the materials ($p < 0.001$; Cohen's $d = 3.64$, CI 2.82-4.30). With the MSS training group, there was no difference in adherence for MSS participants who received extended training over 6 weeks compared to training 10 days over 2 weeks format ($p = .56$; Cohen's $d = .23$, CI = -1.14 to +1.14). As mentioned above, follow-up visits continue such that secondary outcome measures are not presented in detail here. However, we did see that overall self-efficacy increased slightly in the MSS group ($p=.03$) but remained unchanged in the Posit group. The Posit group showed a small reduction in anxiety ($p=.05$) while the MSS group remained stable.

Conclusions: The enrollment and retention data suggest that though perhaps only a minority of eligible patients would be interested in a comprehensive program with this time demand, it is a sizable minority in Arizona and those who enroll do not drop out of the program once they've begun. In addition, these data suggest in-person training sessions are necessary to help patients with MCI implement a memory support system, but that those who receive the training CAN learn to implement such a system. Finally, preliminary efficacy data suggest that these two rehabilitation strategies may impact individual

functioning in different ways with increased self-efficacy with the memory support system and reduced anxiety with a computerized brain fitness task.

Poster 43

NEURODEGENERATIVE-RELATED PROTEINS IN THE EVOLUTION OF THE AGING BRAIN. Maarouf CL, Walker DG, Kokjohn TA, Daugs ID, Hunter JM, Sabbagh MN, Reiman EM, Beach TG, Roher AE. Banner Sun Health Research Institute; Midwestern University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Fundamental questions related to Alzheimer's disease pathophysiology have yet to definitively answered, such as: 1) why do amyloid plaques (AP) and neurofibrillary tangles (NFT) form during aging, 2) why do many cognitively normal elderly people have AP and NFT, 3) are AP and NFT toxic or by-products of a rescue system, and 4) is AD a form of accelerated aging? Determining the biochemical profiles of normal aging and AD will aid in the understanding of these questions.

Methods: Five cohorts were studied: 1) young adults (YA), average age 24 years; 2) youngest-old no plaque controls (YO-NPC), average age 71 years; 3) oldest-old no plaque controls (OO-NPC), average age 93 years; 4) oldest-old high pathology controls (OO-HPC), average age 93 years and 5) oldest-old AD (OO-AD), average age 94 years. Aβ40, Aβ42, tau, α-synuclein, synaptophysin, CD200, TNF-α, GFAP and ApoE levels were quantified by ELISA. Western blots were used to compare quantities of APP and its cleavage products as well as BACE1, neprilysin, IDE, tau, α-synuclein and VEGF.

Results: The YA, YO-NPC and OO-NPC were selected to have no AP neuropathology, while the OO-HPC and OO-AD had high numbers of AP and NFT. As expected, Aβ ELISA values followed the pattern of AP intensity. Tau, α-synuclein, GFAP, CD200 and TNF-α ELISAs showed significant age- and AP-related changes. Western blot analysis revealed significant alterations in APP, BACE1, neprilysin, α-synuclein and VEGF between the YA and OO-NPC. Pro- and anti-inflammatory markers were significantly altered with age and AP pathology. Overall, there was an increase in proteins that degrade APP between YA and nonagenarians.

Conclusions: There are significant age-related changes in the proteins levels in the brain, including those associated specifically with AD neurodegeneration that may play an important role in the development of dementia.

Poster 44

DEVELOPMENT OF A CELLULAR MODEL OF AMYLOIDOGENESIS TO IDENTIFY BACE1 MODULATORS. Macias MP, Decourt B, Gonzales AM, Walker A, Sabbagh MN. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Accumulation of neuritic plaques in the brain parenchyma of Alzheimer's Disease (AD) patients and underlying neuroinflammation are two pathological hallmarks of AD. The main components of plaques, amyloid β-peptides (Aβ) Aβ42 and Aβ40, are formed from sequential cleavage of transmembrane, amyloid precursor protein (APP) by first β- then γ-secretases. Because the stepwise amyloidogenic cleavage cascade is initiated by β-site APP-Cleaving Enzyme-1 (BACE1), great interest is focused on BACE1 inhibition/modulation as a therapeutic strategy for AD. An inflammatory microenvironment and presence of elevated levels of pro-inflammatory tumor necrosis factor alpha (TNFα) have been shown to contribute to neurodegeneration and stimulate Aβ production. In vivo observations include reduced Aβ generation in TNFR1 knockout mice, and recently, following treatment with anti-TNFα therapy, AD subjects exhibited cognitive improvement. Tests on APP23 transgenic mice suggest that the potent anti-cancer TNFα inhibitors, thalidomide and lenalidomide, inhibit BACE1 expression and decrease brain Aβ loads. We wish to develop a cell-based model to address mechanisms of BACE1 modulation and to test, in vitro, the hypothesis that immunomodulatory drugs such as thalidomide and lenalidomide, have direct, inhibitory effects on BACE1-mediated APP-cleavage.

Methods: We are currently performing validation studies on the human neuroblastoma cell line, BE(2)-M17 (hereafter referred to as M17) as a novel in vitro model of BACE 1-mediated cleavage of APP for functional, mechanistic assays of BACE1 expression and activity modulators. For this cellular model system, endogenous RNA expression of APP, BACE1, TNFα, TNF Receptor 1 (TNFR1) and TNFR2 is detected using endpoint RT-PCR analyses. Concurrently, appropriate protein expression of isoforms of APP, BACE1, and TNFα in M17 cells is evaluated by Western blot assays. BACE 1 activity for this study is measured indirectly by ELISA detection of the APP-cleavage end product, Aβ. This validated cellular model will be used to test the potent TNFα inhibitors, anti-cancer drugs thalidomide and lenalidomide, and to detect altered BACE1 expression and activity in direct, quantifiable ways. The M17 cell-based model will be treated with both pharmacologic agents, and drug-regulated changes in the levels of BACE1, APP, TNFα, and Aβ will be measured by quantitative real-time RT-PCR (qRT-PCR), Western blotting and ELISA, compared to control vehicle-treated cells.

Results: Based on our preliminary results, the human neuroblastoma cell line, M17, displays robust, endogenous transcriptional expression of both the APP and BACE1 genes. We confirmed the post-translational validity of the M17 cell system for appropriate representation of the protein isoforms for APP and BACE1 by Western blots, and demonstrate that the β-amyloidogenic pathway end product, Aβ is produced by these cells. Because inflammation, principally TNFα, likely plays a role in Aβ production, we have further determined by end-point RT-PCR and Western blotting, that the M17 cells express basal levels of TNFα and its receptors, TNFR1 and TNFR2.

Conclusions: We believe the BE(2)-M17 human cell system provides a valuable in vitro model for initial, rapid screening of BACE1 inhibitors and modulators. In addition, this cell-based system will help identify the molecular mechanisms of thalidomide and lenalidomide regulation of BACE1 expression for design of future therapeutic strategies to slow or modify the course of disease in AD patients.

Poster 45

KIF6 719ARG CARRIER STATUS ASSOCIATION WITH HOMOCYSTEINE AND C-REACTIVE PROTEIN AND MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE. Malek-Ahmadi M, Sabbagh MN. Banner Sun Health Research Institute, Cleo Roberts Center for Clinical Research; Arizona Alzheimer's Consortium.

Published/Journal Information: submitting to Alzheimer's and Dementia

Background: Recent research has demonstrated associations between statin use, KIF6 719Arg carrier status, and cholesterol levels and mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients. The association between 719Arg carrier status with homocysteine (tHcy) and c-reactive protein (CRP) levels in MCI and AD has not been previously investigated. This relationship is of interest given the established associations between MCI/AD, tHcy, and CRP levels.

Methods: Data from 160 MCI and AD patients with an average age of 77.76±8.15 years were used for the analysis. The sample was comprised of 78 females and 82 males. The Mann-Whitney U test was used to assess group differences for 719Arg carrier status on HC and CRP levels. The association between 719Arg carrier status with tHcy and CRP was analyzed using logistic regression, which adjusted for ApoE ε4 carrier status. For these analyses, tHcy and CRP levels for the study sample were dichotomized into elevated and non-elevated groups using recommended clinical guidelines.

Results: 719 Arg carriers (13.72±14.70 μmol/L) had significantly lower levels of tHcy than non-carriers (15.12±3.96 μmol/L), ($p = 0.008$). No difference in CRP levels between 719 Arg carriers (4.92±9.83 mg/L) and non-carriers (4.24±9.31 mg/L) was found ($p = 0.38$). Logistic regression yielded no significant effect for 719 Arg status on CRP [OR = 1.30 (0.64, 2.67), $p = 0.47$], but did demonstrate a significant effect for tHcy [OR = 0.43 (0.17, 0.65), $p = 0.001$]. Additional analysis of 719 Arg and ApoE ε4 carrier status interaction also yielded a significant effect for tHcy [OR = 0.44 (0.23, 0.87), $p = 0.02$]. tHcy was not significantly associated with ApoE ε4 carrier status [OR = 0.59 (0.52, 1.80), $p = 0.92$].

Conclusions: This study is the first to explore the relationship between KIF6 719 Arg carrier status and tHcy and CRP levels. 719 Arg carriers were more likely to have normal tHcy levels after adjusting for ApoE ε4 status. Individuals who were carriers of both the 719 Arg and ApoE ε4 alleles were more likely to have normal tHcy levels. These results suggest that the KIF6 719 Arg allele might influence cardiovascular pathways that are involved in AD pathogenesis.

Poster 46

DETERMINING THE TISSUE BASIS OF NICOTINE RESCUE IN THE DROSOPHILA PARKINSON'S DISEASE MODEL. Meyer DO, Buhlman LM, Call GB. Midwestern University; Arizona Alzheimer's Consortium.

Background: The Drosophila Parkinson's Disease (PD) model based on homozygous loss of function of the parkin gene has been shown to have both flight muscle degeneration and dopaminergic neuronal loss in the brain. Our previous data also indicates that flies heterozygous for the park25 null allele also experience motor function defects, olfaction loss and decreased lifespan. Interestingly, administration of nicotine to these flies in their food improved or rescued all of the observed deficits. This study was initiated to determine the mechanism of this rescue by histological and genetic methods.

Methods: Histological analysis of the indirect flight muscle and dopaminergic neurons in the brain was performed to determine if the morphology or numbers of these tissues are affected by nicotine treatment. In addition to histological analysis, a genetic mechanism using RNA interference (RNAi) to knockdown Parkin in a tissue-specific manner was also performed to help determine the site of nicotine rescue. These RNAi experiments used either a ubiquitous, a muscle-specific or a neuron-specific driver to express the parkin RNAi in different tissues. Climbing, flight and mortality assays were performed and compared to the heterozygous parkin mutant flies.

Results: Initial results indicate that nicotine does not affect neuron numbers in 20-day-old parkin heterozygotes, nicotine = 12.62 neurons/cluster (n=37) vs. no nicotine = 12.92 neurons/cluster (n=26). Further dopaminergic neuron analysis and muscle morphology will be presented at the meeting. Results of parkin RNAi experiments indicate that flies that have ubiquitous reduction of Parkin phenocopy the parkin heterozygotes. However, the muscle- and neuron-specific knockdown of Parkin appears to have no effect in the behavioral assays.

Conclusions: Our data of the parkin heterozygous flies consistently demonstrate a milder phenotype than that observed in the homozygous parkin null flies. The heterozygous parkin flies do not have any dopaminergic neuron loss, though we did not assess function. The RNAi data indicates that the behavioral deficits observed in the parkin heterozygotes cannot be attributed to only muscle- or neuronal-specific loss of Parkin function. Perhaps both tissues need to be affected to have parkinsonism symptoms in this fly model of PD.

Poster 47

DOSE AND DELIVERY METHOD IMPACT COGNITIVE OUTCOME OF ETHINYL ESTRADIOL ADMINISTRATION IN THE SURGICALLY MENOPAUSAL RAT. Mennenga SE, Gerson JE, Kingston ML, Koebele SV, Acosta JI, Camp BW, Engler-Chiurazzi EB, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.
Published/Journal Information: Not published

Background: Ethinyl estradiol (EE), a synthetic, orally bioavailable estrogen, is the most commonly prescribed form of estrogen in oral contraceptives (Shively, 1998) and is found in at least 30 different contraceptive formulations currently taken by women (Curtis, Overholt, Hopkins & DelConte, 2005). According to a national survey of contraceptive use between the years of 2006 and 2010, an estimated 28% of women of reproductive age were using the birth control pill, for a total of 10.6 million women (Jones, Mosher & Daniels, 2012). EE is also used in hormone therapies (HTs) prescribed to menopausal women, such as Femhrt (Simon, Wysocki, Brandman & Axelsen, 2003). Thus, EE is prescribed clinically to women at ages ranging from post-puberty through reproductive senescence. Importantly, a generation of women who were clinically prescribed EE starting in the 1960's are now becoming part of the aging population and must now face the decision of whether to take estrogen-containing HT. The synthetic hormone EE cannot be converted to estrone (E1) or other weaker forms of estrogens, making EE more potent than the endogenous 17β-estradiol (E2), which is converted to other estrogens (Prokai-Tatrai et al., 2005; Kuhl, 2005).

