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November 15, 2013

Dear Conference Participants,

On behalf of the Sanders-Brown Center on Aging, UK HealthCare, and the symposium planning committee, I am pleased to welcome you to the third annual “Markesbery Symposium on Aging and Dementia.”

The symposium is named in honor and memory of the late William R. Markesbery, MD, founding Director of the Sanders-Brown Center on Aging and Alzheimer’s Disease Center at the University of Kentucky. Dr. Markesbery’s legacy of groundbreaking research at the Center on Aging has formed the bedrock for our quest to understand and treat Alzheimer’s disease and to improve the quality of life of the elderly. We have no doubt that Bill Markesbery’s work will live on for generations to come as we continue the work he started here almost four decades ago.

Over the next two days, in sessions for both the scientific and community audience, you will have the opportunity to hear clinicians and researchers from the University of Kentucky and other institutions share current findings, trends, and latest updates on dementia and aging disorders, particularly as related to Alzheimer’s disease.

In addition to the presentations conducted by some of the world’s leading scientists, we have invited investigators to display posters of their current research on aging and dementia. Please take some time to visit the research poster gallery on display in the atrium and discuss these ongoing studies with the researchers.

We are honored that so many of you have chosen to join us in seeking to expand our knowledge and friendships. I hope the symposium will be both scientifically rewarding and enjoyable.

Sincerely,

[Signature]

Linda J. Van Eldik, Ph.D.
Director, Sanders-Brown Center on Aging & Alzheimer’s Disease Center

Symposium Planning Committee:
Linda Van Eldik, PhD, Chair        Jose Abisambra, PhD        Deborah Danner, PhD        Steven Estus, PhD
Elizabeth Head, PhD               Sally H. Malley              Paula Thomason             Donna Wilcock, PhD

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The Sanders-Brown Center on Aging gratefully acknowledges the support of our sponsors. Their support enables us to provide the highest quality programming.

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Presenting Sponsor for Community Session:

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Location: Pavilion A Auditorium and Atrium of UK Albert B. Chandler Hospital

10:00 am Check-in begins: Receive poster assignment number, ID badge, & program

11:00 Welcome
Linda J. Van Eldik, PhD
Director, Sanders-Brown Center on Aging and Alzheimer’s Disease Center
University of Kentucky

11:15 Role of Immune and Inflammatory Responses in Neurodegenerative Disorders: Potential Targets to Modify Disease Risk and Progression
Malú Tansey, PhD
Associate Professor of Physiology
Emory University School of Medicine

12:15 Box Lunch and Poster Session (Atrium)

1:45 Research at the Sanders-Brown Center on Aging: an Update
Gregory Bix, MD, PhD  Therapeutic Approaches in Stroke
David Fardo, PhD  Inflammation and Alzheimer’s Disease
Peter Nelson, MD, PhD  Neuropathology in Aging and Dementia
Elizabeth Head, PhD  Aging in Down syndrome

3:00 Translational Challenges of Mouse Models of Alzheimer’s Disease
Frank M. LaFerla, PhD
Chancellor’s Professor of Neurobiology and Behavior
Director, Institute for Brain Aging and Dementia
University of California, Irvine

4:00 Poster award presentations and closing remarks
Linda J. Van Eldik, PhD
Malú Tansey, PhD
Emory University School of Medicine

Dr. Tansey is a tenured Associate Professor of Physiology and a member of the Center for Neurodegenerative Diseases (CND) at Emory University School of Medicine in Atlanta. She obtained her B.S/M.S in Biological Sciences from Stanford University in Palo Alto, CA and her Ph.D. from UT Southwestern Medical School in Dallas, Texas. As a post-doctoral fellow at Washington University in St. Louis, she and her colleagues identified and characterized Neurturin and other GDNF Family Ligands (GFLs) and elucidated the signaling mechanisms required for the potent neurotrophic activities of GFLs on neurons. She received the 2000 James O’Leary Prize for Outstanding Neuroscience Research for this work.

Dr. Tansey’s interest in neuroinflammation arose from a short stint in the biotech sector as Head of the Chemical Genetics group at Xencor Inc. in Pasadena, CA where she and her colleagues developed novel inhibitors of soluble Tumor Necrosis Factor (TNF), a potent pro-inflammatory cytokine that has been implicated in a number of chronic neuroinflammatory disorders. She has used these and other immunological tools to investigate the role of immune responses and neuroinflammation in the pathogenesis and progression of neurodegenerative diseases such as Parkinson’s, Alzheimer’s and Huntington’s disease in pre-clinical models of these diseases with funding support from The Michael J. Fox Foundation for Parkinson’s Research, National Parkinson Foundation, Parkinson’s and Movement Disorders Foundation, American Health Assistance Foundation, CHDI/HighQ Foundation and the National Institutes of Health (NIH).

“Role of Immune and Inflammatory Responses in Neurodegenerative Disorders: Potential Targets to Modify Disease Risk and Progression”

In recent years, inflammation has been implicated in the onset and progression of age-related neurodegenerative (ND) diseases, including Parkinson’s (PD) and Alzheimer’s disease (AD). Understanding the precise role of inflammation in these progressive disorders will likely lead to better diagnostic tools and cutting-edge immunomodulatory therapies to prevent or delay disease progression. In vivo evidence for inflammation in ND includes microglial activation, increased expression of inflammatory genes in the periphery and in the central nervous system (CNS), infiltration of peripheral immune cells into the CNS, and altered peripheral immune cell profiles. These findings are recapitulated in various animal models of ND. Recent genome-wide association studies suggest relationships between immune system genes and risk for PD and AD. Given that immune system function is likely to impact disease risk or progression, clinical trials to investigate the potential efficacy of immunomodulatory therapies in early stage disease are warranted but additional basic and translational research will be needed to clarify the role of immunity and inflammation in these chronic neurodegenerative diseases.
Frank M. LaFerla, PhD
University of California, Irvine

Dr. Frank LaFerla is a Chancellor’s Professor and Chair of the Department of Neurobiology and Behavior at the University of California, Irvine. He serves as the Director of the Institute for Memory Impairments and Neurological Disorders, and is also a Fellow of the Center for the Neurobiology of Learning and Memory. Dr. LaFerla received his B.S. in Biology from St. Joseph’s University in Philadelphia. His graduate training was completed at the University of Minnesota where he earned his Ph.D. in the field of virology in 1990. He subsequently was a postdoctoral fellow at the Holland Laboratory of the American Red Cross before moving to Irvine as an assistant professor in 1995.

Dr. LaFerla has received several honors for his research accomplishments including the Ruth Salta Junior Investigator Achievement Award from the American Health Assistance Foundation, Zenith Fellows Award from the Alzheimer’s Association, UCI Chancellor’s Fellow, Distinguished Mid-career Faculty Research Award, UCI Innovation Award and the Promising Work Award from the Metropolitan Life Foundation for Medical Research. He serves on the Scientific Advisory Board for the Orange County Alzheimer’s Association and the Medical and Scientific Advisory Boards for Sonexa Therapeutics, Akeso Health Sciences, and Signum Biosciences. He is also a member of the editorial boards of three scientific journals: Current Alzheimer Research, Neurobiology of Aging, and Neurobiology of Disease.

Dr. LaFerla’s research is focused on understanding the pathogenesis of Alzheimer’s disease, the most common form of dementia among the elderly. His laboratory has developed several transgenic mouse models of neurodegenerative disorders including the first transgenic mouse model of Alzheimer’s disease that recapitulates the two major neuropathological lesions, plaques and tangles. This mouse model, referred to as the 3xTg-AD mice, has been widely distributed to researchers throughout the USA and over 20 countries throughout the world. His laboratory has used this model to understand the relationship between plaques and tangles and how each affects the development of the other, and more significantly, this model has proven to be invaluable for the pre-clinical evaluation of novel therapeutic compounds.

His research group was also among the first to show that stem cell transplantation could be useful for the treatment of cognitive dysfunction. Findings from his lab show that stem cells promote repair not via a cell replacement mechanism but by performing a “nursing” function. Work in his lab shows that the transplanted neural stem cells produce high amounts of the neurotrophic factor, BDNF, which promotes synaptogenesis. Recently, the lab was awarded $3.6 million from CIRM as part of the Early Translation Grant Program to develop an Alzheimer’s disease therapy involving human neural stem cells.

“Translational Challenges of Mouse Models of Alzheimer’s Disease”

Over 35 million people throughout the world are currently afflicted with Alzheimer’s disease (AD). Unless the disease course is altered, it is anticipated that the number of AD patients worldwide will soar, approaching 115 million by the year 2050. Hence, there is an urgent need to identify novel pharmaceutical, lifestyle, and dietary factors that can prevent, delay or retard the progression of AD. Animal models represent a key strategy for identifying and evaluating these therapeutic approaches. Although none of the existing models truly mimics all of the disease features, the models are still valuable, and offer the opportunity to elucidate the underlying mechanism by which these therapies work. We have employed a variety of approaches (genetic, pharmacological, and lifestyle such as diet and cognitive stimulation) to try and reverse the neuropathological lesions and to mitigate the learning and memory deficits in the 3xTg-AD mouse model. Our findings indicate that the timing when treatment is initiated plays a critical role in determining therapeutic efficacy, as some therapies are not effective when administered after extensive pathology has developed. We have also focused efforts on reducing neuronal cell death in brain areas impacted in AD, as reversing cognitive loss is likely to be more challenging following cell loss. Interestingly, we have found that some cell-based therapies can reverse the cognitive deficits without lowering Aβ or tau pathology. Combination therapies (polypharmacy) will likely be required to successfully treat AD in humans. Support: NIH AG-027544 and AG-021982.
Research at the Sanders-Brown Center on Aging: An Update

“Therapeutic Approaches in Stroke”

Gregory Bix, MD, PhD
University of Kentucky

Gregory Bix completed his MD and PhD degrees from Baylor College of Medicine and postdoctoral studies at Thomas Jefferson University. He is currently an Associate Professor in the departments of Anatomy & Neurobiology, Neurology, and Sanders-Brown Center on Aging. He is the Paul G. Blazer, Jr. endowed Professor of Stroke Research at the University of Kentucky. He has published more than 30 papers in reputed journals and has won several research awards.