Methods: Here, in two separate studies using young animals, we tested the cognitive effects of cyclic or tonic EE administration following ovariectomy (ovx). In Study I, we evaluated the cognitive effects of low, medium, and high doses of EE, administered via a daily subcutaneous injection. In Study II, we assessed the cognitive effects of low and high doses of EE, delivered tonically via a subcutaneous osmotic pump, modeling popular tonic contraceptive administration methods. The low and medium doses selected were equivalent to the range of doses currently used in clinical contraceptive formulations; the high dose corresponded to doses previously prescribed to a generation of women when contraceptives first became available and prescribed doses were higher. For each study, cognition was evaluated on a battery of maze tasks tapping several domains of learning and memory.

Results: At the highest dose, EE impaired performance on a spatial working memory task relative to vehicle treatment when delivered cyclically, as well as when delivered tonically. 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. When given tonically at the low dose, EE did not affect performance on any task.

Conclusions: Importantly, of the doses and regimens tested here, only EE at the highest dose impaired several domains of memory and this was seen for both cyclic and tonic regimens. Cyclic and tonic delivery of low EE, a dose that corresponds to the doses most commonly used in the clinic today, resulted in transient and null impairments, respectively, on cognition. Future directions include examining long-term cognitive effects of EE and investigating potential interactions between EE administration at a young age, modeling contraception, and during aging, modeling HT, as well as to determine the mechanism underlying the cognitive impairing effects of high doses of EE.

Poster 48

INTERACTIVE EFFECTS OF SELF-REPORTED MEMORY COMPLAINTS AND HYPERTENSION STATUS ON COGNITIVE PERFORMANCE IN THE ELDERLY. Nguyen LA, Haws KA, Totenhagen JW, Torre GA, Gillespie WL, Fitzhugh MC, Hishaw GA, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Self-reported memory complaints are frequently reported by older adults and have been associated with objective memory performance, but this relationship has not always been observed. Hypertension is a common risk factor for the development of cognitive deficits in aging. We sought to evaluate whether the relation between self-reported memory complaints and objective cognitive performance is influenced by the presence of hypertension in the elderly.

Methods: A sample of 105 neurologically healthy older adults, 70-89 years of age, with (N = 44) and without hypertension (N = 61), completed a subjective scale of memory problems and complaints (Gilewski, Zelinski, & Schaie, 1990). Based on their responses to the scale, subjects were divided into complaining (N = 72) and non-complaining (N = 33) groups. In addition, they completed a battery of neuropsychological tests assessing memory, attention, executive functioning, and processing speed.

Results: After controlling for age, gender, and education, we found main effects of subjective memory complaints ($0.01 \leq p \leq 0.04$) for several measures of memory performance (Buschke Selective Reminding Tests: Sum Recall, Long-Term Storage, Long-Term Retrieval, Continuous Long-Term Retrieval, and Short-Term Retrieval). Significant interactions were observed for subjective memory complaints and hypertension status on all measures of memory performance ($0.001 \leq p \leq 0.05$). Follow-up simple effects analyses of the interaction revealed that hypertensive complainers demonstrated poorer performance on objective measures of long-term memory and greater reliance on short-term recall than the hypertensive non-complainers, who demonstrated better performance on all memory measures. There were no differences in performance on objective memory scores within the non-hypertensive group. After additionally controlling for performance on a measure of intellectual function (WAIS-IV Full Scale IQ), all main ($0.01 \leq p \leq 0.05$) and interactive effects ($0.001 \leq p \leq 0.02$) remained significant.

Conclusions: In neurologically healthy elderly adults, the relation between memory complaints and objective memory performance is influenced by the presence of hypertension. We found that hypertensive complainers showed poorer performance on memory measures than hypertensive non-complainers, whereas the non-hypertensive complainers and non-complainers in our cohort showed no differences in memory performance. Among otherwise healthy, community-dwelling elderly adults with hypertension, self-reported memory complaints may be more reflective of objective cognitive deficits than in those without hypertension.

Poster 49

GREY MATTER VOLUME IN THE ORBITAL PREFRONTAL CORTEX CORRELATES WITH REINFORCER DEVALUATION BUT NOT REVERSAL LEARNING PERFORMANCE IN BONNET MACAQUES. Plange K, Burke SN, Thome A, Engle JR, Trouard TP, Gothard KM, Barnes CA. Evelyn F. McKnight Brain Institute; ARL Div Neural Systems Memory and Aging; Dept Physics & Dept Physiology and College of Medicine, University of Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: 2012 Society for Neuroscience, New Orleans, LA

Background: Behaviors that rely on the prefrontal cortex are particularly vulnerable to the process of normal aging, but the neurobiological changes that occur over the lifespan in the different subregions of this brain structure are not completely understood.

Methods: In the current experiment, young (n = 7) and aged (n = 9) bonnet macaques were trained on reversal learning and reinforcer devaluation tasks using a Wisconsin General Testing Apparatus. The reinforcer devaluation task tests the degree to which response selection can be guided by reward value, by pairing two different food rewards (food 1 and food 2) with distinct sets of objects. Monkeys learn this association over weeks and are then satiated on food 1. Successful performance occurs when the animal selects the objects associated with the non-satiated food 2. In contrast, reversal learning tests an animal's ability to learn that a previously rewarded stimulus is no longer associated with a reward on an object discrimination task. Data from lesion studies suggest that the orbital prefrontal cortex (OFC) is necessary for successful performance on both of these tasks (e.g., Gallagher et al., 1999; Bohn et al., 2003). To assess the extent that OFC structural integrity predicts performance on these two tasks, anatomical MRIs were obtained from 7 young and 6 aged monkeys that had completed both behavioral conditions.

Results: Boundaries of the OFC were manually determined by three independent observers blind to the age and behavioral performance of the animal (high inter-rater reliability was obtained for all comparisons, $r[12] > 0.7$, $p < 0.01$). Although as a group the aged monkeys performed significantly worse than did young animals on both the reinforcer devaluation ($T[14] = 2.07$, $p < 0.05$) and the reversal learning tasks ($T[14] = 3.80$, $p < 0.01$), there was no significant difference in total OFC volume between age groups ($T[12] = 0.88$, $p = 0.15$). While there was no significant correlation between OFC volume and reversal learning performance ($r[12] = -0.22$, $p = 0.46$), a significant correlation was found between OFC volume and performance on the reinforcer devaluation task ($R[12] = 0.61$, $p < 0.05$).

Conclusions: Together these data suggest that OFC grey matter volume is associated with an animal's ability to guide its behavior based on predicted reward value, but not to reverse a previously learned association. Because reinforce devaluation performance requires functional connectivity between the amygdala and the OFC (Baxter et al., 2000), these data suggest that alterations in structural integrity of the OFC may be involved in defective communication between these two brain structures, which disrupts an animal's ability to use reward value to guide behavior. Supported by: McKnight Brain Research Foundation; NIH Grant NS054465; state of Arizona and ADHS; R21MH 086065

Poster 50

MUSCARINIC RECEPTOR DYSFUNCTION IN ALZHEIMER'S DISEASE. Potter PE, Jones D, Monzon N, Slater K, Killpack L, Beach TG. Arizona College of Osteopathic Medicine, Midwestern University; Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Muscarinic receptors have been reported to be uncoupled in the brains of patients with Alzheimer's disease (AD). We have demonstrated receptor uncoupling in patients with AD as well as in those who have neuritic plaques without a diagnosis of dementia (Potter et al, 2011).

Methods: In order to further determine the mechanism underlying this phenomenon, we examined muscarinic signal transduction in four groups of patients; 1) diagnosed with Alzheimer's (AD); 2) age matched controls with many plaques (MP); 3) age matched controls with sparse plaques (SP), and 4) age-matched controls with no plaques (NP). The extent of plaque formation was correlated with loss of cholinergic neurons as assessed by choline acetyltransferase activity (ChAT). Levels of each of the signal transduction markers were measured using Western blot analysis. Levels of β-amyloid were measured using an ELISA assay.

Results: There was no change in the level of the Gq/11 protein; however, there was a shift from the cytosol to the membrane fraction, marked by a significant increase in membrane Gq/11 which was correlated with plaque and β-amyloid levels. Levels of membrane Gq/11 also correlated with ChAT activity. The ubiquitin-binding protein p62 interacts with polyubiquitinated tau and regulates tau degradation. Total p62 levels were significantly decreased as plaque level increased, and there was a significant correlation between ChAT activity and the level of total p62. Membrane Gq/11 and total p62 were also significantly correlated with the extent plaque and tangle formation. Levels of G-protein coupled receptor kinase (GRK) were examined in the four patient groups, as these have been shown to be altered in transgenic mouse models of AD. There was a significant decrease in GRK-2 as plaque levels increased, which correlated with the increase in β-amyloid and loss of ChAT activity. Levels of β-arrestin are currently being measured to determine if there was a change as plaque levels increased, which could indicate a shift in receptor recycling.

Conclusions: Our results suggest that a change in equilibrium dynamics between cytosol and membrane levels of GRK-2 and Gq/11 may occur prior to development of dementia as β-amyloid plaque levels increase. This may, in turn, be in the cholinergic receptor dysfunction in AD. These results also suggest that the decrease in p62 levels may contribute to AD neuropathology, specifically the accumulation of plaques and formation of tangles.

Potter PE, Rauschkolb PK, Pandya Y, Sue LI, Sabbagh MN, Walker DG, Beach TG. Pre- and post-synaptic cortical cholinergic deficits are proportional to amyloid plaque presence and density at preclinical stages of Alzheimer's disease. Acta Neuropathol. 122(1):49-60, 2011

Poster 51

ADVANCING A FUNCTIONAL ASSAY FOR MITOCHONDRIAL CYTOCHROME C OXIDASE: DIAGNOSTIC POTENTIAL IN ALZHEIMER'S DISEASE. Procopio C, Lowry A, Nowak L, Perkins M, Valla J. Midwestern University; WP Carey School of Business Fulton School of Engineering, Arizona State University; Arizona Alzheimer's Consortium.

Published/Journal Information: new

Background: Previous studies have shown that mitochondrial deficits, specifically in cytochrome c oxidase (CO; electron transport chain Complex IV) activity, occur in both brain tissue and blood platelets of Alzheimer's disease (AD) patients. However, existing modes for measuring CO activity are time-consuming and highly variable, limiting the diagnostic potential. Our goal was to create an assay for CO activity that was reliable and could be widely performed (e.g., in standard clinical labs) via an easily-accessible tissue such as blood.

Methods: Platelets, isolated from whole blood by differential centrifugation, were maintained in buffered suspension and anti-coagulated with EDTA and prostaglandin. A histochemical method based on the redox turnover of the CO substrate, cytochrome c, was applied. The redox-active marker for the reaction was diaminobenzidine (DAB), which continually reduces endogenous cytochrome c, and is itself then oxidized to a precipitating colored polymer. Buffer composition, pH, and ionic strength were optimized to increase enzyme-mediated DAB polymerization rates. Enzyme specificity was verified with co-incubation with potassium cyanide, a specific inhibitor of CO. Stained platelets were centrifuged in specialized tubes such that densitometric imaging could be used for measurement of DAB precipitation.

Results: Earlier work with this assay indicated that the rate of enzyme turnover was far below the level required for detection of a functional deficit that could yield clinical differentiation (AD vs control) in an aged human sample. Subsequent experimentation and optimization has increased the enzymatic rate in the assay by a factor of ~3, decreasing the required incubation time from 60 min to 20 min, while maintaining signal-to-noise as well as the overall simplicity and low cost of the original protocol. Notably, the revised assay does not require the addition of exogenous enzyme substrate, but is able to utilize endogenous mitochondrial cytochrome c, greatly reducing cost and complexity. Hypothetically, very-low-ionic strength buffering removes the rate-limiting association-dissociation step of the enzyme-substrate interaction, speeding reaction velocity, and our results are consistent with that hypothesis. The assay yielded high inter-rater reliability, repeatability, and a typical dose-response curve under cyanide inhibition.

Conclusions: Current work focuses on finalizing the assay protocol for an upcoming preliminary clinical trial to determine sensitivity and specificity in AD patients and controls and a subsequent multi-site trial toward regulatory approval. Given its ease of performance, low equipment demands, and low cost, this new assay could fill a significant need by providing pre-symptomatic diagnosis or broad-based population screening.