Dr. Bix’s research focus is on the role of extracellular matrix in stroke, the fourth leading cause of mortality in the United States. Vascular matrix components are often very sensitive to proteolytic processing/degradation in models of focal cerebral ischemia. Often such processing will generate biologically active matrix fragments. One focus of his lab is to determine how select matrix fragments affect the neurovascular unit, the functional multicellular unit that is perturbed in stroke. Another focus of Dr. Bix’s research is to determine what role these matrix fragments could play in neurodevelopment involving processes that are often recapitulated in response to CNS injury.

“Inflammation and Alzheimer’s Disease”

David Fardo, PhD
University of Kentucky

Dr. Fardo holds a Bachelor's degree in Mathematics & Statistics from Miami University, a Master's in Statistics from the University of Kentucky and both a Master's and PhD in Biostatistics from Harvard University. He currently serves as an Assistant Professor of Biostatistics and as a consultant for the university-wide Center for Clinical and Translational Sciences. His research interests include statistical genetics, genome-wide association studies, gene-by-environment interaction, causal inference and statistical methodologies in public health applications.
“Neuropathology in Aging and Dementia”

Peter Nelson, MD, PhD
University of Kentucky

Dr. Peter Nelson is a Professor of Pathology & Laboratory Medicine and Sanders-Brown Center on Aging at the University of Kentucky. He is an experimental neuropathologist focusing on Alzheimer’s disease. Dr. Nelson is the Director of the Neuropathology Division of the Pathology Department, and he also directs the brain bank and the Neuropathology Core of the UK Alzheimer’s Disease Center. He is responsible for the Alzheimer’s Disease Center brain autopsies. These autopsies are performed with profound respect for the volunteers who are enabling us to help combat this dreadful disease.

In addition to duties as a neuropathologist, Dr. Nelson is an experimental researcher focusing on the molecular neurochemistry of the human brain — in health and in neurodegenerative disease — particularly in the context of RNA biology. The study of small regulatory RNAs is a relatively new and unexplored research field with much potential. Dr. Nelson’s work has focused on microRNAs (miRNAs). He invented new techniques to analyze and manipulate these small molecules, and studies how miRNA biology is altered in neurodegenerative diseases. Dr. Nelson seeks both to understand how miRNAs contribute to disease pathogenesis, and to explore how specially-designed RNAs may be applied for therapeutic strategies.

“Aging in Down Syndrome”

Elizabeth Head, PhD
University of Kentucky

Dr. Head is an Associate Professor of Molecular & Biomedical Pharmacology and Sanders-Brown Center on Aging. Her research goals are to identify interventions that may prevent the onset and/or progression of Alzheimer’s disease and thus promote healthy brain aging.

Individuals with Down syndrome are at a high risk for developing Alzheimer’s disease because they have an extra copy of chromosome 21. On this chromosome is a gene that is strongly linked to the development of Alzheimer’s disease. Dr. Head is conducting a study that is following learning and memory changes with aging in adults with Down syndrome (www.uky.edu/DSAging). The good news is, not everyone with Down syndrome will develop dementia. Study participants undergo neuropsychological tests, a neurological and physical examination and magnetic resonance imaging. In addition, blood samples are drawn and a variety of protein levels are measured. This will help in understanding why and who will develop dementia. Importantly, if we follow people who do not develop dementia we may be able to learn how to prevent this from occurring in others.
1

Determining the effects of neuroinflammatory phenotypes on amyloid deposition in APP/PS1 transgenic mice

Erica Weekman • Tiffany Sudduth • Abby Greenstein • Donna Wilcock, PhD

Physiology, University of Kentucky

Student

The polarization of neuroinflammatory phenotypes has been described in early Alzheimer’s disease (AD), yet the impact of these different phenotypes on the pathology of AD remains unknown. The goal of the current study was to determine whether an M1 neuroinflammatory phenotype affects amyloid pathology. To address this we injected Adeno-Associated Virus serotype 8 (AAV-8) expressing IFNγ into the frontal cortex and hippocampus of both the right and left hemispheres of the brain in wildtype and APP transgenic mice. Mice were then sacrificed at 4 or 6 months. The neuroinflammatory phenotype and microglial activation were measured by qPCR and immunohistochemistry, respectively.

We found that AAV-8 expressing IFNγ led to an M1 and M2b phenotype. This was determined by qPCR for the M1 markers IL-1ß, IL-6 and IL-12 and the M2b markers CD86, FCGR1 and FCGR3. Microglial activation assessed by CD11b showed increased activation at 4 and 6 months. Quantification of amyloid beta showed an increase only at 6 months.

Overall, we found that IFNγ AAV-8 expression promotes an M1 and M2b phenotype and produces an increase in microglia activation and amyloid beta production.

2

Cognitive deficits associated with aging differ from those seen in parkinsonian macaques tested on the same tasks

Zhiming Zhang, MD • Richard Grondin, PhD

Anatomy and Neurobiology, University of Kentucky

Faculty

Mild cognitive impairment (MCI) is associated with aging and Parkinson’s disease (PD), even in the earliest stages of the disease. In addition, mild parkinsonian signs are also frequently seen in individuals older than 65 years. The coexistence of mild motor and cognitive impairments in both PD and elderly individuals can confound the diagnosis of PD or age-related MCI. Therefore, there is a need to characterize cognitive deficits related to normal aging from those related to early stage PD. In the present study, eighteen cynomolgus monkeys were used including, 6 aged animals (>18 years old), 6 animals lesioned with MPTP (9-11 years old), and 6 middle-aged animals (9-14 years old). All animals were video recorded for behavioral evaluation of motor function and tested for cognitive impairments using delay matching-to-position (DMTP) and delay matching-to-sample (DMTS) tasks. Behavioral assessments of motor function revealed that bradykinesia was seen in aged animals, and mild rigidity of the upper and lower extremities was observed in parkinsonian monkeys. Cognitive testing revealed that aged animals were predominantly impaired at the longer delay for the DMTS task, whereas MPTP-treated parkinsonian animals were predominantly impaired on visuospatial-related tests, namely the DMTP task. In addition, parkinsonian monkeys were slower at learning the DMTS task compared to aged and middle-aged animals. Furthermore, age-associated cognitive declines were only found on the DMTS but not on the DMPT test. Our results suggest that cognitive impairments seen in animals with MPTP-induced parkinsonism differ from those seen in aged animals. Overall, our data suggests that different brain regions and circuitries may contribute to cognitive impairments seen in PD versus those seen in normal aging.
Age-associated changes of cerebrospinal fluid amyloid-β and tau in cynomolgus monkeys

Yi Ai, MD • Zhiming Zhang, MD
Anatomy and Neurobiology, University of Kentucky

Staff

Nonhuman primates (NHPs) are useful for the study of age-associated changes in the brain in a model that is biologically proximal to humans. For example, with age, all NHPs analyzed to date develop β-amyloid plaques as seen in humans. Nevertheless, it is still unknown whether NHPs have human-like age-associated change in β-amyloid (Aß) and tau protein in cerebrospinal fluid (CSF). The present study was to attempt to specifically address the issue. CSF levels of Aß and phosphorylated tau (p-tau) were measured in 29 cynomolgus monkeys with ages ranging from 4-22 years old. The result from the present study revealed significant age-associated declines in levels of Aß 42 but not of Aß 40 and p-tau among different age groups. This finding appears in parallel with changes of human aging, in which decreased levels of Aß 42 can be seen in normal older adults, and supports that cynomolgus monkey would be a useful model for studying age-related neurological disorders associated that Alzheimer-like cerebral proteopathy.

Synaptic protein changes in the posterior cingulate in Alzheimer's disease

Stephen Scheff 1 • Mubeen Ansari1 • Milos Ikonomovic2 • Elliott Mufson3
1Center on Aging, University of Kentucky • 2Neurology, University of Pittsburgh • 3Neurological Sciences, Rush University Medical Center

Faculty

Functional imaging studies have identified the posterior cingulate cortex (PC) (BA23) as an area affected early in the progression of Alzheimer’s disease (AD). Prior research from our laboratory demonstrated significant synaptic loss in both the hippocampus and inferior temporal cortex in individuals with mild cognitive impairment (MCI). We have also shown a loss of synapses in the PC in AD. Since the PC has direct connectivity with the medial temporal lobe, we tested whether or not synaptic change occurs in this region early in the disease progression. We quantified changes in several key synaptic proteins using short postmortem (PMI) cases from the ADC at the University of Kentucky and Rush Medical Center. Clinical diagnosis was based on neuropsychological testing within 12 months prior to death resulting in subjects categorized as no cognitive impairment (NCI), MCI, and AD. All groups were age and PMI matched. In addition, samples were analyzed for changes in soluble Abeta1-42 and [3H]PiB binding. Both the AD and MCI cohorts showed a significant decline in both pre and post synaptic proteins compared to the NCI group. AD and MCI groups were significantly different from each other. The changes in synaptic proteins significantly correlated with the subject’s Mini Mental State Examination (MMSE). Although levels of soluble Abeta 1-42 were significantly increased in both AD and MCI, there did not appear to be any significant association with the different synaptic proteins. In contrast, [3H]PiB binding showed a very strong association with both pre and post synaptic changes. This is the first study to evaluate changes in both pre and post synaptic proteins in this paralimbic association region as a function of disease progression, which may signal a region involved early in the disease process.
Synaptic protein alterations in the progression of Alzheimer's disease

Mubeen Ansari, PhD • Stephen Scheff, PhD
Sanders-Brown Center on Aging, University of Kentucky

Alzheimer’s disease (AD) is a progressive disorder characterized by a loss of memory and a general decline in cognitive function. The loss of synapses in many association regions of the neocortex may underlie these cognitive changes. Synaptic proteins are critical to the function of the nervous system and play essential roles in not only synapse formation and maintenance, but also the regulation of neurotransmission. Several studies have reported synaptic alterations in early stages of the disease such as mild cognitive impairment (MCI). It is unclear whether specific synaptic proteins are altered at this early stage. The present study evaluated the levels of several different key synaptic proteins representing both pre and post synaptic elements. Short postmortem autopsy tissue from the inferior temporal (IT) and inferior parietal (IP) cortical areas was obtained from individuals with no cognitive impairment (NCI), MCI, mild AD (mAD) and AD. Western-blot analysis demonstrated that several key presynaptic proteins — synapsin-I, synapse-associated protein 97 (SAP-97), growth associated protein 43 (GAP-43), and synaptophysin declined with the progression of the disease, as well as postsynaptic proteins: PSD-95 and drebrin. In contrast, synapse-associated protein 25 (SAP-25) and synaptobrevin were upregulated early in the disease progression and then declined in late AD. There were also some differences between the IT and IP. These results underscore the idea that changes in synaptic proteins are a dynamic process and differentially affected in the disease process. The next major question is to determine what mechanisms are responsible for the change in synaptic proteins (e.g. soluble amyloid, oxidative stress) and what can be done to slow down the process.

Aged rats appear less affected by acute psychosocial stress than young

Heather Buechel • Jelena Popovic • Katie Anderson • Olivier Thibault, PhD • Eric Blalock, PhD
Molecular and Biomedical Pharmacology, University of Kentucky

In healthy young subjects, acute stress influences cognition, sleep architecture, and hippocampal synaptic properties. However, little work has investigated acute stress’ influence on aged subjects, who often suffer from impaired cognition and dysregulated sleep. We tested the long-standing hypothesis that aged animals should be more sensitive than young to the influence of acute psychosocial stress. To address this, we implanted young and aged subjects with wireless telemetry devices, and measured cognitive performance, sleep architecture and hippocampal synaptic properties in control and acute stressed young and aged animals (n = 9-11/ group). Subjects were trained in the Morris water maze for 3 days, stressed (restrained) for 3 hours, and given a water maze probe trial. After the probe trial, rats were returned to their housing room and post-stress sleep architecture was measured. The following morning, hippocampi were prepared for electrophysiological measures of synaptic activity. Aged animals showed significant water maze performance deficits, deep sleep reduction, and synaptic weakening. Interestingly, acute stress made young animal measures more aging-like, while aged subjects appeared relatively insensitive to the exposure (e.g., younger animals showed slower maze performance, reduced deep sleep and weakened synaptic behavior). Results suggest that acute stress may have age-selective influences on cognition, sleep architecture and underlying synaptic behavior.
Brain insulin exposure: acute and intranasal effects on calcium electrophysiological biomarkers of aging and memory

Shaniya Maimaiti • Katie Anderson • Chris DeMoll • Benjamin Rauh • Eric Blalock • Nada Porter • Olivier Thibault

Molecular and Biomedical Pharmacology, University of Kentucky

Student

Background and Objectives

Metabolic syndrome is generally defined as a constellation of symptoms consisting of insulin resistance, compensatory hyperinsulinemia, dyslipidemia, hypertension, and central obesity. As insulin secretion begins to fail, the syndrome frequently converts to Type 2 diabetes mellitus (T2DM) and hyperglycemia. While the impact of T2DM in aging is recognized in the periphery, it is also becoming clear that insulin resistance exists in the brain. To combat this decreased insulin signaling in the brain, several labs have used intranasal insulin therapy and showed improved cognition and memory. Indeed, brain insulin signaling, and in particular decreased insulin sensitivity has been reported as a mediator of decreased cognitive function and an important pathological player in brain aging and AD. Our objective was to test the impact of intranasal insulin on brain aging as well as the effect of insulin on electrophysiological measures of brain aging.

Methods

Here, we tested the impact of short- Humalog® or long-acting insulin Levimir® on cognitive function in 21 months-old F344 rats. Thirty aged animals received daily doses of Levimir® at 3 concentrations (10/group) equivalent to those used in several clinical trials (0.143, 0.286 or 0.571 IU/ Kg/ day), while ten aged rats received daily Humalog® doses of 0.143 IU/ Kg/ day, others received saline. Treatment lasted for 11-18 days with training on the Morris water maze task starting on the fifth day. A subset was used to test for the impact of intranasal insulin on peripheral glucose levels. In a subset of animals, electrophysiological characterization, with a focus on the Ca2+-dependent afterhyperpolarization (AHP) was undertaken to determine whether enhanced insulin signaling specifically targets and improves hippocampal Ca2+-dependent processes that are dysregulated with aging. Further, in most pre- and clinical trials intranasal insulin formulation contained zinc, however, this metal has been shown to alter Ca2+-dependent signaling in the brain. We, therefore, also tested the zinc-free insulin formulation Apidra® for acute effects on hippocampal electrophysiology.

Results and Conclusions

Compared to the animals receiving the middle dose, animals receiving the low and the high dose Humalog® showed improved performance on the 24 hr recall task. Based on evidence that Levimir® did not alter the AHP following intranasal treatment, but that acute Apidra® significantly reduced the AHP ex-vivo, we propose here that insulin’s action may be short acting and transient. These approaches also provide evidence that the AHP may be a cellular mechanism for improved performance in response to intranasal insulin therapy. Once a day intranasal insulin exposure therefore, appears able to have a significant impact on hippocampal processes, partially reversing some aspects of the aging phenotype (i.e., the AHP).
POSTER ABSTRACTS

8

Loss of brain substance in AD is steady and predictable: in vivo with validation at autopsy

Charles Smith, MD 1 • Erin Abner, PhD 2 • Gregory Jicha, MD, PhD 2 • Linda Van Eldik, PhD 2 • Frederick Schmitt, PhD 2 • Steven Scheff, PhD 2 • Clinton Wellnitz, MD 3 • Peter Nelson, MD, PhD 2

1Neurology and Radiology, University of Kentucky • 2Sanders-Brown Center on Aging, University of Kentucky • 3Phoenix, AZ

Faculty

Imaging studies have shown declines in brain volume over time in unconfirmed Alzheimer's disease (AD) at an annualized rate of 1.5%. Here we imaged two groups of subjects in life: 30 undergoing clinical MRI scans for evaluation of cognitive symptoms and 47 cognitively normal persons who underwent a research MRI protocol. There were 26 in the clinical group and 14 in the research group who were later diagnosed with definite AD at autopsy. Despite differences in imaging protocols and cognitive status at scan, in both groups two variables best predicted fresh brain weight in definite AD: total cerebral volume at scan, and years from scan to autopsy. Age at scan, education and gender were not salient. A least squares statistical model incorporating these two variables plus group status had a robust adjusted Rsquare of 0.85, and predicts a linear loss of 22.8 grams/year in the clinical group (t=6.8, p<0.0001), and a similar 24.8 grams/year in the research group (t=3.1, p=0.004). The surprising observation is the constant loss of cerebral substance in AD over a wide range of clinical, cognitive and imaging starting points.

9

The Alzheimer's-associated gene: CD2AP, is a positive regulator of anatomical neuroplasticity

Ben Harrison, PhD • Jeff Petruska, PhD
Kentucky Spinal Cord Injury Research Center, University of Louisville

Fellow

Recent genome-wide association studies compiled from large data sets have uncovered novel polymorphisms highly associated with late-onset Alzheimer's (LOA). One such variant is a single nucleotide polymorphism in the first intron of CD2-associated protein (CD2AP). How this variant affects Alzheimer's-related pathology is unknown. Coming from a completely different perspective studying gene transcription profiles of anatomical neuroplasticity, we observed that CD2AP is upregulated during collateral sprouting of axons. Gain/loss of function manipulations of CD2AP in primary neurons showed that this gene is a positive regulator of axonal growth. These data in addition to subsequent mechanistic studies are presented for consideration in the wider context of neuroplasticity disruption during Alzheimer’s disease. Supported by US-EPA Contract RFQ-RT-12-00140 (JDP and PGS, Co-PI), NIH grants NS062993 (PGS), NS069633 (PGS)
Age and organ specific changes in mitochondrial bioenergetics in brown Norway rats

Jignesh Pandya, PhD 1 • Andrea Sebastian 1 • Joyce Royland, PhD 2 • Robert MacPhail, PhD 2 • Patrick Sullivan, PhD 1 • Prasada Rao Kodavanti, PhD 2

1SCoBIRC, Department of Anatomy and Neurobiology, University of Kentucky • 2U.S. Environmental Protection Agency (US-EPA), NHEERL/ORD, Research Triangle Park, NC 27711

Staff

Mitochondria are central regulators of energy homeostasis and play a pivotal role in mechanisms of cellular senescence and age-related neurodegenerative and metabolic disorders. However, mitochondrial bioenergetic parameters have not been systematically evaluated under identical physiological conditions within multiple organ samples in diverse age-groups. In the present study, we used the Seahorse Extracellular Flux Analyzer (Seahorse Bioscience XF-24) to compare four different life-stages of male Brown Norway rats [i.e. 1 Month- Young (Y), 4 Month- Adult (A), 12 Month- Middle-Aged (M) and 24 Month- Old-Aged (O)]. We measured mitochondrial bioenergetic parameters in five brain regions [brain stem (BS), frontal cortex (FC), cerebellum (CER), striatum (STR), hippocampus (HIP)] and three peripheral organs [heart (HRT), liver (LVR), lung (LNG)]. Ficoll-purified mitochondrial samples (15-40 µg/well) from the eight tissues (n=5 animals/group) were analyzed for NADH-linked, pyruvate-malate (PM) substrate-driven maximal (State V) respiratory rates, ATP synthesis capacity (State III) and proton leak (State IV). Additionally, FADH-linked maximal respiratory (State VSucc) rates were assessed in all samples. In general, all the regions of the brain followed identical patterns where the maximal respiratory capacities (State V and State VSucc) were reduced as a function of increasing age (Y>A>M=O). The State III respiration in BS, CER and HIP demonstrated a similar pattern as observed for the maximal respiratory capacities (Y>A>M=O); whereas the FC and STR displayed the highest State III rates in the adult group amongst all the age group tested here (A>Y≥O≥M). The proton leak (State IV) remained unaffected. When respiratory rates were measured in peripheral organs, the State V and State III rates were highest in younger animals followed by gradual decline with aging as evident in both HRT (Y>A=O>M) and LNG (Y>A=O=M). In LVR, the FADH-linked respiration was greater than NADH-linked bioenergetics. In LVR, the NADH-linked respiratory parameters remained unchanged amongst all the age groups tested; whereas the FADH-linked maximal respiratory (State VSucc) rates increased gradually as a function of age (Y<A<M=O).