Poster 52

THE PATTERN OF CEREBRAL HYPOMETABOLISM AND ITS ASSOCIATION WITH CLINICAL RATINGS IN COGNITIVELY NORMAL OLDER ADULTS WITH AND WITHOUT SIGNIFICANT FIBRILLAR AMYLOID BURDEN: FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE. Protas HD, Chen K, Reschke C, Roontiva A, Liu X, Parks S, Lee W, Bauer III R, Ayutyanont N, Thiyyagura P, Koeppe RA, Jagust W, Foster NL, Weiner M, Fleisher AS, Reiman EM, ADNI. Banner Alzheimer's Institute; U Michigan; UC Berkeley; U Utah; UC San Francisco; Arizona Alzheimer's Consortium.

Background: It has been suggested that fibrillar amyloid-β (Aβ) begins to accumulate prior to regional cerebral metabolic rate for glucose (CMRgl) and clinical declines. In this study, a voxel-based partial least squares (PLS) algorithm was used to 1) characterize the CMRgl pattern that best distinguished cognitively normal "fibrillar Aβ positive and negative" older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI), 2) compare the resulting FDG PET PLS subject scores in the Aβ positive and negative subjects, and 3) compare the extent to which these scores were associated with lower clinical ratings in each of the two subject groups.

Methods: positivity was characterized in 225 cognitively normal subjects, 76±6 years of age, using a mean cortical-to-cerebellar florbetapir SUVR threshold previously found to be associated with moderate or frequent neuritic plaques (Fleisher et al., 2011).βA A PLS routine in SPM environment was used to characterize the CMRgl pattern that best distinguished the resulting 71 Aβ positive and 154 Aβ negative subjects, characterize and compare their resulting FDG PET PLS subject scores, characterize and compare the extent to which the PLS scores were associated with clinical decline using the MMSE or ADAS-Cog, and determine the extent to which findings were solely attributable to fibrillar Aβ burden or APOE ε4 gene dose in each subject group.

Results: The CMRgl pattern that best distinguished the Aβ positive from Aβ negative subjects included significantly lower measurements in posterior cingulate, parietal, and temporal regions. The resulting FDG PET PLS scores were significantly different in the Aβ positive and negative groups (p=8e-12). They were significantly associated with poorer MMSE and ADAS-Cog scores in the Aβ positive group(r=-0.50, p=9.1e-6; r=0.52,p=3.0e-6) but only significant for ADAS-cog in the Aβ negative group(r=0.16,p=0.05). The PLS score associations with MMSE or ADAS-Cog were stronger in the Aβ positive than in Aβ negative subjects(p=4.3e-4,p=2.2e-3). These results remained after correction for fibrillar Aβ or APOE-ε4 gene dose.

Conclusions: Fibrillar Aβ burden in cognitively normal older adults is associated with a characteristic pattern of cerebral metabolism, and the metabolic pattern in those with fibrillar Aβ positive had stronger associations with poorer clinical ratings.

Poster 53

EFFECTS OF SELF-REPORTED SLEEP QUALITY ON COGNITIVE FUNCTIONING IN HEALTHY OLDER ADULTS. Reid BA, Haws KA, Totenhagen JW, Torre GA, Gillespie WL, Fitzhugh MC, Bergfield KL, Hishaw GA, Alexander GE. University of Arizona; Evelyn F. McKnight Brain Institute; Arizona Alzheimer's Consortium.

Background: Normal aging has been associated with declines in specific cognitive domains including memory, executive function, and information processing speed. However, substantial heterogeneity exists in these age-related changes. One factor that may contribute to individual differences in cognitive performance is sleep quality. Few studies have explored sleep as a possible mediator of cognitive aging, and findings from those have been variable. The goal of this research was to investigate whether self-reported long-term sleep quality is associated with differences in cognitive functioning in healthy older adults and to determine which cognitive domains are preferentially affected by diminished sleep quality.

Methods: Participants were 202 community-dwelling, neurologically healthy older adults aged 50-89 (mean age= 70±10.4; M/F= 105/97; MMSE= 29±1.2). All subjects underwent medical screening and a battery of cognitive tests. Criteria from the Pittsburgh Sleep Quality Index (PSQI) were used to assess self-reported sleep quality over a one-month interval. Scores from neuropsychological tests in the domains of memory, executive function, complex attention, and processing speed were tested in relation to PSQI scores using linear regression.

Results: After age, gender, and education level were entered as initial covariates, poorer sleep quality on the PSQI was significantly associated with poorer performance on the Rey Complex Figure Test Delayed Recall ($p=0.015$) and the WAIS-IV Symbol Search ($p=0.038$). Additionally, these associations between sleep quality and performance remained significant when controlling for hypertension status in the cohort.

Conclusions: Our results indicate that self-reported poor sleep quality is related to poorer cognitive performance, with memory and processing speed preferentially affected. These findings suggest that sleep quality may be an important factor affecting cognitive functioning in healthy aging. Further research is needed to evaluate how differences in sleep quality relate to differences in brain structure and function in the context of cognitive aging.

Poster 54

ASSOCIATION BETWEEN THE ALZHEIMER'S DISEASE-RELATED HYPOMETABOLIC CONVERGENCE INDEX AND CLINICAL RATINGS IN COGNITIVELY NORMAL OLDER ADULTS WITH AND WITHOUT SIGNIFICANT FIBRILLAR AMYLOID BURDEN: FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE. Roontiva A*, Chen K*, Ayutyanont N, Protas H, Liu X, Thiyyagura P, Lee W, Reschke C, Parks S, Bauer III R, Koeppe RA, Jagust W, Foster NL, Weiner M, Fleisher A, Reiman EM, ADNI. Banner Alzheimer's Institute; U Michigan; UC Berkeley; U Utah; UC San Francisco; Arizona Alzheimer's Consortium.

Background: We previously developed a voxel-based hypometabolic convergence index (HCI) to characterize, in a single measurement, the extent to which the pattern and magnitude of hypometabolism in a person's flourodeoxyglucose positron emission tomography FDG PET image corresponds to that in patients with the clinical diagnosis of Alzheimer's dementia (Chen and Ayutyanont et al., 2010). In this study, we characterized and compared HCIs and their relationship with poorer clinical ratings in cognitively normal "fibrillar Aβ positive and negative" older adults from the Alzheimer's disease Neuroimaging Initiative (ADNI).

Methods: Florbetapir PET scans from 225 cognitively normal subjects 76±6 years of age were used to characterize mean cortical-to-cerebellar standard uptake value ratios (SUVRs) and classify the images as fibrillar Aβ positive and negative using an SUVR threshold previously found to be associated with moderate or frequent neuritic plaques (Fleisher et al., 2011). FDG PET scans from 71 Aβ positive and 154 Aβ negative subjects were used to generate HCIs, compare this index, and relate them to lower MMSE and higher ADAS-Cog scores (i.e., measures of clinical severity) in the two subject groups.

Results: Aβ positive groups had significantly higher HCIs than the Aβ negative groups ($p=0.0024$). HCIs were significantly associated with poorer MMSE and ADAS-Cog scores in the Aβ positive group ($r=-0.38$, $p=0.001$ and $r=0.36$, $p=0.002$, respectively) but not in the Aβ negative group ($r=0.007$, $p=0.936$ and $r=0.06$, $p=0.458$, respectively).

Conclusions: Fibrillar Aβ burden in cognitively normal older adults is associated with an AD-related index of cerebral hypometabolism, and this index is associated with poorer clinical ratings in those who are Aβ positive.

Poster 55

FLORBETAPIR PET, FDG PET AND MRI IN DOWN SYNDROME (DS) SUBJECTS WITH AND WITHOUT SYMPTOMATIC ALZHEIMER'S DISEASE (AD). Sabbagh MN, Chen K, Rogers J, Liebsack C, Bandy D, Belden C, Fleisher AS, Thiyyagura P, Liu X, Parks S, Jacobson S, Malek-Ahmadi M, Reiman EM. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: A link between Down's syndrome (DS) and Alzheimer disease (AD) is widely recognized. Most individuals with DS will manifest AD by the age of 50. Trisomy 21 results in a 4 to 5-fold increase in expression of the APP gene and accelerated deposition of β-amyloid. Compared to normal controls (NCs), brain imaging studies in late-onset AD (LOAD) have demonstrated increased fibrillar β-amyloid binding and a characteristic and progressive pattern of regional reductions in glucose metabolism and gray matter volume. This study aimed to assess the difference of the measures based on these 3 neuroimaging modalities among young/old DS, DS-with dementia (DSWD), and NC subjects.

Methods: There were 9 NC (3F, 6M) participants, 12 DS (7F, 5M) participants without dementia, and 5 DSWD (3F, 2M) participants, all consented or assented depending on established capacity. Of the 26 participants enrolled, two who received cognitive testing but did not tolerate imaging procedures. 24 participants underwent cognitive testing, volumetric MRI, florbetapir PET (n=24) and FDG-PET. SPM8 was used for voxel-wise data analysis (FDG, MRI and florbetapir) using predefined regions of interest (ROI). Mean cortical-to-pontine florbetapir SUVRs (standard uptake value ratios) were calculated cortical and pontine reference regions-of-interest (ROIs).

Results: Mean cortical-to-pontne florbetapir SUVRs were significantly higher in DSWD subjects than in DS or NCs (ANOVA with pair-wise comparisons, $p<0.001$) and associated with progressively higher SUVRs in the NC, DS and DSWD groups (1.15±0.06, 1.27±0.09 and 1.54±0.21, respectively, linear trend, $p=0.00002$). Regional-to-whole brain glucose metabolism and gray matter volumes were lower in DSWD patients than in DS patients in XX, XX, and XX regions known to be preferentially affected by AD ($P<0.001$, uncorrected for multiple comparisons).DS (DS-AD) patients than both older compared to young DS (older or young DS) in the regions known to be affected by LOAD.

Conclusions: In comparison with DS patients and NCs, DSWD subjects have significantly greater fibrillar Aβ buden, as well as significantly lower glucose metabolism and gray matter volume in AD-affected regions, similar to that observed in LOAD. DS.. The differences occur between 36 and 50 years of age. Additional studies are needed to expand our samples, track these changes over time, and provide sample size estimates for clinical and preclinical AD trials in patients with DS.

Poster 56

DIMINISHED PLACE FIELD DENSITY AND DIRECTION-DEPENDENT LEARNING IN THE AGED RAT. Schimanski LA, Lipa P, Barnes CA. Evelyn F. McKnight Brain Institute and ARL Division of Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: 2012 Society for Neuroscience, New Orleans, LA

Background: Remembering the locations of specific stimuli within an environment becomes more difficult during senescence. The changes in neural information processing underlying this age deficit are not yet fully understood.

Methods: In this study, the simultaneous activity of ensembles of hippocampal CA1 principal neurons ('place cells') was recorded from 6 young adult (9-12 month) and 6 aged (26-28 month) male F344 rats, while they learned the locations of eye-blink stimuli on a circular track. Rats were trained to run alternating clockwise and counterclockwise laps on this circular track with a barrier at 12 o'clock, where they received food reward. Using electrical stimuli applied to the eyelid, the animals were conditioned to blink at two distinct locations on the track: one eye-blink stimulus location was conditioned in only the clockwise running direction while the other one was only administered in the counterclockwise direction.

Results: As reported by Schimanski et al. (2011), young and old rats exhibited equivalent accuracy of the blink response at both conditioned locations, but old rats were less successful in restricting the blink response to the conditioned running direction. Here we examine place field firing properties of young and old pyramidal cells under these conditions in more detail. When the number of place fields identified per CA1 pyramidal cell was measured in both running directions, the aged rats exhibited fewer place fields per cell than did young rats.