In summary, the comparative data analysis of this study gives valuable insight about the metabolic status of various organs that could potentially lead to age-associated changes in neurodegenerative or metabolic disorders. Additionally, the observed changes in mitochondrial bioenergetics will serve as a basic platform to elucidate chemically-induced life-stage susceptibility mechanisms important in community health-related research. (This abstract does not necessarily reflect USEPA policy). Supported by US-EPA Contract RFQ-RT-12-00140 (JDP and PGS, Co-PI), NIH grants NS062993 (PGS), NS069633 (PGS)
Dopaminergic modulation of memory and affective processing in Parkinson depression*

Lee X. Blonder1,2,3 • John T. Slevin3,4 • Richard J. Kryscio1,5,6 • Catherine A. Martin7 • Anders H. Andersen8,9 • Charles D. Smith3,8,9 • Frederick A. Schmitt,1,2,3,7

1Sanders-Brown Center on Aging, 2Department of Behavioral Science, 3Department of Neurology, University of Kentucky • 4Veterans Administration Medical Center, Lexington, KY • 5Department of Statistics, 6Department of Biostatistics, 7Department of Psychiatry, 8Department of Anatomy & Neurobiology, 9Magnetic Resonance Imaging and Spectroscopy Center, University of Kentucky

Faculty

Objectives
Depression is common in Parkinson’s disease (PD) and is associated with cognitive impairment. Dopaminergic medications are effective in treating the motor symptoms of PD, however, little is known regarding the effects of dopaminergic pharmacotherapy on cognitive function in depressed Parkinson (dPD) patients. The objective of this research was to examine dopaminergic modulation of cognitive performance in depressed versus non-depressed Parkinson patients.

Methods
This five-year crossover study compared cognitive function in depressed and non-depressed PD patients at two time-points: (1) following overnight withdrawal of anti-parkinsonian medication, and (2) after usual daily regimen of dopaminergic medications. A total of 28 mild to moderate non-demented, right-handed, idiopathic PD patients participated. Ten of these patients were depressed according to DSM IV criteria.

Results
To examine the effect of dopaminergic pharmacotherapy on neuropsychological test performance as a function of PD mood status, we compared mean response using an analysis of covariance for a crossover design with depression as the between subjects factor (present or absent) and dopaminergic medication status as the within subjects factor (on or off), tested in random order. Age and National Adult Reading Test- revised Full scale IQ scores served as covariates. Interactions between depression and medication status were statistically significant for the facial affect naming test (p=0.016) and the Hopkins Verbal Learning-revised Total Recall (p=0.011), Delayed Recall (p=0.010), and Recognition/Discrimination sub-scores (p=0.045). In all cases, dPD patients performed significantly more poorly while on dopaminergic medication than while off. The opposite pattern emerged for the non-depressed PD group.

Conclusions
Dopaminergic medications used to treat PD have opposite effects depending upon the mood state of the PD patient. DPD patients performed significantly worse in verbal memory and facial affect recognition while on dopaminergic medication whereas non-depressed PD patients improved. The administration of anti-parkinsonian medication to dPD patients may carry unintended risks. Future studies are required to determine the optimal therapeutic approach.

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Dopaminergic modulation of medial prefrontal cortex deactivation in Parkinson depression

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Objectives
Depression is common in Parkinson’s disease (PD) and is associated with cognitive and emotional abnormalities. Dopaminergic medications are effective in treating the motor symptoms of PD; however, little is known regarding the effects of dopaminergic pharmacotherapy on brain function in depressed Parkinson (dPD) patients. The objective of this research was to examine dopaminergic modulation of patterns of brain activation/deactivation to emotional stimuli in depressed versus non-depressed Parkinson patients.

Methods
This five-year crossover study used neuroimaging to compare brain function in depressed and non-depressed PD patients at two time-points: (1) following overnight withdrawal of anti-parkinsonian medication, and (2) after usual daily regimen of dopaminergic medications. A total of 28 mild to moderate non-demented, right-handed, idiopathic PD patients participated. Ten of these patients were depressed according to DSM IV criteria. Using functional magnetic resonance imaging (fMRI), PD patients were shown photographs of happy, angry, sad, and neutral facial expressions interspersed with periods of rest.

Results
Results indicate varying levels of deactivation within the midline default mode network along with activation changes in the lateral prefrontal cortex (PFC). To examine the effect of dopaminergic pharmacotherapy on brain activity as a function of PD mood status, we compared the mean deactivation response within an anatomical region of interest located in ventro-medial PFC. An analysis of variance for a crossover design was used with depression as the between subjects factor (present or absent) and dopaminergic medication status (on or off) and emotion category (angry, happy or sad) as within subjects factors. The analysis revealed a significant three-way interaction between depression, medication status and emotion category (p=0.013). Depressed PD patients have greater deactivation in the ventro-medial PFC while on dopaminergic medication whereas the non-depressed patients show greater deactivation in this region off drugs. An interaction effect of the opposite direction was seen for the activation response in lateral PFC with greater task-related activation in depressed PD patients off medication compared to on.

Conclusions
Dopaminergic medications used to treat PD have opposite effects depending upon the mood state of the PD patient. Depressed PD patients exhibited a failure to suppress the default-mode activity in ventro-medial PFC during external stimulation with photographs of emotional faces. Suppression of the default-mode activity was restored by dopaminergic medication. The inverse effect in lateral PFC also supports the view of reciprocal limbic-cortical function and negative mood state.

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Sleep alterations in 5XFAD mice, a model of Alzheimer's disease

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Sleep perturbations including fragmented sleep with frequent night-time awakenings and daytime naps are common in patients with Alzheimer’s disease (AD), and constitute a major factor for institutionalization of these patients. The extent to which these changes in sleep-wake patterns contribute to or are the result of AD progression is poorly understood. This study aimed at examining alterations in sleep-wake patterns in a well-characterized double transgenic mouse model of AD, called 5XFAD which exhibits an early onset and robust AD pathology. These mice have five distinct human mutations in amyloid precursor protein (APP) and Presenilin1 (PS1) engineered into two transgenes driven by a neuron specific promoter (Thy1), and thus develop severe amyloid deposition at an early age. Age-matched (4-6 months old) male and female 5XFAD mice (males: N=10; females: N=7) were monitored and compared to wild-type littermate controls (males: N=7; females: N=11) for various sleep traits using a non-invasive, high throughput, automated piezoelectric system. Sleep-wake patterns were recorded under baseline conditions (undisturbed) for 3 days and after sleep deprivation of 4 hours, which in mice produces a significant sleep debt and challenge to sleep homeostasis. Under baseline conditions, 5XFAD mice exhibited shorter bout lengths (14% lower values for males and 21% for females) as compared to controls (p<0.001). In females, the 5XFAD mice also showed 11% less total sleep than WT (p<0.01). After sleep deprivation, reduced bout length was also found in 5XFAD mice of both sexes during the succeeding 8 hours (p<0.05 at multiple time points). Bout length reductions were greater during the night (the active phase for mice) than during the day, which does not model the human condition of disrupted sleep at night (our inactive phase). However, the overall decrease in bout length suggests increased fragmentation and disruption in sleep consolidation that may be relevant to human sleep. The AD mice may serve as a useful model for testing therapeutic strategies to improve sleep consolidation in AD patients.
Inhibition of neuronal p38α MAPK, but not p38β MAPK, provides neuroprotection against three different neurotoxic insults

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The p38 MAPK pathway plays a key role in pathological glial activation and neuroinflammatory responses. Our previous studies demonstrated that microglial p38α and not the p38β isoform is an important contributor to stressor-induced proinflammatory cytokine up-regulation and glia-dependent neurotoxicity. However, the contribution of neuronal p38α and p38β isoforms in neurodegenerative responses to neurotoxic agents is not known. In the current studies, we used primary cortical neurons from wild type or p38β knockout mice, or wild type neurons treated with two highly selective inhibitors of p38α to test the relative importance of p38α and p38β in neurodegenerative responses to toxic insults. Neurons were treated with one of three neurotoxic insults (L-glutamate, sodium nitroprusside, oxygen-glucose deprivation), and neurotoxicity was assessed by measuring neuron death and neurite degeneration. The results showed that L-glutamate, sodium nitroprusside, and oxygen-glucose deprivation induced substantial neuronal death and neurite degeneration, and the degree of neurotoxicity induced in neurons from wild type and p38β knockout mice was not significantly different. In contrast, selective inhibition of neuronal p38α was protective against all three neurotoxic stimuli. Our results show that neuronal p38β is not required for neurotoxicity induced by multiple toxic insults, but that p38α in the neuron contributes quantitatively to the neuronal dysfunction responses. These data are consistent with our previous findings of the critical importance of microglia p38α compared to p38β, and continue to support selective targeting of the p38α isoform as a potential therapeutic strategy. Support: NIH R01 NS064247; NIH F32 AG037280

Alzheimer’s associated gene PICALM: expression and splicing in the human brain

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GWAS have identified a series of single nucleotide polymorphisms (SNP)s that are associated with Alzheimer’s disease. We studied SNP, rs3851179, near the gene phosphatidylinositol-binding clathrin assembly protein (PICALM) for its effect on expression and splicing of PICALM. Expression: Quantified total PICALM mRNA in 60 brain cDNA samples, using qPCR. In linear regression analyses of PICALM that included microvessel markers, AD, sex and rs3851179; rs3851179 (p<0.027) and microvessel content (p< 0.001) associated with PICALM expression. Splicing: Over 700 clones were sequenced to evaluate the abundance and relative distribution of splice variants present. PICALM has multiple splice variants, which lack exons encoding functional protein motifs. Sequencing the cloned isoforms we found that exons 13, 14,15,18 and 19 were variably spliced and isoform lacking exon 13 is the most abundant isoform. Expression of isoforms lacking exon 13 associated with rs3851179 genotype (p<0.022). We targeted the latter part of the gene, exon 17-20, to investigate allelic expression imbalance (AEI) using semiconductor-sequencing technology. Individuals heterozygous for rs76719109, located in exon 17, were used to study the ratio of G/T allele in cDNA and genomic DNA. We analyzed the G : T allelic ratio, the variant lacking exons 18 and 19 showed unequal allelic expression in 8 individuals (p-value < 0.001). One individual was an outlier, showing overall AEI. The isoform lacking exon 18-19 appears to be under genetic control and is the subject of current investigation.
Clinically relevant intronic splicing enhancer mutation in myelin proteolipid protein leads to progressive microglia and astrocyte activation in CNS

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Introduction
Mutations in proteolipid protein (PLP), the most abundant myelin protein in the CNS, cause the X-linked dysmyelinating leukodystrophies, Pelizaeus-Merzbacher disease (PMD) and Spastic Paraplegia Type 2 (SPG2). Point mutations, deletion, and duplication of the PLP1 gene cause PMD/SPG2 with varying clinical presentation. Deletion of an intronic splicing enhancer (ISEdel) within intron 3 of the PLP1 gene is associated with a mild form of PMD. Clinical and preclinical studies have indicated that mutations in myelin proteins, including PLP, can induce neuroinflammation, but the temporal and spatial onset of the reactive glia response in a clinically relevant mild form of PMD has not been defined.

Methods
A PLP-ISEdel knockin mouse was used to examine the behavioral and neuroinflammatory consequences of a deletion within intron 3 of the PLP gene. Mice were characterized functionally using the open field task, elevated plus maze, and nesting behavior. Quantitative neuropathological analysis was conducted for markers of astrocytes (GFAP), microglia (IBA1, CD68, MHCII) and axons (APP).

Results
The PLP-ISEdel mice exhibited behavioral deficits in the open field and nesting behavior at 2 months, which did not worsen by 4 months of age. A marker of axonal injury (APP) increased from 2 months to 4 months of age. Striking was the robust reactive glia response which was also progressive. In the 2 month old mice, the gliosis was most apparent in white matter rich regions of the brain. By 4 months of age the gliosis had become widespread and included both white as well as gray matter regions of the brain.

Conclusions
Our results indicate, along with other preclinical models of PMD, that a reactive glia response occurs following mutations in PLP gene, which may represent a potentially clinically relevant, oligodendrocyte-independent therapeutic target for PMD.
Age-related neuroinflammatory responses in spinal cord injury

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The incidence of spinal cord injury (SCI) among older individuals has increased in recent years. According to the Kentucky Injury Prevention and Research Center, in 2007, 61% of all non-fatal SCIs were sustained by individuals >45 years old. Aged animals have reduced rates of recovery, residual locomotor deficits, and increased areas of pathology and demyelination after SCI compared to young animals, but the mechanisms behind these age-related differences are not well understood. Macrophages are a hallmark of CNS trauma and can facilitate repair or pathology in the injured spinal cord. Age is a key regulator of macrophage function, and aging is associated with increased activation of pathological macrophage phenotypes. Therefore, we hypothesize that age-related differences in the macrophage response may contribute to functional recovery after SCI. To address this hypothesis, we compared the inflammatory response in young (3-4 month old) and aged (10-16 month old) mice after laminectomy receiving either a sham or a moderate contusion SCI (50-75 Kdyne Infinite Horizons). We detected a significantly dampened pro-reparative macrophage response to SCI in aged vs. young animals (indicated by decreased expression of Arginase-1 and Fizz1). We also investigated the effect of age on functional recovery with the Basso mouse scale (BMS), grid walk, and DigiGait system. Our results indicate that aged mice exhibited worse functional deficits when compared to young mice. Collectively, these data demonstrate an important role for age in changes of inflammatory responses and functional recovery in the context of SCI. Most clinical therapies are being examined in individuals regardless of age and are based upon data generated almost exclusively using young animals. Our data highlight the potential for immunomodulatory therapies to have decreased efficacy in aged individual receiving SCI and highlight the need to elucidate the cellular mechanisms contributing to age-related differences in functional recovery.
Can targeting the proinflammatory cytokine surge following traumatic brain injury improve pathological outcomes?

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Traumatic brain injury (TBI) and its associated morbidity are major public health issues with an unmet need for therapeutic interventions that alter pathology progression and improve longer-term neurologic outcomes. The pathogenesis of neurologic damage following TBI is complex and is the result of both the immediate primary impact injury and secondary mechanisms that are more amenable to therapeutic intervention and develop in the minutes to weeks following the initial insult. Post-traumatic glial activation and increased production of proinflammatory cytokines is an early secondary event that contributes to pathology progression in both animal models and human head injury patients. Selective pharmacological attenuation of the acute proinflammatory cytokine surge, therefore, offers the potential for altering pathology progression and later stage neurologic sequelae. MW01- 2-151WH (151WH) is a novel, CNS-penetrant small molecule drug (Hu et al., 2007, Bioorg Med Chem Lett 17:414) that selectively restores injury- or disease-induced overproduction of proinflammatory cytokines towards homeostasis, with resultant improvement in neurologic outcomes. It is efficacious in a closed-head, pneumatic compression injury model (Lloyd et al., 2008, J Neuroinfl 5:28) and attenuates later susceptibility to second hit injuries or pathology development when administered during the critical post-trauma window (Chrzaszczy et al., 2010, J Neurotrauma 27:1283). We report here that 151WH attenuates the post-injury cytokine surge in a midline fluid percussion model when administered briefly after TBI. Diffuse brain injury was induced by moderate fluid percussion injury in young adult mice, and the temporal profile of proinflammatory cytokine production determined. Inflammatory cytokines (IL-1β, IL-6, CXCL1, TNFα) were elevated in the cortex within 1 hr post-injury compared to uninjured sham, with significant peak responses occurring within 9 hrs post-injury. By 24-48 hrs post-injury, most of the cytokines were at or below sham levels. Drug administration at low doses (1.5 or 5 mg/kg) post-injury during the initial phase of the cytokine response led to a significant reduction in the levels of cytokines seen at 6 hrs post-injury. Our results extend the potential clinical utility of 151WH to diffuse brain injury and add to the growing body of evidence that this class of drugs offers a potential new therapeutic approach to CNS disorders characterized by proinflammatory cytokine overproduction as a mechanism of pathology progression.
Role of the calcineurin/NFAT pathway in astrocytic glutamate uptake: Implications for Alzheimer's disease

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One of the essential functions of astrocytes is the prevention of excitotoxicity via the removal of excess glutamate from the extracellular milieu. Astrocytic glutamate uptake, carried out primarily by the type 2 excitatory amino acid transporter (EAAT2), accounts for as much as 90% of total glutamate uptake in some brain regions, like the hippocampus. During the progression of Alzheimer's disease (AD), hippocampal EAAT2 protein levels drop off by nearly 75% and correspond to increased activity of the protein phosphatase calcineurin (CN) and the transcription factor, NFAT. Moreover, loss of EAAT2 levels in primary astrocytes in response to inflammatory insults or pathogenic amyloid-β (Aβ) peptides is largely prevented by inhibition of CN/NFAT activity. In the present set of studies, we used primary astrocyte cultures and intact APP/PS1 (5XFAD) mice to further investigate the role of astrocytic CN/NFAT signaling in AD-related glutamate dysregulation. Whole-cell voltage clamp recordings revealed that CN/NFAT activity directly leads to reduced glutamate uptake in primary cortical astrocytes, whereas selective inhibition of astrocytic CN/NFAT signaling in 5XFAD mice using adeno-associated virus (AAV) vectors led to a significant (p <0.05) increase in hippocampal protein levels for EAAT2, but not EAAT1. These results are generally very consistent with our earlier studies on primary astrocyte cultures and postmortem human brain tissue and suggest that astrocytic CN/NFAT activity negatively affects glutamate regulation during the progression of AD. Moreover, these findings may explain why astrocyte specific inhibition of CN/NFAT signaling improves hippocampal synaptic plasticity and cognitive function in 5XFAD mice, as demonstrated by our recently published work. Ongoing studies are using glutamate sensitive microelectrode arrays and patch clamp electrophysiology to directly determine the extent to which astrocytic CN/NFAT activity regulates basal and synaptically-released glutamate levels in 5XFAD mice.

Organo-selenium promotes beta amyloid degradation in APP/PS1 Mice

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Amyloid β peptide (Aβ) has been identified as central to the onset and development of Alzheimer’s disease (AD) by causing oxidative stress/damage and neuron degeneration. Accumulation of Aβ in brain may be the result of increased production, decreased clearance or a combination of the two. Previous studies show treatment of mice expressing mutant APP and mutant presenilin-1 (APP/PS1 mice) with an organo-selenium (Sel-Plex) enriched diet led to decreased Aβ1-42 deposition. To determine if Sel-Plex mediated decreases in Aβ deposition were due to decreased production or increased degradation we treated APP/PS1 mice with Sel-Plex from 5 to 9 months of age and quantified levels of PBS-, SDS-, and FA-soluble Aβ 1-42 and levels of proteins involved in Aβ production (presenilin-1, nicastrin, BACE-1) and Aβ degradation (neprilysin, insulin degrading enzyme). Our data show Sel-Plex significantly decreased levels of all three Aβ pools although levels of enzymes involved in Aβ production were not significantly altered. We did observe a significant elevation of levels of neprilysin, a primary protein responsible for Aβ clearance. Overall, the data suggest protective effects of Sel-Plex in APP/PS1 mice are due to enhanced Aβ degradation.

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The astrocytic gap junction protein connexin 43 exhibits calcineurin-related changes in phosphorylation status during the progression of AD

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Alzheimer’s disease (AD) is associated with neuroinflammation characterized by microglial and astroglial activation that arises in the early stages of the disease. Upon activation, astrocytes upregulate calcineurin (CN), a protein phosphatase involved in inflammatory signaling and in the production of pro-inflammatory cytokines. These inflammatory mediators can disrupt gap junction (GJ) coupling through impairment of GJ proteins, including the most abundant astrocytic GJ protein connexin 43 (Cx43). Previous work has shown that Cx43 is selectively dephosphorylated at Ser 368 in primary astrocytes by CN. However, the functional implications of this dephosphorylation event in AD are not well-understood. In the current study, we treated primary astrocyte cultures with the Ca2+ mobilizers ionomycin and phorbol ester (Ion/PE), or with the pro-inflammatory cytokine IL-1β, in the presence or absence of the CN inhibitor cyclosporine. Using Western blot to measure the levels of dephosphorylated Cx43, we found that treatments with Ion/PE and IL-1β resulted in a significant increase in the level of dephosphorylated Cx43 relative to untreated samples (p<0.05). Similarly, we prepared human hippocampal membrane fractions from non-demented subjects (n=10), subjects with mild cognitive impairment (MCI) (n=14), and subjects with AD (n=21), and used Western blot to measure the levels of dephosphorylated Cx43. The results showed a significant increase in the level of dephosphorylated Cx43 in MCI samples relative to non-demented samples (p<0.01), which occurred in parallel to elevated CN signaling. The results suggest that activation of CN leads to increased levels of dephosphorylated Cx43 which occurs selectively in MCI, and may contribute to early clinical progression of AD through disruption of astrocytic gap junctions. Ongoing studies focus on the functional ramifications and the development of novel reagents to modulate the CN-Cx43 interaction.