Conclusions: These data suggest a subtle difference between age groups in how the CA1 'map,' or population code represents the same environmental experience. Moreover, when we applied a random sampling algorithm to the place field data (Monte Carlo method), the outcome showed that the number of bidirectional fields observed in young and old rats was close to what one would expect from 'accidental' overlap of firing in opposite direction trajectories, given the situation that each unidirectional field was randomly positioned to occur in either the clockwise or counterclockwise direction. Taken together, these findings imply that because the number of CA1 place fields per cell is reduced during aging, the number of bidirectionally-active place fields also must decline accordingly. These age-dependent alterations of the population code may contribute to the reduced ability of aged rats to discriminate one running direction from another in learning this location- and direction-dependent version of eye-blink conditioning. Supported by: McKnight Brain Research Foundation; NIH Grant AG012609

Poster 57

INFLAMMATORY CYTOKINES IL-1 BETA AND TNF-ALPHA CAUSED DISTURBANCE IN INSULIN SIGNALING REGULATION IN HUMAN ASTROCYTES. Schmitz CT, Serrano G, Walker DG, Lue L-F. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Both type-2 diabetes mellitus (DM) and Alzheimer's disease (AD) are leading causes for high morbidity and mortality in elderly population. Emerging evidence also indicated that these two diseases are risk factors for each other, which could be further compounded by another metabolic disorder, obesity, a risk factor for developing DM and cardiovascular diseases. The incidence rates of these diseases are of great concerns. A lack of comprehensive preventive and intervention strategies for these interlinked diseases could lead to a severe crisis for the healthcare cost and patient care. Regardless of recent research progress in both diseases, the understanding of how these two diseases interact mechanistically is still emerging. The major mechanisms through which DM may influence the pathogenesis of AD include insulin resistance, and impaired insulin and insulin growth factor receptor signaling. Because chronic inflammation is a risk factor, pathological feature, and disease mechanism in both Alzheimer's disease and DM, in this study, we investigate how inflammatory cytokines that are present in AD brain and in DM patients could affect the regulation of insulin signaling. Astrocytes are the major glial cells in the brain that synthesize and store energy sources (glycogen), and also an inflammatory cell type. We used this cell type to test the hypothesis that inflammatory cytokines IL-1beta and TNF-alpha dysregulate insulin receptor signaling pathway by affecting the phosphorylation of insulin receptor substrate (IRS-1) and glycogen synthase kinase (GSK) beta.

Methods: To determine how inflammatory stimuli change astrocyte response to glucose and insulin fluctuation, a series of experiments were conducted in cultured human astrocytes. Cells were exposed to glucose concentrations at normal and high levels (low, normal, and high glucose) for short (24 hours) and long (72 hours) durations with the treatments of IL-1beta and TNF-alpha—inflammatory cytokines that could induce insulin resistance. Cells were lyzed when the experiments were terminated and the cell lysates were collected. These were analyzed by standard western blot techniques to detect the insulin/insulin growth factor receptors signaling molecules, such as IRS-1 and an IRS-1 kinase—GSK-3beta.

Results: We first summarized our findings from IL-1beta treatment in astrocytes. IL-1beta significantly increased the levels of phospho-IRS-1 at serine 636/639 (p-IRS-1) in normal glucose-containing medium at 24 hours. However, IL-1beta effects significantly reduced the ratio of p-IRS-1 to total IRS-1 in 72 hour-treatment with normal glucose medium. The reduction of this ratio was due to a significant increase in the level of total IRS-1 without increasing p-IRS-1. This means that IL-1beta treatment could increase the availability of IRS-1 as the kinase substrate in 72 hour-experiment. Whether IL-1beta changed the ability of GSK-3beta to act on its substrate was measured by the availability of the phospho-GSK-3beta at serine 9 (p-GSK-3beta) in the same cell lysates. The lower the amount of p-GSK-3beta, the higher the chances for GSK-3beta to be phosphorylated at a tyrosine residue, which could in turn increase the kinase interaction with IRS-1. The results showed that 72-hour IL-1beta did not affect either total GSK-3beta or p-GSK-3beta in normal glucose medium. Nevertheless, in the short-term treatment (24 hours), IL-1beta significantly increased the amount of p-GSK-3beta without increasing the total levels of GSK-3beta. This could still have potential to exert negative effects on the ability of GSK-3beta to interact with IRS-1. Thus, 24 hour-treatment with IL-1beta could indirectly facilitate tyrosine phosphorylation on IRS-1 protein. In summary, IL-1beta caused treatment time-dependent differential effects in IRS-1 and GSK-3beta in normal glucose-containing medium. We also examined the effects of TNF-alpha. Our results displayed that TNF-alpha did not affect any of the measures in IRS-1 system regardless of glucose

concentrations in the medium and duration of treatment. When analyzing GSK-3beta proteins, we found that TNF-alpha significantly induced both the amount of p-GSK-3beta and the ratio of p-GSK-3beta to total GSK-3beta in normal glucose medium at 24 hours. This result suggested that TNF-alpha could also facilitate insulin signaling by increasing the chance to phosphorylate tyrosine residue on IRS-1. This is due to increases in p-GSK-3beta as this would reduce its binding with IRS-1 as a kinase substrate and in turn, increase the chance for IRS-1 to be phosphorylated at tyrosine.

Conclusions: In summary, our findings demonstrated that inflammatory and insulin resistance inducing cytokines, such as IL-1beta and TNF-alpha, could cause disturbance in the insulin signaling regulation in astrocytes. These cytokines are also known to change astrocyte activation states through autocrine and paracrine mechanisms. Therefore, we proposed that inflammation in AD could lead to abnormal regulation of insulin signaling (This study is funded by Arizona Alzheimer's Consortium).

Poster 58

FEASIBILITY STUDY OF NEEDLE CORE BIOPSY OF THE FRONTAL LOBE FOR TAU STAGING IN ALZHEIMER'S DISEASE. Serrano GE, Carew J, Carter N, Chiarolanza G, Dugger BN, Hidalgo J, Intorcia A, Mariner M, Saxon- LaBelle M, Watson-Henry J, Sue LI, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The clinical diagnosis of Alzheimer's disease (AD) has many challenges and it is widely accepted that histological examination is the best indicator of AD. The main challenge for a precise clinical diagnosis of AD is that neither clinical examination nor available biomarkers provide the needed sensitivity and specificity. This is a major impediment to finding new therapeutic agents due to decreased perceived effect size in clinical trials. Even though in-vivo quantification of β-amyloid (Aβ) plaques is now possible with PET amyloid imaging, AD is best staged using the distribution of neurofibrillary tangles or abnormally phosphorylated tau (p-tau) and this is not yet possible through imaging or other clinical means.

Methods: We conducted a study of needle core biopsy of the frontal lobe cortex of autopsied subjects to determine if it was possible to predict tau staging in AD. We did immunohistochemistry for Aβ and p-tau on needle cores (18 gauge needle) from fixed tissue from 100 subjects with different clinicopathological diagnoses. Four needle cores of approximately 10 mm each were collected from the crest of the superior frontal gyrus at the level of the head of the caudate nucleus. Cores were dehydrated and embedded in paraffin. Every section was collected and stained for Hematoxlyin and Eosin, p-tau (AT8 antibody) and Aβ (6E10 antibody). All the cores were scored using CERAD templates and were compared to the original whole-brain pathological diagnosis made by the neuropathologist at Banner Sun Health Research Institute (TGB).

Results: We found that cortical biopsy scores for Aβ and p-tau correlated significantly ($p>0.01$) with the original pathological findings for frontal cortex. In addition, we were able to detect amyloid plaques in the cores with a sensitivity that ranged from 57-87% and specificity that ranged from 95-100%, depending on the cutoff scores chosen. Abnormally phosphorylated tau was detected with a sensitivity that ranged from 92-100% and a specificity that ranged from 40-80%. Furthermore, using the best sensitivity/specificity combination to detect phosphorylated tau in frontal cortical cores (96/84%) we were able to predict Braak neurofibrillary tangle stage V or VI with high sensitivity and specificity (87/93%).

Conclusions: These results indicate that in vivo needle core biopsy of the frontal lobe may be a feasible means to clinically stage AD subjects for clinical trials.

Poster 59

HYPERBOLIC RICCI FLOW FOR LATERAL VENTRICULAR SURFACE REGISTRATION. Shi J, Thompson PM, Wang Y. Arizona State University; UCLA; Arizona Alzheimer's Consortium.

Published/Journal Information: MICCAI Workshop: International Workshop on Multimodal Brain Image Analysis (MBIA) 2012

Background: Alzheimer's disease (AD) presents a severe and growing public health crisis. The frequency of the disease doubles every 5 years after age 60, afflicting 1% of those aged 60 to 64 and 30%-40% of those over 85. Computational anatomy methods have been widely used in clinical neuroimaging to map the profile of disease effects on the brain. MRI-based measures of atrophy in several structures, including the whole brain, hippocampus, ventricular enlargement, etc., supporting their validity as markers of AD. Among them, the ventricular enlargement is a highly reproducible measure of disease progression, owing to the high contrast between the cerebrospinal fluid (CSF) and the surrounding brain tissue on T1-weighted images. However, the branchy structure of the lateral ventricle imposes a great challenge on the analysis with surfaces to study local morphology. Here we propose a surface registration method based on conformal parameterization with hyperbolic Ricci flow and report the preliminary results in our study.

Methods: We propose to apply the hyperbolic Ricci flow method to introduce a conformal parameterization to a lateral ventricular surface. We then apply the Klein model to convert the concave parameterization into a convex canonical space which is suitable for registration in the parameter domain. The details of the algorithm are as follows: first, we introduce 1 cut on each of the 3 branches of the lateral ventricular surface. The cuts are made consistent across subjects considering their geometric locations in the Euclidean space. Second, we conformally map the surface to the hyperbolic plane and isometrically embed it in the Poincaré disk. Third, we compute the Klein model of the parameterization to obtain a convex polygon domain for further registration.

Results: We have tested the new method on a pair of lateral ventricular surfaces, one of which is an HIV/AIDS patient and another is a healthy control subject. Similar to AD, lateral ventricles in HIV/AIDS also underwent severe enlargement. Here we used it as a preliminary study, which will guide our future research on AD lateral ventricles. In our experiment, by observation, we found that although the lateral ventricular surface of the patient has much larger volume than that of the control and larger Poincaré and Klein domains, their Klein disks are quite similar. This provides a promising initial condition for accurate registration. Furthermore, compared with prior holomorphic flow method, surface conformal parameterization with the hyperbolic Ricci flow introduces no singularities and all information of the surface can be retained for registration.

Conclusions: The hyperbolic Ricci flow is a stable method to compute conformal parameterizations for surfaces with complicated topologies, such as lateral ventricles. The preliminary experiment demonstrated its validity and feasibility. Our future work will be to apply this method on large-scale AD dataset. Various registration methods, as constrained harmonic map and fluid registration, can be applied to register surfaces across subjects for analyzing the ventricular morphology in AD.

Poster 60

ACTIVITY REGULATED TRANSCRIPT IDENTIFICATION IN THE HIPPOCAMPUS AND THE GENETIC ASSOCIATION WITH AD RISK. Siniard AL, Corneveaux JJ, Turk M, Allen A, Chawla M, Reiman R, Rose H, Barnes CA, Huentelman MJ. TGen; Arizona Alzheimer's Consortium; University of Arizona.

Background: Next generation RNA sequencing (RNA-Seq) provides the capability to construct an unbiased whole-genome transcriptome map, digitally quantify transcript levels, and interrogate splice form abundance. It has been widely established that in response to neuronal activity specific RNA species redistribute within one hour or less to neuronal dendrites where local translation can occur. Much is left to be discovered about the function of these dendritic mRNAs, however, evidence suggests that they play a key role in synaptic plasticity and transmission. Dysfunction of synaptic plasticity is indicated in such disorders as Alzheimer's and Parkinson's disease, mental retardation, depression, epilepsy and chronic pain. We hypothesize that the creation of a complete catalog of activity regulated transcripts will enable a hypothesis-driven investigation of these disease and others with a focus entirely on activity regulated genes.

Methods: In this study we utilized RNA-Seq to identify transcripts from small amounts of total RNA obtained from laser-capture microdissected (LCM) regions of the hippocampus (Dentate Gyrus, CA1, and CA3) of Fisher344 rats. The soma and neuropil regions were compared in caged control animals and MECS-treated (maximal electroconvulsive shock) animals sacrificed at 60 minutes post treatment. We utilized an analytical approach to identify those transcripts that were significantly differentially compartmentalized within each hippocampal subregion in response to MECS treatment.

Results: Key findings that were differentially compartmentalized in the dentate gyrus include Apoe and Cst3 (known AD risk genes), Slc1a2 or EAAT2 (glutamate transporter known to be expressed in the synapse), and Ndrg2 (known to play a role in neurite outgrowth). Top transcripts that were differentially expressed following MECS treatment and were enriched in the neuropil include Calmodulin and Arc (known activity regulated transcripts and IEGs), Psd95 (key protein component of the post synaptic density), and multiple ribosomal protein encoding RNAs. Top transcripts that were differentially expressed following MECS treatment and were enriched in the soma includes six known activity regulated IEGs including Cox-2, Egr1, arcadlin, Homer 1, Egr4, and Fos.

Conclusions: Validating known and uncovering novel activity regulated transcripts suggests that RNA sequencing is a valuable tool for identifying and quantitating differentially compartmentalized RNAs. Further understanding of the activity regulated transcriptome will offer valuable insight into the biology of the neuronal environment and may provide new avenues to explore pharmaceutical therapies to treat neurological disease.