IL4 and TNFα / INFγ anti-inflammatory cytokine treatments alter the microglial phenotype of BV-2 cells at optimal time points

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Microglial cells are the resident macrophages of the CNS and monitor the brain parenchyma for pathologic activity and damage. Microglia are capable of a range of activation patterns which are observed during the progression of degenerative disorders such as Alzheimer’s disease (AD). In vitro models such as BV2 microglia cell lines can be used to investigate microglial activity in response to extracellular stimulants. Microglia undergo phenotypic adaptation in response to mediators such as IL4 and TNFα/ INFγ cytokines. Formerly, microglia were categorized into M1 (classical) or M2 (activated) phenotype. However, analogous to peripheral macrophages, microglia are currently considered to be phenotypically heterogeneous. Microglial phenotypes are on a polarized spectrum ranging from neurotoxic, M1, to neuroprotective roles, M2a. Hence, it is therapeutically beneficial to enhance the M2α phenotype in AD patients. The aim of this study was to determine the optimal time points at which microglial phenotypes in BV2 cells occur in response to IL-4 and TNFα/ INFγ cytokine treatments. Quantitative RT-PCR was used to assess the fold change of the marker expression of microglial phenotypes. Our findings have shown that BV2 cells display dynamic gene profiles and changing activation states across a time course. Concurring with the literature, our study shows that IL-4 and TNFα/ INFγ mainly induce the select activation states of M2a and M1 phenotypes respectively. This study has refined the time points at which these activation states occur. Furthermore, it provides a point of reference and a contribution towards therapeutic alteration of the microglial immune response in AD.
Evaluating the mechanisms for anti-inflammatory and neuroprotective properties of flavonoids in alcohol neurotoxicity

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Objective
Neurodegenerative diseases associated with ageing are complex and involve a wide spectrum of mechanisms. An emerging mechanism is the development of excessive neuroinflammation that ultimately contributes to neuronal loss and a well-established mechanism is excitotoxicity mediated by hyperglutamatergic function. Both these mechanisms are present in ethanol (EtOH) induced neurodegeneration where neuroinflammation is enhanced and n-methyl-D-aspartate (NMDA) receptor mediated excitotoxicity occurs during EtOH withdrawal (EWD). These mechanisms are extensively studied individually in relation to EtOH neurotoxicity. Therefore, we sought to investigate the neuroimmune adaptations produced by EtOH exposure and assess their impact on excitotoxicity in an in vitro model of EtOH induced neurotoxicity. Additionally, both these mechanisms can potentially be attenuated by agonists at the alpha7 nicotinic acetylcholine receptor (nAChR). Therefore, we sought to identify and characterize novel natural products, from a large plant extract library, targeting this nAChR subtype.

Methods/Results
We developed an organotypic hippocampal slice culture (OHSC) model from neonatal rats in which toxicity associated with alcohol can be assessed. Slices are treated with EtOH for 10 days and toxicity (as measured by propidium iodide uptake) is induced by exposure to either NMDA and/or lipopolysaccharide (LPS) during EWD (24h). Media samples are then collected and assayed for tumor necrosis factor alpha (TNFalpha) and nitric oxide (NO) content. While LPS did not produce toxicity, it potentiated NMDA toxicity under control conditions. However, and surprisingly, NMDA toxicity was blunted by LPS under EWD conditions. On the other hand, while NMDA did not elicit or enhance the inflammatory response, EtOH exposure and EWD blunted inflammation. In parallel, we developed a high throughput smart screen using radioligand binding which identified the extract of Solidago nemoralis as selective for the alpha7 nAChR. Further characterization led us to the discovery of specific flavonoids which are not only selective for alpha7 nAChR but are potent anti-oxidants and anti-inflammatory molecules.

Conclusions
While there is a clear interaction between inflammation and excitotoxicity in neurodegeneration associated with alcoholism, the situation is more complex than the original hypothesis. However, alpha7 nAChRs remain nonetheless a potential target to attenuate both inflammation and excitotoxicity. Furthermore, plant derived flavonoids with selectivity for this receptor represent an exciting novel class of compounds with multifunctional pharmacology that are potentially valuable for the treatment of neurodegenerative diseases.
Alzheimer's disease protective polymorphism promotes alternative splicing of CD33

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Recent genome-wide association studies have identified the single nucleotide polymorphism (SNP) rs3865444, located 372 base pairs upstream of CD33, as a modulator of Alzheimer's disease (AD) susceptibility. Here, we seek to identify CD33 isoforms expressed in the human brain, quantify expression of these isoforms in brain, and evaluate the correlation between the expression of these isoforms and rs3865444. Our long-term goal is to develop therapies that mimic the effects of protective SNPs in order to combat AD onset.

CD33 is a member of the sialic acid-binding immunoglobulin-like lectin (SIGLEC) family, which is expressed on microglia in brain. CD33 is expected to have an immunosuppressive effect on microglia when bound to sialic acid, which may be found on proteins decorating the surface of amyloid plaques in AD brain. Thus, increased expression of functional CD33 is expected to increase AD risk by preventing microglial activation and clearance of amyloid.

CD33 typically contains seven exons. Characterization of CD33 splicing in the brain identified multiple variably spliced exons and introns. When we quantified expression of total CD33 in cDNA prepared from 30 AD and 30 non-AD brains, we found no significant association between total CD33 expression and rs3865444, but found that total CD33 expression was increased in AD brains. We proceeded to quantify expression of the exon 2 deleted form of CD33 (D2 CD33), finding a significant association between rs3865444 genotype and exon 2 splicing. The AD-protective minor allele of rs3865444 promotes increased skipping of CD33 exon 2, which encodes the sialic-acid binding domain. Quantification of the intron 1 retained form of CD33 (I1 CD33) showed that rs3865444 also promotes increased retention of intron 1, which leads to production of a prematurely truncated CD33 protein. Thus, we conclude that the minor allele of rs3865444 functions to decrease AD risk by inhibiting CD33 function, thus enabling microglial mobilization against amyloid. We propose that an antibody treatment that clears surface CD33 or masks CD33 exon 2 will be therapeutic against AD.
Intracranial administration of Gammagard IVIg lowers amyloid and modulates neuroinflammatory profiles along a different time-course than anti-Aβ IgG — implications for mechanism of action

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Gammargard IVIg is a therapeutic approach to treat Alzheimer’s disease currently in phase 3 clinical trials. Despite the reported efficacy of the approach, the mechanism of action is poorly understood. We have previously shown that intracranial injection of anti-Aβ antibodies into the frontal cortex and hippocampus reveals important information regarding the time-course of events once the agent is in the brain. In the current study we compared Gammagard IVIg, mouse pooled IgG and the anti-Aβ antibody 6E10 injected intracranially into the frontal cortex and hippocampus of 9 month old APP/PS1 mice. We established a time-course of events ranging from 24 hours to 21 days post-injection.

Gammagard IVIg and pooled mouse IgG both significantly reduced amyloid deposition to the same degree as the 6E10 anti-Aβ antibody; however, the clearance was much slower to occur, happening between the 3 day and 7 day time-points. In contrast, as we have previously shown, amyloid reductions were apparent with the 6E10 anti-Aβ group at the 1-day time-point. Also, neuroinflammatory profiles were significantly altered by the antibody treatments. APP/PS1 transgenic mice at nine months of age typically exhibit an M2a inflammatory phenotype. Anti-Aβ IgG stimulated a brief M2b state, peaking at 2 days and resolving completely by 7 days. In contrast, Gammagard IVIg and pooled mouse IgG both stimulated an M2b response that peaked at 7 days and was sustained through the 14 day time-point, only resolving by 21 days.

Because the neuroinflammatory switch occurs prior to the detectable reductions in amyloid deposition, we hypothesize that the Gammagard IVIg and pooled mouse IgG act as immune modulators and this immune modulation is responsible for the reductions in amyloid pathology. Future studies will focus on this mechanism of action to determine whether immune modulation avoids the cerebrovascular adverse events that have plagued the anti-Aβ immunotherapy approaches.
Unique electrophysiological signatures of mild cognitive impairment and Alzheimer disease

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Event-related potentials (ERPs) to repetition effects are potential biomarkers of preclinical Alzheimer disease (AD). Changes in working memory are among the earliest clinical symptoms of patients with the stage of AD termed amnestic mild cognitive impairment (aMCI). We have previously reported that older adults (NE) show characteristic changes in early, frontal repetition effects relative to young adults and that the frontal effect interacts with working memory. In this study we measured ERPs of working memory repetition effects generated by older patients with healthy cognitive aging and patients experiencing stages of early AD to test whether they might identify patients at risk of AD.

ERPs were measured during a hybrid delayed-match-to-sample/repetition task. ERPs were processed using standard techniques. Stimuli were two-dimensional, black-and-white 8.3 cm x 5.8 cm pictures of common objects presented with a black background. 37 age- and education-matched participants – 16 NE, 13 aMCI, 8 AD – were recruited from the well-characterized UK-ADC elderly control cohort or from tertiary care clinics associated with the Sanders-Brown Center on Aging. All participants provided written informed consent before participation. The study was approved by the Institutional Research Board of the University of Kentucky.

ERP repetitions were dichotomized into initial and subsequent presentations. Repetition effects were dissociated into earlier (300-600 ms) and later (600-900 ms) time windows. ERPs were analyzed as 3 x 2 x 2 (Group X Retrieval Status X Repetition) mixed-factorial ANOVAs at the respective electrodes and time-windows.