Poster 61

CHANGING CHARACTERISTICS OF NEURAL STEM CELLS ACROSS THE LIFESPAN DURING AGING. Smith K, Barnes CA, Corenblum M, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Our present study is directed at understanding how the brain changes during the normal aging process. It has been shown that active stem cells, which continually generate new nerve cells, are in fact present in the aging brain. These cells, termed neural stem cells when present in the brain, can both self-renew and become the more mature cells of the nervous system such as neurons, astrocytes, and oligodendrocytes. In rodents, primates, and humans, the largest population of these cells exists in the Subventricular Zone. Although neural stem cells exist in this region throughout life, they are also depleted over a lifetime, making them an intriguing target for study with respect to aging. While other studies have compared these cells at the young and old endpoints of the aging spectrum, a comprehensive characterization that fully illustrates the details of how and why the population changes with age has not been conducted.

Methods: Neural stem cells (NSCs) were obtained from the subventricular zones of Fisher 344 rats spanning an aging continuum of 0 (post natal), 2 (adolescent), 9 (mature), 15 (middle-aged), and 24 (old) months. The cells were characterized in vitro, focusing on proliferative capacity (by measuring the incorporation of Bromodeoxyuridine and a serial dilution assay), survival (using a Live/Dead cell assay), and ability to differentiate (quantification of neurons, astrocytes, and oligodendrocytes with immunocytochemistry).

Results: The dilution assay indicated that adolescent and mature cells formed significantly greater numbers of neurospheres than the middle aged and old cells at every dilution level. Concurrent with this, a significant decline in the fraction of BrdU labeled cells was observed with increasing age. Interestingly, in both the dilution and BrdU assays, NSCs isolated from the middle-aged animals showed greater impairment in proliferative ability compared to the cells from old animals. In support of this proliferation data, the survival of NSCs did not show any significant differences between adolescent, mature, and old age groups, but the middle-aged cells displayed a considerably greater fraction of dead cells. With respect to differentiation, the number of oligodendrocytes remained fairly constant, neuronal differentiation declined, and astrocytic differentiation increased with age.

Conclusions: The overall results indicate (1) increased senescence, (2) reduced survival, proliferation, and neuronal differentiation of NSCs as aging progresses, and (3) suggests a particular vulnerability of cells during middle-age which will merit further analysis.

Poster 62

SLEEP SPINDLE ACTIVITY IN DOWN SYNDROME: EFFECTS OF OBSTRUCTIVE SLEEP APNEA AND COGNITIVE CORRELATES. Spanò G, Werchan D, Nyhuis C, Edgin JO. University of Arizona; Arizona Alzheimer's Consortium.

Background: Recent studies have demonstrated that patterns of high frequency (11-16 Hz) EEG activity (sleep spindles, SS) correlate with IQ and memory consolidation and thus, may represent a biomarker of processing efficiency in the brain. For instance, SS activity has been shown to be reduced in certain neurological (e.g., schizophrenia) and neurodevelopmental disorders (e.g., autism). Given these findings, more work is needed to determine the patterns of SS activity in special populations. Individuals with Down syndrome (DS) show intellectual disability and are impacted by poor sleep - upwards of 80% of this population may have obstructive sleep apnea (OSA).

Methods: In the present study we assessed SS activity during polysomnography recordings in 42 individuals with DS ages 7-18 years (M age: 11.14, SD: 3.22). Presence of OSA and spindle counts were manually scored by a certified polysomnography technician. Participants also completed a customized battery of neuropsychological measures for DS (Edgin et al., 2010).

Results: Individuals with DS exhibited marked reductions in the density of spindles in Stage 2 (M: 1.30, SD: 1.17) compared to the same age group from previous work (M: 4.44, SD: 0.57; Nicolas et al., 2001). Ninety-three percent of our sample fell two SD below the normal range for SS density. Furthermore, SS density was correlated with arousals during REM sleep ($r = -0.45$, $p = 0.01$). Finally, SS density related to nonverbal IQ ($r = -0.35$, $p = 0.04$), response mapping reversal ($r = 0.34$, $p = 0.04$), cognitive flexibility ($r = -0.39$, $p = 0.03$) and processing speed ($r = 0.39$, $p = 0.03$).

Conclusions: These results suggest abnormal SS activity in those with DS. Given the correlation between SS activity and cognition, further investigations are needed to better understand the effects of reductions in SS on learning and memory processes measured pre- and post-sleep.

Poster 63

COALITION AGAINST MAJOR DISEASES: ADVANCEMENT OF CSF AND NEUROIMAGING BIOMARKERS AS DRUG DEVELOPMENT TOOLS TO ENABLE CLINICAL TRIALS IN MCI. Stephenson D, Hill D, Beckett L, Boccardi M, Carrillo M, Cole PE, Dean R, Fox N, Frisoni G, Gordon M, Isaac M, Jeromin A, Kelleher T, Meibach R, Novak G, Romano G, Schwarz A, Shaw L, Simon A, Raunig D, Soares H, Suhy J, Vanderstichele H, Yu P, Wang H, Hill D. Critical Path Institute; IXICO Ltd; University of California at Davis; Fatebenefratelli; Alliance for Aging Research; Bristol-Myers Squibb; Alzheimer's Association; Eli Lilly and Company; University of Antwerp; University College London; Boehringer-Ingelheim; European Medicines Agency; NextGenSciences; Novartis; Janssen; AstraZeneca; University of Pennsylvania; CeroraInc; ICON Medical Imaging; Synarc; ADxNeuroSciences; US Food and Drug Administration; Arizona Alzheimer's Consortium.

Published/Journal Information: ADPD 2013

Background: The EMA and FDA biomarker qualification programs enable sponsors to use biomarkers in a qualified context of use during the development of new drug candidates. The objective of the Coalition Against Major Diseases (CAMD) Alzheimer's Disease (AD) biomarker teams is to qualify cerebrospinal fluid (CSF) and hippocampal volume measurements as biomarkers for enrichment of clinical trials with patients who have mild cognitive impairment (MCI) due to AD.

Methods: The regulatory path involves (i) comprehensive literature reviews using defined criteria with a major attention to biomarker standardization, harmonization, and cut point determination; and (ii) a research plan including analysis of biomarker performance in observational natural history studies (e.g., ADNI) to estimate the degree of enrichment and impact on future clinical trials aimed to effectively treat patients with MCI.

Results: Elevated levels of CSF tau and/or p-tau, together with reduced Aβ1-42 in patients with episodic memory impairment, is a useful means of predicting those patients more likely to progress from MCI to AD dementia during the course of a clinical trial. The measurement of low hippocampal volume is proposed as an enrichment biomarker to select MCI patients that progress to AD dementia. The potential impact of CSF or volumetric MRI biomarkers on clinical trial enrichment, sample size reduction, and clinical trial design will be reported.

Conclusions: Biomarker qualification aims to de-risk drug development and accelerate the timeline for drug development. An integrated pre-competitive consortia approach based on data and resource sharing catalyzes the path for advancing to regulatory qualification.

Poster 64

BMI AND BDNF ARE ASSOCIATED WITH MEMORY TASKS IN OLDER ADULT FEMALES.

Stickel A, Kawa K, Ryan L, Huentelman MJ. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Rates of obesity in the American population are rising among all demographics, including the older adult population. Given that some older adults face cognitive declines in executive functioning with normal aging, it is imperative to investigate the effects of body mass index (BMI)—a weight related measure-- on these types of cognitive tasks. A recent study has demonstrated greater declines in the protein BDNF (brain derived neurotrophic factor) which has been associated with higher BMI in older adult females (Pillai et al., 2012). BDNF is especially important for long term potentiation in the hippocampus where it is expressed through the BDNF Val66Met gene. The Val/Val genotype of BDNF is considered protective/advantageous on a broad range of cognitive tasks compared to Met carriers. The present study examined associations between BMI, BDNF genotype (Val/Val versus Met carriers) and performance on simple and complex processing speed, as well as verbal and visual memory tasks.

Methods: BMI was calculated for 46 older adult females, ages 65 and older. All participants were in either the normal ($18.5 \leq x < 25$) or overweight ($25 \leq x < 30$) BMI categories. A battery of neuropsychological tests that included the Trails Making Test (Partinton & Leiter, 1949) and the Wechsler Memory Scale III (Wechsler, 1997) was completed. Performance on the mentioned tests was compared across BDNF Val66Met genotypes (Val homozygotes (n = 17); Met carriers (n = 29)). Groups were matched on age and education. We hypothesized BMI to be negatively associated with performance in all tests, across BDNF genotype.

Results: BMI was not related to Trails Making B in either Val/Val or Met carriers ($r(15)= .30$, $p > .05$ and $r(27)= .03$, $p > .01$, respectively), controlling for age and education. However, with regard to memory tasks Met carriers displayed positive correlations between BMI and performance on the Wechsler Memory Scale Visual Immediate Memory Index and Wechsler Memory Scale Visual Delayed Memory Index ($r(27)= .40$, $p < .05$ and $r(27)= .41$, $p < .05$, respectively) controlling for age and education. This was a surprising finding given that increases in BMI were expected to coincide with decreases in verbal memory performance. Val/Val genotypes did not show a significant relationships between BMI and performance on the Wechsler Memory Scale Visual Immediate Memory Index and Wechsler Memory Scale Visual Delayed Memory Index ($r(15)= .13$, $p > .05$ and $r(15)= .03$, $p > .05$, respectively). No group demonstrated significant correlations between BMI and performance on the Wechsler Memory Scale Auditory Immediate and Delayed Memory Indices (all $p > .05$).

Conclusions: Taken together, these findings suggest that in female Met carriers higher BMI is a protective factor for visual memory processes. However, this study only investigated females who were overweight and not obese. Perhaps, a nonlinear relationship exists in which older female Met carriers who reach obesity begin to show decreases in memory performance compared to those who are only overweight. Thus, it is important to further investigate interactions between BMI and individual BDNF genotypes on brain structure in individuals who are obese as well.

Poster 65

THE EFFECT OF ZUMBA ON COGNITION IN HEALTHY APOE E4 CARRIERS AND NONCARRIERS. Stonnington CM, Locke DEC, Hentz JG, Dueck AC, Geda YE, Tariot P, Caselli RJ. Mayo Clinic in Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Exercise has been shown to protect against cognitive decline. Zumba is a dance-exercise that provides aerobic conditioning while requiring sustained attention for changing dance steps. We set out to test the hypothesis that visuospatial working memory would improve after 6 months of twice-weekly Zumba.

Methods: Participants were healthy cognitively normal females, 55 to 80 years old, randomized to either Zumba or Control home-based exercise for 6 months. At baseline, 3 months, and 6 months, participants underwent a battery of neuropsychological tests, quality of life, and physical activity measures. Our primary outcome measure was the Groton Maze Learning test (GMLT) total errors, which assesses visuospatial working memory and error monitoring. Because distributions of scores were skewed, instead of comparing adjusted means we used the Pearson chi-square test to compare the percentage of women whose score improved by more than half the baseline standard deviation.

Results: Participants did not differ in baseline characteristics. At last follow-up more women in the Zumba group (n=30) improved in GMLT Total Errors (P=0.04) and Delis-Kaplan Executive Functioning System color word interference inhibition trial (P=0.04) than in the Control group (n=23). No differences were observed at last follow-up in other cognitive measures, quality of life measures, or total exercise. A stratified analysis by Apolipoprotein E (APOE) ε4 status showed no interaction between APOE status and group outcome.

Conclusions: In this study, 6 months of Zumba dance was associated with improved measures of working spatial memory and response inhibition. Improvements may have been related to the repeated practice of learning and inhibiting dance moves in Zumba.

Poster 66

REGULATION OF APP PROCESSING USING ANTIBODY FRAGMENTS REDUCES STRESS INDUCED TOXICITY IN CELL MODELS OF ALZHEIMER'S DISEASE. Suryadi V, Emadi S, Boddapati S, Sierks M. Arizona State University; Arizona Alzheimer's Consortium.

Background: One of the most important neuropathological characteristics of Alzheimer's disease is the aggregation and deposition of the protein beta-amyloid. Beta-amyloid is produced by proteolytic processing of the Amyloid Precursor Protein (APP). Production of beta-amyloid from APP is increased when cells are subject to stress since both APP and beta-secretase are upregulated by stress. An increased beta-amyloid level promotes aggregation of beta-amyloid into toxic species which cause an increase in reactive oxygen species (ROS), caspase-3 activity and a decrease in cell viability. Therefore reducing beta-amyloid generation is a promising method to control cell damage following stress. We have isolated a recombinant antibody fragment, iBSec1, which selectively blocks beta-secretase processing of APP by binding the APP substrate as opposed to blocking the enzyme active site. Here we show that iBSec1, when added extracellularly to mammalian cells overexpressing APP, reduces stress induced toxicity.

Methods: Different mammalian cells expressing APP treated with different concentrations of hydrogen peroxide to induce stress. Cells were also simultaneously treated with different concentrations of iBSec1 to inhibit beta-secretase processing of APP. Differences in toxicity of cells treated with or without iBSec1 were assayed by measuring changes in levels of ROS, Caspase 3 and mitochondrial health (XTT).