The NE and aMCI groups performed similarly, though the aMCI group showed disproportionately slow reaction times for non-matching stimuli. The AD group was slower and had poorer accuracy than both other groups, but all groups showed comparable repetition effects. In the 600-900 ms time-window, repeated measures ANOVAs revealed a significant effect of repetition and a significant retrieval status X repetition interaction frontally (ps < 0.01). Repeated stimuli were associated with reduced amplitude, and the interaction resulted from a larger repetition effect for matching stimuli (ps < 0.05). In the 300-600 ms time-window, repeated measures ANOVAs revealed a significant effect of repetition, a significant retrieval status X repetition interaction, and a significant group X retrieval status X repetition interaction posteriorly (ps < 0.05). Repeated stimuli were associated with increased mean P3 amplitude, and the interaction resulted from a larger repetition effect for non-matching stimuli (ps < 0.01). The group X retrieval status X repetition three-way interaction resulted from an increase of the repetition effect of non-match stimuli for the AD group (ps < 0.05).

The early repetition effect, but not the late repetition effect, is sensitive to group differences, and the late repetition effect is insensitive to working memory retrieval status effects posteriorly. This study revealed new evidence of early posterior repetition effects and late frontal repetition effects, especially in patients with AD. Patients with AD may compensate for decline via the early posterior repetition effect taking on functions of the early frontal repetition effect.
Neurodegeneration-associated instability of ribosomal DNA
Justin Hallgren, MS • Maciej Pietrzak, PhD • Peter Nelson, MD, PhD • Michal Hetman, MD, PhD
1Pharmacology and Toxicology, University of Louisville • 2Neurological Surgery, University of Louisville • 3Pathology and Lab Medicine, University of Kentucky
Student
Homologous recombination (HR)-mediated instability of the repetitively organized ribosomal DNA (rDNA) has been proposed as a mediator of cell senescence in yeast triggering the DNA damage response. High individual variability in the content of human rDNA suggests that this genomic region remained relatively unstable throughout evolution. Therefore, quantitative real time PCR was used to determine the genomic content of rDNA in post mortem samples of parietal cortex from 14 young- and 9 elderly individuals with no diagnosis of a chronic neurodegenerative/neurological disease. In addition, rDNA content in that brain region was compared between 10 age-matched control individuals and 10 patients with dementia with Lewy bodies (DLB) which involves neurodegeneration of the cerebral cortex. Probing rRNA-coding regions of rDNA revealed no effects of aging on the rDNA content. Elevated rDNA content was observed in DLB. Conversely, in the DLB pathology-free cerebellum, lower genomic content of rDNA was present in the DLB group. In the parietal cortex, such a DLB-associated instability of rDNA was not accompanied by any major changes of CpG methylation of the rDNA promoter. As increased cerebro-cortical rDNA content was previously reported in Alzheimer’s disease, neurodegeneration appears to be associated with instability of rDNA. The hypothetical origins and consequences of this phenomenon are discussed including possibilities that the DNA damage-induced recombination destabilizes rDNA and that differential content of rDNA affects heterochromatin formation, gene expression and/or DNA damage response.

Development of a lateral flow device for the early detection of mild and moderate traumatic brain injury
Melissa Bradley-Whitman, PhD • Kelly Roberts • Stephen Scheff, PhD • Mark Lovell, PhD
1Sanders Brown Center on Aging, University of Kentucky • 2Sanders Brown Center on Aging, Anatomy and Neurobiology, and Spinal Cord and Brain Injury Research Center, University of Kentucky • 3Sanders Brown Center on Aging, Chemistry, University of Kentucky
Fellow
Approximately 1.7 million US civilians sustain traumatic brain injury (TBI) annually as a direct result of falls, motor vehicle accidents, and sports related injuries. Additionally, the incidence of TBI is significantly higher in military populations, even during peace time. While severe TBI is readily detectable in both military and civilian populations, the detection of mild TBI in both populations is limited. Current studies directed toward the quantification of circulating biomarkers of brain injury by enzyme linked immunoassays (ELISAs) are temperature sensitive and routinely require 12-16 hrs for completion, well outside potential therapeutic windows. In the current study we identified a novel marker of TBI, visinin like protein 1 (VILIP-1), a neuron specific Ca2+-sensor protein, that is released into circulating blood post-injury. Furthermore, we developed a point-of-care lateral flow device (LFD) that allows for sensitive and rapid detection (<10min) of elevated levels of VILIP-1 in serum. For preliminary studies, young, male Sprague-Dawley 344 rats were subjected to mild or moderate TBI using a controlled cortical impact (CCI) and blood samples taken via tail nicks pre-injury and 1, 3, and 4 hrs post injury. Our results showed significantly (P < 0.05) elevated levels of VILIP-1 were detected in serum 1, 3, and 4 hrs post injury in both mild TBI and moderate TBI compared to surgery naive animals. Receiver operating characteristic curves for mild and moderate TBI at all-time points studied showed 100% sensitivity and 100% specificity at cutoffs greater than 212.3 ng/ml for mild TBI and 511.2 ng/ml for moderate TBI 1 hr post injury, 198.3 ng/ml for mild and 796.4 ng/ml for moderate TBI at 3 hrs post injury and 1246.0 ng/ml and 1476.0 ng/ml for mild and moderate TBI 4 hrs post-injury. Overall, the data suggest that serum levels of VILIP-1 may be a useful circulating biomarker of TBI that is rapidly generated and can be quantified in a potentially useful therapeutic window.
Alterations in calpain isoform expression and activation in Alzheimer’s disease  

Colin Rogers, PhD 1 • Sarbani Ghoshal, PhD 1 • Peter Nelson, MD, PhD 2 • James Geddes, PhD 1  

1SCoBIRC, University of Kentucky • 2Sanders Brown, University of Kentucky  
Fellow

Increases in intracellular calcium are thought to contribute to the two hallmark pathologic features of Alzheimer’s disease (AD): neurofibrillary tangles (NFTs) composed of aggregated tau protein; and senile plaques composed primarily of β-amyloid (Aβ) protein. These pathologies are prevalent in the hippocampus and many cortical regions including the pre-frontal cortex and cingulate cortex, with the cerebellum being less vulnerable. Calpains are calcium-activated proteases thought to contribute to NFT and plaque formation making them a potential target for AD prevention and treatment. Currently, seven calpain isoforms (Calpain-1, -2, -5, -7, -10, -12 and -15) have been identified in the CNS. Previous studies in a mouse AD model revealed increased expression of calpain-10 and -12, whereas in humans, AD causes increased expression and activation of calpain-2 in the hippocampus. However, the expression levels of CNS calpains have not been examined in the brain of patients with mild cognitive impairment (MCI) or AD and were the focus of this study. mRNA and protein was isolated from the cerebellum, pre-frontal cortex and posterior cingulate from age-matched controls (n=10), MCI (n=10) and AD (n=10) post-mortem human brain samples. mRNA and protein expression of calpain-1, -2, -5, -7, -10, -12 and -15 were evaluated by qPCR and western blot analysis, respectively. In AD, but not MCI, calpain-2 mRNA and protein levels increased in the pre-frontal cortex and posterior cingulate. Calpain-10 mRNA levels also increased in the pre-frontal cortex and posterior cingulate with AD, but western blot analysis revealed autolysis. Calpain-1 mRNA and proteins levels decreased in the posterior cingulate; however, the decrease in protein levels may be due to N-terminal autolysis as well. Autolysis, indicative of activation, of calpain-1 and -10 in the AD tissues, may reflect calpain activation associated with the disease, but might also be the result of postmortem activation. Calpain-5 and -7 mRNA and protein levels were not altered in any of the brain regions examined. Calpain-12 was not expressed at measurable levels. In summary, significant elevations in calpain-2 and -10 expression and calpain-1 and -10 activation were observed in the posterior cingulate cortex obtained post-mortem from individuals with AD, but were not altered in MCI. Taken together these findings suggest that individual calpain isoforms are involved in the progression of MCI to AD.
Developing models to study the impact of cerebrovascular disease on Alzheimer’s pathology

Holly Brothers, PhD • Tiffany Sudduth • Erica Weekman • Kaitlyn Braun • Clare Latta • Donna Wilcock, PhD

1Sanders-Brown, University of Kentucky

Fellow

Dementia is not defined by a single cause or pathology, and is most often attributed to Alzheimer’s disease (AD, ~70%) or vascular dementia (VaD, ~17%), yet a considerable number of dementia cases (20-50%) share aspects of both. Our goal is to develop models to study the commonalities and differences between these forms of dementia. Better understanding can improve diagnosis of dementias within this spectrum, inform interpretation of clinical data which may be confounded by co-morbidity, and direct therapeutic approaches.

In order to better understand the co-morbidities of AD and VaD, we will combine aspects of VaD and AD in unique mouse models. We will model aspects of VaD by generating cerebrovascular pathology using two methods; a dietary model of microhemorrhage-inducing hyperhomocysteinemia (HHcy) (Sudduth et al., 2013) and chronic hypoperfusion produced by bilateral common carotid artery stenosis (BCAS). We will use two genetic murine models of AD pathology; the rTg4510 which overexpresses mutant human tau, and APP/PS1 transgenic mouse that develops amyloid pathology. Finally, we will combine the VaD models with the AD pathology models in order to approximate aspects of mixed dementia. None of these model a ‘pure’ disease state, nor the full spectrum of pathology within a disease state. Nevertheless, these combinations will enable us to investigate the relationship between cerebrovascular risk factors and AD pathologies, as they relate to dementia in VaD, mixed dementia and AD.

This poster will summarize our previous investigations of HHcy and HHcy treatment in APP/PS1 mice, review work using the BCAS model, outline our planned studies using HHcy in rTg4510 mice and BCAS in rTg4510 and APP/PS1 mice, make predictions and present preliminary data.
Kentucky’s Memory Café at two years: lessons learned

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Education and Information Transfer Core, Alzheimer’s Disease Center, Sanders-Brown Center on Aging, University of Kentucky

Student

Background
Alzheimer’s disease (AD) is a life altering illness that is perceived by many as a malediction. Many times families dealing with memory loss are met with overwhelming feelings of fear, hopelessness, embarrassment, insecurity, and isolation. As caregivers cope with a brain disease, they may refrain from social interactions to avoid burdening others with the challenges of the disease or to avoid stigma.