Results: Addition of hydrogen peroxide to cells showed a concentration dependent increase in ROS and Caspase 3 activity and a decrease in cell viability as determined by XTT. The increase in stress induced toxicity caused by addition of hydrogen peroxide was dramatically decreased by simultaneously treating the cells with iBSec1 to block the increase in beta-amyloid levels resulting from the upregulation of APP and beta-secretase.

Conclusions: Cellular stress increases ROS generation, Caspase-3 activity and decreases cell viability. Levels of beta-amyloid increase in cells following stress due to the upregulation of APP and beta-secretase activity, resulting in the formation of toxic aggregate species. Here we show that we can selectively control proteolytic processing of APP to inhibit beta-amyloid generation and reduce stress induced toxicity in cell models of AD. Since stress also upregulates APP and beta-secretase levels in healthy neurons, tailoring APP processing away from beta-amyloid generation may be an effective way to reduce stress induced toxicity in healthy neurons as well.

Poster 67

LOCALIZATION OF THE CORTICOSTERONE-SENSITIVE ORGANIC CATION TRANSPORTER 3 (OCT3/SLC22A3) MRNA AND PROTEIN IN THE MALE RAT BRAIN VIA IN SITU HYBRIDIZATION AND IMMUNOHISTOCHEMISTRY. Talboom JS, Molinaro J, Tompkins HC, Mumaw L, Lowry CA, Renner KJ, Orchinik M. Arizona State University; University of Colorado; University of South Dakota; Arizona Alzheimer's Consortium.

Background: The organic cation transporter 3 (OCT3/Slc22a3) is a low affinity and high capacity polyspecific monoamine transporter found in the human and rat brain. OCT3 is believed to clear extraneuronal monoamines (e.g., serotonin, norepinephrine, and dopamine), thereby helping to terminate their signal after release. OCT3 may complement other specific (e.g., SERT, DAT, and NET) or polyspecific (e.g., PMAT, OCT1, and OCT2) transporters in regions of the brain that are innervated by monoaminergic terminals. However, OCT3 is unique in that it is the only known monoamine transporter inhibited by physiological levels of corticosterone (CORT) in the rat. Among other stress-related neural processes, CORT-mediated inhibition of OCT3 may modulate the hypothalamic-pituitary-adrenocortical (HPA) axis via alterations in monoaminergic neurotransmission. We hypothesize that OCT3 functions in hierarchical systems regulating the HPA axis, including areas of the hippocampus, the amygdala, and the hypothalamus, to increase extracellular monoamine concentrations during the acute stress response.

Methods: We determined the location of OCT3 mRNA via in situ hybridization (ISH) and protein via immunohistochemistry (IHC). This was done primarily to resolve previous contradictory findings in the literature regarding the location and distribution of OCT3 in the rat brain. To examine OCT3 mRNA localization in the brains of young adult male Sprague-Dawley® rats, digoxigenin (DIG)-labeled OCT3 riboprobes were in vitro transcribed in a process starting with RNA isolated from the rat brain. These riboprobes were then used to perform ISH in rat brain sections following a standard DIG ISH protocol. Separate brain sections were processed for OCT3 IHC following a standard chromogen protocol.

Results: Our results indicated that OCT3 mRNA is found throughout the hippocampus, amygdala, and hypothalamus. Furthermore, the OCT3 mRNA distribution corresponded to the OCT3 protein distribution in these brain regions.

Conclusions: These data support the conclusion that CORT-sensitive OCT3 is expressed in brain regions that mediate behavioral and neuroendocrine stress responses, which may lead to a better understanding of CORT-mediated regulation of the HPA axis.

Poster 68

EXPLORING THE MECHANISM OF NICOTINE-MEDIATED RESCUE OF A DROSOPHILA MODEL OF PARKINSON'S DISEASE. Techau JA, Call GB, Buhlman LM. Midwestern University; Arizona Alzheimer's Consortium.

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Background: Parkinson's disease (PD) is characterized by the death of dopaminergic neurons in the substantia nigra pars compacta, leading to motor and non-motor dysfunction. Epidemiological studies suggest that tobacco smoking can decrease incidence of sporadic PD and delay onset of motor symptoms; subsequent in vivo and in vitro studies have shown that nicotine can be neuroprotective in sporadic PD models. We have previously demonstrated that long-term nicotine exposure can rescue the pathological phenotype of heterozygous parkin loss-of-function mutant strain of Drosophila melanogaster. More specifically, nicotine increases median lifespan and improves motor and olfactory deficits in these flies.

Methods: We sought to determine whether the protective effect of nicotine was mediated through activation of the Drosophila nicotinic acetylcholine receptor (DnAChR) or via DnAChR-independent mechanisms. To this end, we co-administered nicotine and mecamylamine, a nonselective nAChR antagonist, from day one, post eclosion and measured median lifespan, climbing, flying and olfaction.

Results: We have found that nicotine-mediated improvements in survival and climbing persist in the presence of mecamylamine.

Conclusions: Our results suggest that nicotine elicits its protective in a DnAChR-independent manner.

Poster 69

SENESCENCE MODIFIES THE STRUCTURE OF INFORMATION ENCODING IN THE MEDIAL TEMPORAL LOBE. Thome A, Lipa P, Erickson CA, Barnes CA. Evelyn F. McKnight Brain Institute; ARL Division of Neural Systems, Memory & Aging, University of Arizona; Arizona Alzheimer's Consortium.

Published/Journal Information: 2012 Society for Neuroscience, New Orleans, LA

Background: Primates are remarkably adept at categorizing and remembering visual objects. The ability for organisms to discriminate and recall previously encountered information is critically dependent on the integrity of the medial temporal lobe (MTL) and inferior temporal cortex (ITC) (e.g., Mahut et al., 1982; Zola-Morgan et al., 1994; Buffalo et al., 2000). Lesions of these structures produce profound deficits on a variety of recognition memory and perceptual discrimination tasks. Data across a number of species indicate that these processes are similarly disrupted in senescence (e.g., Moss et al., 1988; Burke et al., 2011). However, the neural mechanisms underlying age-related deficits are poorly understood. Information processing in the ventral visual stream is believed to proceed along a hierarchy of association, in which the responses in one region reflect the conjunctions of stimulus features represented discretely in upstream cortical areas (e.g., Barlow, 1961; Mishkin et al., 1983). Single-unit recording studies in primates have demonstrated that neurons in these regions represent information via population codes (e.g., Tanaka et al., 1991; Gross, 1992; Logothetis et al., 1995). However, the stability of a population code rests on the reliability of the responses of individual neurons. One theory of cognitive aging proposes that deficits in perceptual discrimination may be tied to deficits in sensory processing (e.g., Baltes and Lindenberger, 1997; Li and Lindenberger, 2002). Selective degradation of sensory information in lower level sensory areas may result in instability of information representation in higher level association areas. A number of theoretical and empirical findings now indicate that behavioral accuracy may rely on the stability of these responses.

Methods: To test this hypothesis we recorded the activity of 1633 units from 2 old and 3 young chronically implanted rhesus macaques (macaca mulatta) during two different visual tasks.

Results: A variety of analytical techniques were used to examine the tuning characteristics on individual neurons, as well as the underlying signal to noise ratio. These data show that in aged animals there exists a significant decrease in quality of information encoding across the hippocampus (CA3/CA1) as well as upstream cortical structures (EC/PRC/TF).

Conclusions: These results provide not only validation of a number of theoretical proposals and behavioral results, but further open new avenues for the development of cognitive and therapeutic approaches. Supported by: McKnight Brain Research Foundation; NIH Grant AG003376

Poster 70

SINGLE CHAIN VARIABLE FRAGMENT SPECIFIC FOR TRIMERIC TAU AS A TOOL TO STUDY ALZHEIMER'S DISEASE. Tian H, Davidowitz E, Moe J, Sierks M. Department of Chemical Engineering, Arizona State University; Oligomerix Inc; Arizona Alzheimer's Consortium.

Published/Journal Information: Neuroscience 2012 - Society for Neuroscience

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the presence of amyloid plaques and neurofibrillary tangles. A major component of the extracellular neurofibrillary tangles is tau, a microtubule associated protein, which plays a crucial role in assembly and stabilization of microtubules. While fibrillar aggregates of tau are found in the neurofibrillary tangles, increasing evidence implicates oligomeric tau in disease progression. Reagents that can selectively recognize different tau variants can be effective tools to study the role of tau aggregation in AD. We showed previously at Neuroscience 2011 that a synthetic trimeric tau species is toxic to human neuroblastoma cell line and its cholinergic-like form.

Methods: A novel biopanning technique was developed that combines phage display single chain variable fragment (scFv) libraries with atomic force microscopy (AFM) to isolate scFvs selective for desired protein morphologies. This protocol was used to isolate scFvs that selectively bind the toxic trimeric tau form but no monomeric or fibrillar tau. The selected clone scFv was expressed from HB2151 bacterial culture and purified on Ni-NTA agarose resin column. Its diagnostic potential was evaluated by its ability of detecting pathological tau specied, which was performed on a dot blot assay with patients human brain extracts dots probed by soluble scFv.

Results: The selected scFv clone F9T has the desired specificity for oligomeric tau and expresses and purifies efficiently from bacterial culture. When used to probe post-mortem human brain tissue, F9T discriminates between AD and non-demented (ND) samples taken from the middle temporal gyrus (MTG). These results suggest that F9T is an excellent reagent for use as a potential diagnostic for AD and other tauopathies. Future applications of this technology will be to develop a sensitive and reliable test of utilizing F9T scFv to distinguish AD from ND CSF samples and whether F9T scFv can block toxicity of trimeric tau.

Conclusions: 1.Single clone scFv phage F9T isolated from a phage display antibody library selectively binds a neurotoxic trimeric tau species but does not bind monomeric or fibrillar tau or other control proteins such as BSA. 2.F9T can efficiently express soluble scFv that is readily purified. 3.F9T scFv reacts with post-mortem human brain tissue and distinguishes AD from ND tissue based on Braak stages. 4.F9T has promise as a biomarker reagent to facilitate early diagnosis and staging of AD and as a therapeutic to block toxicity of extracellular aggregated tau.

Poster 71

MAGNETIC RESONANCE MORPHOMETRY IN A MOUSE MODEL OF NIEMANN PICK TYPE C DISEASE. Totenhagen J, Yoshimaru E, Erickson R, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Background: Niemann Pick Type C (NPC) disease is genetic, rare, and fatal. The primary cause of the disease is a defect in the NPC1 gene, causing dysfunction of the transmembrane protein NPC1, found in lysosomes and late endosomes throughout the body. The lack of NPC1 protein function results in a buildup of cholesterol and glycolipids in cells, leading to progressively worsening symptoms including ataxia, dystonia, dysarthria, dysphagia, and dementia. Diagnosis is most often made during childhood with death occurring prior to adulthood. No proven effective treatments or cures are currently available, but several are in development and testing. The Npc1-/- mouse model has a complete lack of functional Npc1 protein, resulting in a phenotype resembling a severe form of human NPC disease. The Npc1-/- model has been used in many studies of proposed NPC treatments including cyclodextrins which have been shown to reduce neurological disease symptoms. Advancements in high resolution MR imaging of rodent brains has allowed techniques such as tensor based morphometry (TBM) to be applied to preclinical disease studies of neurodegenerative diseases. In this work, high-resolution in vivo images of Npc1-/- are analyzed to measure volumes of discrete brain regions with an atlas based approach as well as examine brain atrophy within and across brain regions with a TBM-based analysis.

Methods: High resolution T2-weighted in vivo brain images were obtained from WT and Npc1-/- mice at 3, 6, and 9 weeks of age, covering a range from an early presymptomatic disease state to near end stage of the Npc1-/- model. A 7T Bruker Biospec system was used for imaging experiments with a 4-channel phased array surface coil and animal bed system with ear bars and bite bar for head fixation. Animals were anesthetized with isoflurane gas and temperature maintained with a circulating heated water system. A 3D fast spin echo sequence was used for data collection with the following parameters:. TR=1800 ms, ETL=8, Echo Spacing=10 ms, TEeff=40 ms, FOV=30 x 17 x 9.6 mm3, 100um isotropic resolution, and scan time: 60:08 (min:sec). Datasets were semi-automatically segmented to isolate the brain from surrounding tissue, and corrected for surface coil signal inhomogeneity using the N4ITK algorithm. The SyN image registration algorithm implemented in the advanced normalization tools (ANTS) software package was used to register each segmented brain to a labelled MRI in vivo mouse brain atlas. The registration to a labeled mouse brain atlas allowed the volume measurement of 20 individual brain structures. Brain templates were created with algorithms included in the ANTS software package using the symmetric normalization (SyN) algorithm. Registering segmented brains to the created templates allows visualization of regional brain volume changes by examining maps of the determinants of the Jacobian matrix of the deformation transformation for each voxel.

Results: Differences in white matter contrast, ventricle size, and overall brain size and shape are visible in T2-weighted images at 9 weeks of age, particularly in the areas of the corpus callosum, lateral ventricles, and cerebellum. Atlas-based volumetric measurements reveal six brain regions differing in size between WT and Npc1-/- mice. Templates of the WT and Npc1-/- brains and maps of determinant values of the Jacobian matrix of the volume transformation of the Npc1-/- template to WT provide visualization of changes in volume within and across brain regions.

Conclusions: Past studies of the Npc1-/- mouse model have reported a decrease in overall brain size and cerebellar volume with manual region tracing of ex vivo 2D datasets. The current work demonstrates that several brain structures including the cerebellum are reduced in size in the Npc1-/- mouse, and can provide additional insight into neurodegenerative status during treatment studies.

Poster 72

ROCK INHIBITOR DEVELOPMENT FOR COGNITIVE ENHANCEMENT AND BLOCKADE OF TAU PHOSPHORYLATION. Turk MN, Adams MD, Wang T, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium; Arizona State University; Midwestern University; Evelyn F. McKnight Brain Institute at the 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, Y27362, 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: H4-tau cells were treated using 15 different ROCK inhibitors across a 96 hour timecourse, with fresh drug-containing media added every 24 hours. The ratio of Serine 396 phosphorylated tau (p-tau) to total tau was measured using ELISA at each of 8 timepoints. All drug treatments were compared against the corresponding timepoint for vehicle treated cells.

Results: Fasudil was the only drug to decrease the p-tau to total tau ratio ($p=0.017$). Of note, Y27362 did not decrease this ratio ($p=0.2188$). Several novel ROCK inhibitors decreased the p-tau to total tau ratio. Of these drugs, T343 had the greatest difference ($p=0.003$). 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.

Conclusions: 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 necessary 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.

Poster 73

ENHANCED DELIVERY AND IMAGING OF NEUROTHERAPEUTICS VIA US, MRI, SPECT.

Valdez M, Yoshimaru E, Ingram P, Totenhagen J, Forbes A, Moore S, Helquist P, Matsunaga T, Witte R, Furenlid L, Liu Z, Erickson R, Trouard T. University of Arizona; University of Notre Dame; Arizona Alzheimer's Consortium.

Background: Treatment of neurological disorders is hampered by the inability of drugs to cross the blood-brain barrier (BBB). Over the last several years, novel techniques that use focused ultrasound (FUS) energy in combination with microbubble (uB) contrast agents have been developed that reversibly open up the BBB. Foundational studies have been carried out in several animal models, including mice. BBB opening is readily verified with MRI using gadolinium contrast agents. This does not give specific information about the delivery of actual drugs to the brain. To address this point, we have initiated studies combining FUS-mediated BBB opening with high-resolution single photon computed tomography (SPECT) of radiolabeled I-123-beta-cyclodextrin (I-123-BCD) in mice. BCD is a promising treatment for Niemann-Pick type C (NPC) disease, a childhood affliction that involves errors in cholesterol trafficking and results in neurodegeneration and death in the early teen years. BCD has shown promising results in animal models of NPC disease when delivered directly into the brain. Although this work focuses on NPC disease, it is adaptable to other neurological diseases such as Alzheimer's disease.

Methods: Mice were imaged prior to BBB opening in a 7T Bruker Biospec MRI system. A 72 mm ID birdcage coil was used for excitation and a 4-channel phased array coil was used for reception. The mice were secured in an MRI cradle with ear bars and a bite bar. Rapid whole-brain 3D T1-weighted GRE images (5 minute acquisition) were obtained prior to and after IP injection of Gd-DTPA. BBB opening utilized a 40 uL bolus of custom gas filled uBs that were injected into the tail vein, followed by a 120 uL saline flush. Immediately after the injection, 3.3 MHz FUS was transcranially administered to the mouse brain. Thirty 2-second sonications were delivered with a 5 second pause between sonications (37% duty cycle, 6 ms pulse width, 0.80 MPa peak negative pressure). A custom built positioning apparatus was used to position the FUS transducer (30 mm diameter, 49.4 mm focal length) such that its focal spot was within the brain of the mouse. After FUS, the mice were returned to their original position in the MRI magnet and identical T1-weighted imaging was carried out for 30 minutes. T1-weighted 2D spin-echo images were also obtained. Other mice underwent the same procedure, except that no FUS was applied. Mice were allowed to recover and showed no obvious deficits in neurologic function. Within 3 hours of the MRI procedure, pairs of mice were injected with I-123-BCD and imaged simultaneously using a custom-built y-ray scintigraphy system to verify the injection of I-123-BCD. Following this, mice were individually imaged on a custom built SPECT/CT imaging system to determine the distribution of I-123-BCD in the brain. Finally, mice were sacrificed and 1 mm excised brain slices underwent autoradiography to verify in vivo measurements.

Results: MRI image enhancement maps after the administration of Gd-DTPA, uBs and FUS showed a strong increase in signal in the brain parenchyma in the mouse after receiving FUS. Diffusion of Gd-DTPA through the tissue was apparent 90 minutes post FUS. y-ray scintigraphy images of the two mice showed greater signal intensity in the brain region of the animal that received FUS compared to the control animal. The SPECT/CT imaging system showed increased signal in the brain of the experimental mouse. This increase was confirmed by a 4.8 times increase in signal in autoradiographic images of brain slices.

Conclusions: This demonstrated that focal BBB opening procedures allow passage of I-123-BCD into the brains of mice. While these experiments are directed towards NPC disease, they could have a significant impact on other common neurological disorders (e.g. Alzheimer's and Parkinson's).

Poster 74

IDENTIFICATION AND NEUROPATHOLOGY OF AN ALZHEIMER'S DISEASE CASE WITH THE TREM-2 RS75932628 VARIANT POLYMORPHISM. Walker DG, Whetzel A, Lue L-F. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Recent genome wide association studies have identified new single nucleotide polymorphisms (SNPs) associated with increased risk of Alzheimer's disease (AD). A number of recently identified SNPs are present in genes with inflammatory-related functions. One such gene is Triggering receptor Expressed on Myeloid Cell (TREM)-2 where the SNP rs75932628 has a substitution of T for C that could result in a change in an amino acid within the coding sequence from arginine to histidine (R47H). One recent study showed that possession of the T form of SNP rs75932628 resulted in an odds ratio of 4.5 (Guerreiro et al, NEJM, 2013; 368: 117-127). As this SNP could result in an alteration in the amino acid sequence of this protein, it can be considered a genetic mutation. TREM-2 is an anti-inflammatory receptor whose activation results in the down regulation of inflammatory signaling whose primary role is to reduce inflammation. One of its natural ligands is heat shock protein 60 (Hsp60) that can be expressed on the surface of apoptotic cells. At present, it is not known whether the R47H substitution results in loss or gain of function in TREM-2, but it is hypothesized that this substitution might result in exacerbated neuroinflammation in AD affected brains. We had previously demonstrated that treatment of human brain microglia with amyloid beta peptide resulted in significant down regulation of TREM-2 mRNA expression (Walker et al., J.Leuk.Biol, 2006; 79: 596-610).

Methods: A simple polymerase chain reaction based restriction fragment length polymorphism technique was developed and used to discriminate between C/C, C/T and T/T forms of rs75932628 using the restriction endonuclease HhaI in samples of DNA from neuropathologically-diagnosed non-demented (ND) and AD cases. The presence of the risk T allele resulted in loss of the restriction endonuclease site. We screened 52 AD cases and 64 ND cases for the presence of this SNP.

Results: We identified a single AD case with the C/T heterozygous form of the TREM-2 rs75932628 polymorphism out of the AD cases screened (1.9%), while none of the ND cases were positive (0%). 4 allele, whose brain showed a high burden of amyloid plaques and neurofibrillary tangles and limited amounts of Lewy body pathology.εThe affected subject was an 87 year-old male with a 12 year history of dementia and a single copy of the apoE This degree of pathology was similar to other AD cases of a similar age and disease duration so the consequence of the TREM-2 polymorphism is not immediately apparent. Brain tissue samples are available from this case to study the biochemical features of TREM-2 protein affected by this potential mutation.

Conclusions: We have maintained a DNA library for 15 years derived from neuropathologically diagnosed cases that are represented in the Banner Sun Health Research Institute brain bank. With the identification of new AD risk genes, this library has become a valuable tool for validating some of these new genes as the neuropathology of each case represented in our DNA library has been fully characterized. An example of the value of this resource is that we have identified a new case with this significant novel TREM-2 polymorphism/mutation. Using brain tissues from this case, we have the potential to study the function of this protein in brain and its role in AD pathology. Funded by grants from the Arizona Alzheimer's Consortium and from the Banner Sun Health Research Institute.

Poster 75

STUDIES OF CD33, A NEW RISK FACTOR FOR ALZHEIMER'S DISEASE, IN HUMAN BRAINS AND HUMAN MICROGLIA. Walker DG, Whetzel A, Lue L-F. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
Published/Journal Information: Unpublished work to date

Background: Recent genome wide association studies have identified new single nucleotide polymorphisms (SNPs) associated with increased risk of Alzheimer's disease (AD). A number of recently identified SNPs are present in genes with inflammatory-related functions. One gene is CD33, where SNP rs3865444 with a substitution of A for C resulted in moderate increased risk of AD in several different population groups. CD33, also known as sialic-acid binding Ig-like lectin (Siglec)-3, is a transmembrane receptor expressed by myeloid cells. As the CD33 intracellular domain contains an immunoreceptor tyrosine-based inhibition motif (ITIM) binding and activation of CD33 results in induction of anti-inflammatory signals mediated by src homology region 2 domain-containing phosphatase (SHP)-1, SHP-2 and SHIP. The polymorphism rs38654444 is located 373 bp upstream from the closest exon of CD33; two other Siglec genes map in the vicinity of this polymorphism but as they are 71,179 bp and 94,396 bp distant, CD33 is the most likely affected. How much of a risk factor to AD is possession of this polymorphism requires further study, in addition, nothing is known about CD33 function in human brains. To understand how CD33 protein might be involved in AD pathology, some fundamental expression and functional studies of this protein in normal and AD affected human brains are required. Using a collection of DNA samples derived from neuropathologically-diagnosed cases, also with tissue and microglia from some of these cases, the goals of this study were to not only determine if possession of SNP rs3865444 associated with increased AD pathology in our cases and altered expression of CD33 in brain, but also to address how CD33 might be involved in AD mediated inflammation.

Methods: A polymerase chain reaction based restriction fragment length polymorphism technique was developed to discriminate between C/C, C/A and A/A forms of rs3865444 using the restriction endonuclease NlaIII in samples of DNA from neuropathologically-diagnosed non-demented (ND) and AD cases. Real time PCR was used to detect and quantify expression of CD33 mRNA in RNA samples from human brain, and cell cultures derived from human microglia, human astrocytes, human endothelial cells and human neurons. Western blot and immunohistochemistry procedures were carried out using standard techniques to detect and localize CD33 protein in brain tissue samples. A rabbit monoclonal antibody to CD33 (Epitomics-AbCAM, Cambridge, MA) was the most able to detect full length CD33 protein (67kD) in human brains.

Results: Using two sets of DNA and tissue brain samples, we have genotyped 118 ND and AD brains and shown that the C/A genotype was overrepresented in our AD population, while the A/A genotype was underrepresented. These results did not meet statistical significance due to the scarcity of A/A genotype in the AD population studied. Further samples will be analyzed to increase the numbers of A/A genotypes identified. Comparison of neuropathological plaque-load in the ND cases, which being from aged subjects had significant amounts of pathology, indicated increased plaque levels in A/A genotype cases, but similar tangle levels compared to C/A cases. Western blot analysis of inferior temporal cortex samples of CD33 genotyped ND and AD cases indicated a significant increase in CD33 levels in the AD cases. This is the first demonstration of CD33 protein in human brain. Preliminary results showed that highest mean protein levels of CD33 were present in C/C genotyped cases, with lower levels in C/A cases and the lowest with the A/A genotype. Additional samples with rarer A/A genotype need to be analyzed to confirm this finding. In vitro studies have shown CD33 mRNA expression by human microglia, and surprisingly human brain vascular endothelial cells, but not human astrocytes. As there have been no studies of CD33

expression by human microglia, we have used cells isolated from 6 autopsy cases to measure CD33 and identify how expression is affected by stimuli such as amyloid beta peptide or inflammatory cytokines present in excess in AD brains.

Conclusions: CD33 is a significant anti-inflammatory signaling receptor involved in multiple inflammatory processes. Our study has suggested for the first time involvement of this protein in human brain with increased expression in AD affected brains. Indication is that the rs3865444 polymorphism, a risk factor for AD, affects expression of CD33 and amyloid plaque load, but these analyses need to be extended to larger numbers of samples. These results support the hypothesis that disturbance of inflammatory regulatory systems in brain could have a role in AD pathology. Funded by grants from the Arizona Alzheimer's Consortium and from the Banner Sun Health Research Institute.

Poster 76

MITOCHONDRIA-TARGETED PHARMACEUTICAL NANOCARRIERS FOR ANTIOXIDANT DELIVERY. Weissig V, Gaudenti D, Boger B. Midwestern University; Arizona College of Osteopathic Medicine; Arizona Alzheimer's Consortium.

Background: Excessive reactive oxygen species (ROS) can be highly detrimental to cellular function and consequently lead to apoptosis. A majority of ROS originate in the mitochondria. Oxidative stress occurs when antioxidant systems are overwhelmed by ROS. Endogenous antioxidant systems or enzymes control oxidative stress under physiological conditions. However, these systems maybe easily compromised resulting in a variety of pathologies associated with oxidative stress such as ischemia-reperfusion injury, atherosclerosis, arthritis, hepatitis, stroke, drug induced toxicity, and aging. Therefore, administration of an exogenous antioxidant may allow for better compensation during conditions of increased oxidative stress.

Numerous attempts are currently being made to deliver a large variety of endogenous or non-endogenous antioxidant molecules into cells as well as to or into mitochondria. However, most of the strategies explored focus on one particular redox active species only, thereby essentially neglecting the interdependence of all intracellular redox systems. Ideally, a combination of hydrophilic and hydrophobic antioxidants including enzymes such as superoxide dismutase, catalase and glutathione peroxidase should be delivered into cells suffering from pathological oxidative stress.

Liposomes and in particular mitochondria-targeted liposomes present themselves as ideal nanocarriers for a combination of antioxidants due to their ability to encapsulate hydrophilic low-molecular compounds as well as proteins into their aqueous inner space and hydrophobic molecules in their phospholipid bilayer membrane.

Methods: Here we present first preliminary data involving the incorporation of glutathione, α-tocopherol and a short-chain derivative thereof into mitochondriotropic stearyl triphenylphosphonium (STPP) liposomes composed either of saturated and unsaturated phospholipids.

Results: We demonstrate that both vitamin E derivatives formulated into non-saturated STPP liposomes are capable of rescuing 4T1 cells from oxidative stress. However, this rescuing effect is reduced once the non-saturated lipids in STPP liposomes are replaced with saturated lipids.

Conclusions: We are currently exploring unsaturated STPP liposomes in combination with a series of redox protective agents for protecting cells from an excessive load of ROS.

Poster 77

KETONE BODIES IMPROVE LEARNING, MEMORY AND MITOCHONDRIAL COMPLEX I ACTIVITY IN APP TRANSGENIC MICE. Yin J, Han P, Tang Z, Schweizer F, Reiman EM, Maalouf M, Shi J. Barrow Neurological Institute; University of California, Los Angeles; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common cause of memory impairment in older adults. Increasing evidence suggests that the accumulation of amyloid beta (Aβ) in mitochondria causes mitochondrial failure in AD. Mitochondrial dysfunction has been associated with the preclinical and clinical stages of AD. Our in vitro experiments have shown that ketone bodies (acetoacetate and β-hydroxybutyrate) enhance mitochondrial activity and protect neurons from toxicity induced by soluble oligomer beta amyloid 42.In this study, we investigated the protective effect and mechanism of ketone bodies on learning and memory in an AD animal model.

Methods: 4 month-old transgenic APP mice (PDGFB-APPSwInd) (n=11-14) and B6 control mice (n=12-14) were administered subcutaneously with β-hydroxybutyrate (BHB,600mg/kg/day) and acetoacetate (ACA,150mg/kg/day) or vehicle solution for two months. All mice underwent behavioral tests, including Morris Water Maze, Novel Object Recognition and Accelerating Rotarod test. Brain tissues were analyzed for mitochondrial respiration chain (Complex I) activity.

Results: After 2-months of ketone treatment, APP mice showed significantly improvement of learning and memory. During the four-day learning periodin Morris water maze, the escape latency in APP mice without treatment were significant longer than that of B6 controls (67.38±5.26 s vs48.33±5.13 s, $p<0.01$) on day 4. In comparison with untreated APP mice, ketone treated APP had reduced latency (49.01±5.45s, $p<0.05$) on day 4, a longer time on the target platform(15.02± 2.64svs 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 vs12.48± 3.97s,$p<0.05$), and no significant behavioral differences on the Rotarod test. In comparison with untreated APP mice, ketone administration was associated with a transiently higher ketone level and a higher mitochondrial complex I activity in APP mice.

Conclusions: Ketone bodies improve the learning, memory and mitochondrial complex I activity in a mouse model of AD. These findings provide a foundation for the use of ketones and ketogenic interventions in treatment and prevention of AD.

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NOVEL FTO INHIBITOR MODULATES MICRORNA. Zheng G, Shen L, Zaidi A, Iacoban P, Rowles J, He C, Olsen M. University of Chicago; Midwestern University.

Background: 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.

Methods: HeLa 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. HeLa cells were also cultured and treated with vehicle or FTO inhibitor, total mRNA was isolated, labeled with Cy5, and analyzed by microarray.

Results: Numerous microRNAs were either up-regulated or down-regulated by the novel FTO inhibitor. Up-regulated microRNA include miR-505, 575, 4444, 4505, 4638-5p, 4732-5p, and 4753-5p. Down-regulated microRNA include miR-34b-3p, 362-3p, 486-3p, 4485, 4701-5p, 4717-5p, 6509-3p, 6514-3p, and 6722-5p. Analysis of targeted mRNA indicates modulation of numerous genes, including mitochondrial transporters and CNS receptors.

Conclusions: 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.

Additional Abstracts

CHARACTERIZING COGNITIVE AGING IN HUMANS WITH LINKS TO ANIMAL MODELS.
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Background: With the population of older adults expected to grow rapidly over the next two decades, it has become increasingly important to advance research efforts to elucidate the mechanisms associated with cognitive aging, with the ultimate goal of developing effective interventions and prevention therapies. Although there has been a vast research literature on the use of cognitive tests to evaluate the effects of aging and age-related neurodegenerative disease, the need for a set of standardized measures to characterize the cognitive profiles specific to healthy aging has been widely recognized.

Methods: Here we present a review of selected methods and approaches that have been applied in human research studies to evaluate the effects of aging on cognition, including executive function, memory, processing speed, language, and visuospatial function. The effects of healthy aging on each of these cognitive domains are discussed with examples from cognitive/experimental and clinical/neuropsychological approaches. Further, we consider those measures that have clear conceptual and methodological links to tasks currently in use for non-human animal studies of aging, as well as those that have the potential for translation to animal aging research.

Results: Having a complementary set of measures to assess the cognitive profiles of healthy aging across species provides a unique opportunity to enhance research efforts for cross-sectional, longitudinal, and intervention studies of cognitive aging.

Conclusions: Taking a cross-species, translational approach will help to advance cognitive aging research, leading to a greater understanding of associated neurobiological mechanisms with the potential for developing effective interventions and prevention therapies for age-related cognitive decline.

ANGIOTENSIN RECEPTOR BLOCKADE ACCELERATES FUNCTIONAL RECOVERY AND ALTERS INTRASPINAL EXPRESSION OF INFLAMMATORY GENES FOLLOWING SPINAL CORD COMPRESSION INJURY. Jones TB, Robbins EA, Shlifer IG, Manning D, Jones CB. Arizona College of Osteopathic Medicine; Midwestern University; Arizona Alzheimer's Consortium.

Background: Recently, the renin-angiotensin system (RAS) has been shown to affect neuroinflammation in a variety of central nervous system (CNS) disorders, including Alzheimer's disease. However, its effect on the neuroinflammatory response to spinal cord injury (SCI) has not yet been studied. Thus, we sought to determine whether inhibition of RAS improves post-injury locomotor function and whether this was associated with changes in the expression of inflammatory genes in the injured spinal cord.

Methods: Female, Sprague-Dawley rats were treated with losartan (angiotensin II type 1 receptor (AT1R) blocker), captopril (angiotensin converting enzyme (ACE) inhibitor) or vehicle (i.p., sid), beginning one day after lateral compression SCI. Functional recovery was assessed using the Basso, Beattie, Bresnahan (BBB) Locomotor Rating Scale. Rats were sacrificed at 7, 14 or 28 days post injury (dpi) and the tissues processed for PCR or immunohistochemical analyses.

Results: We show that rats treated with losartan or captopril have improved functional recovery compared to vehicle-treated rats. Quantitative PCR analyses of 108 RAS or immune-related genes revealed the expression of all RAS components including renin, ACE1, ACE2, angiotensinogen, AT1R and angiotensin II type 2 receptor (AT2R) in the spinal cords of injured and uninjured rats and the induction of pro-inflammatory genes over 28 dpi.

Conclusion: Treatment with losartan or captopril resulted in significant changes in gene expression that may account for the observed improvement in BBB over vehicle-treated controls. These data indicate that manipulation of RAS by blocking AT1R or ACE improves functional recovery and causes changes in gene expression in rats following SCI. Thus, further exploration of therapeutic intervention of RAS following SCI and other CNS inflammatory diseases appears warranted.

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DEVELOPMENT AND IMPLEMENTATION OF THE NATIONAL ALZHEIMER'S PREVENTION REGISTRY. Langbaum JB, High N, Aisen PS, Albert MS, Brown K, 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; Innolyst; Geoffrey Beene Foundation; Lou Ruvo Cleveland Clinic; Columbia University; Mayo Clinic; Harvard University; Alzforum; University of California San Francisco; University of Arizona; TGen; Arizona Alzheimer's Consortium.

Background: To help advance the evaluation of promising Alzheimer's disease (AD) prevention therapies, we have launched the national, 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. The Registry aims to enroll 100,000 people by mid-2013; 250,000 by mid-2015.

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 basic contact and demographic information and answer two questions related to their experience with AD. Additional information can be completed after joining through surveys at their convenience and discretion. Eblasts will be used to notify registrants about online surveys, prevention-focused studies and trials, and whom to contact to explore the possibility of their participation.

Results: Prior to launching the Registry, a national message testing survey was conducted, revealing that 60% of adults would likely join the Registry and 63% would encourage others to enroll. The Registry had a pilot launch in May 2012, with official launch in October 2012. To date 9,157 have joined. Registrants are predominantly women (79%), report a family history of dementia (67%), have no diagnosis of cognitive impairment (97%), and a mean age of 55.8 (SD 13.7; median age 57). 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, activities are underway to enroll racial and ethnic minorities, as well as work with a large number of researchers to help increase enrollment within their catchment areas.

SEPARATING LEXICAL-SEMANTIC ACCESS FROM OTHER MNEMONIC PROCESSES IN PICTURE-NAME VERIFICATION. Smith JF, Braun AR, Alexander GE, Chen K, Horwitz B.
National Institute on Deafness and Other Communication Disorders; University of Arizona; Arizona Alzheimer's Disease Consortium; Arizona State University; Banner Alzheimer's Institute; Banner Good Samaritan Medical Center.

Background: We present a novel paradigm to identify the shared and unique brain regions responsible for non-semantic, non-phonological,abstract, audio-visual memory versus linguistically mediated audio-visual memory using a longitudinal functional magnetic resonance imaging experiment.

Methods: Twelve healthy, young adult participants were trained to associate eighteen novel visual-auditory stimulus pairs containing linguistic content of which participants were unaware. Participants were presented with the visual stimuli and tested on their recollection memory for the associated auditory stimuli immediately after the initial learning phase and again after four weeks. The hidden linguistic content of the pairs was then revealed to the participants and they were tested again on their recollection of the pairings in this linguistically informed state.

Results: There was substantial overlap between the regions involved in recognition of non-semantic, non-phonological associations and linguistically mediated recognition memory (i.e., naming), suggesting a strong relation between them. Contrasts between sessions identified the left angular gyrus and middle temporal gyrus as key players in the linguistic audio-visual memory network. Left inferior frontal regions were active for both linguistic and nonlinguistic audio-visual memory suggesting the region is responsible for more generic forms of auditory memory than only phonology as previously proposed. Functional connectivity between the angular gyrus region and the left inferior frontal gyrus and left middle temporal gyrus did increase for linguistic memory.

Conclusions: The results are consistent with the hypothesis that the same regions participate in audiovisual memory regardless of the linguistic content but that these regions are reorganized with the inclusion of additional regions into linguistic networks.