Objectives/Methods
Located at the Living Arts and Science Center, the Lexington Café provides a stigma-free and mentally stimulating environment for caregivers and those with memory loss to socialize, and share stories and experiences, while enjoying an interesting menu, a visually appealing setting, and interactive performances. Offered once a month for two hours, the main goal of the Café is socialization to combat the isolation often experienced by families dealing with memory and thinking problems. Individuals with a range of memory problems and types of diagnoses are welcome. Staff members facilitate discussion and interaction.

Results
The popularity of the Café has grown, increasing from 3 to 6 families in the first few months of the program to 8 to 10 by the end of the first year. Currently in 2013, 12 to 16 families regularly attend. Excellent attendance, with limited promotion, suggests community need and evaluations from participants have documented the program’s value. Most participants have a mild or moderate memory loss, but the 20% who are severely impaired are also able to participate and enjoy the Café.

In June 2013, mail surveys assessing how well the Café met its objectives were completed and returned by 21 guests, more than half of our active participants. Ratings for each objective were extremely positive: over 4.5 on a 5.0 scale. The survey generated responses including the following: “...made me take my blinders off and love my husband for what he is NOW becoming”. “It’s nice to know that we are not on this path into dementia alone.”

Conclusion
Participant feedback has led to format changes. As suggested, we have expanded art and music experiences. Currently, for at least part of the program, guests may be exposed to the arts interactively by joining invited performers in physical movement, dancing, and/or singing. The utilization of a variety of performers from the Lexington community enhances the social involvement between Café families and their community. Several graduate students from Center on Aging research laboratories volunteer regularly at the Café to enrich their understanding of families affected by the disease.

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CpG methylation patterns and non-CpG methylation in the human rDNA promoter identified by next generation bisulfite sequencing

Maciej Pietrzak, PhD ¹ • Grzegorz Rempala, PhD ² • Michal Hetman, MD, PhD ³

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Fellow

Nucleolar dysfunction that results in altered ribosomal biogenesis has been reported in several neurodevelopmental and neurodegenerative diseases including Prader-Willi syndrome, Rett syndrome, Alzheimer’s disease, Parkinson’s disease and Huntington’s disease. Dynamic methylation of 26 CpG sites in the human rDNA promoter alters ribosomal biogenesis rate by changing the pool of transcriptionally active copies of rDNA genes.

Here we show the results of next generation bisulfite sequencing (NGBS) analysis of genomic DNA from the parietal cortex of individuals with mild cognitive impairment (n=10), Alzheimer’s disease (n=10), ataxia-telangiectasia (n=7) and age-matched controls (n=19). Genomic DNA was bisulfite converted, bar coded and analyzed using Roche 454 technology. For each sample, 64 to 8261 individual rDNA promoter clones covering 26 CpG methylation sites were sequenced. Such an uneven representation suggested that quantitation of individual mCpG densities may be inaccurate. Indeed, there was a poor correlation between data from NGBS and the quantitative HpaII-qPCR assay. However, by pooling sequences of a large number of rDNA promoter clones for each group of donors, qualitative analysis of patterns of CpG site co-methylation was performed at the individual rDNA unit level. In all groups, there was an overall trend towards co-methylation for all analyzed pairs of 26 CpG sites. However, such a trend appeared diminishing in an age- and neurodegeneration-dependent manner. Hierarchical clustering revealed that three CpGs from the rDNA core promoter region were associated with similar patterns of co-methylation. The strongest co-methylations were observed within this cluster. Finally, non-CpG (CpH) methylation was detected at several sites with one of them confirmed using the PspGI-qPCR assay.

Taken together, CpGs of the rDNA promoter tend to co-methylate, CpG sites of the rDNA core promoter produce similar patterns of co-methylation including their own co-methylation and non-CpG methylation is present in human brain rDNA.
Immunotherapy in combination with behavioral enrichment: beta-amyloid changes in a canine model of aging

Paulina Davis 1 • Tina Beckett 2 • M. Paul Murphy, PhD 2 • Ginevra Giannini 3 • Edward Barrett, PhD 3 • Elizabeth Head, PhD 1

1Molecular and Biomedical Pharmacology, University of Kentucky • 2Biochemistry, University of Kentucky • 3Lovelace Respiratory Research Institute

Student

Alzheimer’s disease (AD) is characterized by cognitive decline and hallmark neuropathologies, senile plaques (SPs) and neurofibrillary tangles. SPs contain β-amyloid (Aβ), cleaved from the amyloid precursor protein (APP). Several therapeutic strategies being developed for AD focus on reducing the production or deposition of Aβ. The canine model is useful for testing potential therapeutic agents. Canines produce APP with 98% homology to human APP, develop Aβ neuropathology, and cognitive decline with age similar to AD patients. Active immunization with fibrillar Aβ1-42 (IMM) for 2 years in aged canines has shown to significantly decrease brain Aβ and maintain executive function, while other measures of cognition remained unchanged (Head et al., 2008). However, behavioral enrichment (BEH) improved cognition (Milgram et al 2005) without reducing brain Aβ (Pop et al., 2010). We hypothesized that IMM combined with BEH would provide larger cognitive benefits and further reduce neuropathology, as compared to controls or individual IMM and BEH alone.

Forty aged beagles (10.5-13.6 y) were placed into one of four groups: controls (Alum adjuvant only), fibrillar Aβ1-42 + Alum vaccine, BEH with Alum, and combination treatment (IMM+BEH). Immunized animals received 0.5mg fibrillar Aβ 1-42 subcutaneously each month for a total treatment time of 18 months. Dogs receiving BEH were housed with a kennel mate, had novel play toys each week, and were taken for a 20 minute walk outdoors three times per week. Animals were treated for 18 months. Insoluble Aβ (formic acid extracted) and Aβ plaque load (6E10, anti-Aβ 1-42) in the prefrontal cortex were measured by sandwich ELISA and immunohistochemistry, respectively. When compared to non-IMM groups, both insoluble Aβ1-40 (F(1,34)=8.79 p=0.006) and 1-42 (F(1,34)=5.61 p=0.024) were significantly reduced in IMM animals. IMM significantly reduced 6E10 (F(1,34)=56.51 p<0.0005) and Aβ 1-42 (F(1,34)=33.04 p<0.0005) plaque load. An overall reduction in 6E10 (F(1,34)=4.08 p=0.052) and Aβ 1-42 (F(1,34)=3.87 p=0.058) plaque load due to BEH was also seen. A significant additive affect from BEH and IMM was seen in clearance of Aβ 1-42 plaque load (F(1,34)=6.54 p=0.016). Extent of neurogenesis and growth factor levels will be measured. In summary, IMM significantly reduced Aβ as previously reported but BEH did benefit from IMM in measures of the extent of plaque formation.

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Age-related increases in functional brain connectivity during task switching are compensatory

Jonathan Hakun, PhD • Zude Zhu, PhD • Nathan Johnson, PhD • Brian Gold, PhD
Anatomy & Neurobiology, University of Kentucky

Fellow

Older adults tend to show higher brain activation in the prefrontal cortex (PFC) than younger adults during executive tasks. However, fewer studies have explored the possibility of age-related changes in functional connectivity between the PFC and other regions. To address this we compared both standard activation magnitudes and task-related functional connectivity (fC) differences between younger and older adults. Results indicated that age-related activation increases in the PFC were associated with poorer behavioral performance. In contrast, in older adults increases in fC between the left dorsolateral PFC and ventral visual pathway (e.g. left and right inferotemporal cortex) were associated with better task switching performance (greater fC = faster response-time). This finding suggests that PFC over-recruitment is commensurate with an age-related shift in brain network dynamics. Further, age-related increases in network connectivity between the PFC and visual object identification pathways may operate in compensation for a loss of neural efficiency with age.

Mechanisms of age-related brain activation increases in frontal cortex

Zude Zhu, PhD • Jonathan Hakun, PhD • Nathan Johnson, PhD • Brian Gold, PhD
Anatomy & Neurobiology, University of Kentucky

Fellow

Older adults often show higher functional brain imaging activations in frontal cortex than younger adults. Here we addressed the possible influences of task difficulty and brain structure on age-related activation increases in frontal cortex. Groups of younger (N = 32) and older (N = 33) participants completed a task switching paradigm while functional magnetic resonance imaging (fMRI) was performed. In addition, estimates of white matter (WM) integrity were acquired with diffusion tensor imaging. Our fMRI analysis revealed significant age-related over-recruitment in the right insula and right dorsolateral prefrontal cortex (DLPFC). Across groups, activation magnitude in the right insula activation magnitude was associated with longer reaction time (RT), whereas in the right DLPFC activation magnitude was associated with lower WM integrity. Subsequent mediation results indicated that the observed relationship between age and activation in the right insula was accounted for by task difficulty (RT). In contrast, the observed relationship between age and activation in the right DLPFC was accounted for by WM integrity. These results suggest that age-related activation increases in regions of right frontal cortex may be differentially influenced by task difficulty and WM integrity.
Beyond general slowing in older adults: faster engagement of frontal cortex during working memory

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Faculty

Introduction

A large body of cognitive aging literature has reported consistent findings that older adults show slowed neural processing speed and increased engagement of frontal cortices in memory tasks. However, there have been limited studies examining the temporal and spatial dynamics of response sequences of cortical networks involved in working memory retrieval in cognitively normal young and older adults. Using time-sensitive and localized event-related potentials (ERP) measures, we provide new evidence that generally slower processing time during a working memory task in older adults is partially due to the fact that older adults engaged frontal cortex several hundred milliseconds earlier compared to young adults. The “detour” to frontal lobe contributes to age-related differences in reaction times for performance-matched during visual working memory.

Methods

Fourteen older (age 65-75) and 14 younger (age 18-28) cognitively normal adults recruited from general community in central Kentucky performed a modified delayed match-to-sample task under electroencephalography recording. The standardized low-resolution brain electromagnetic tomography (sLORETA) method (Pascual-Marqui, 2002) was applied to identify sources contributing to networks involved during working memory retrieval in young and older brains.

Results

Although the older adults’ memory accuracy did not differ from younger adults, we observed age-related differences in spatiotemporal dynamics of neural mechanisms underlying working memory retrieval. The young participants identified nonmatches significantly faster than matches behaviorally, with little ERP responses at frontal site. In contrast, older adults’ reaction times in identifying memory nonmatches were as slow as identifying matches, with augmented frontal responses to memory nonmatches. Most interestingly, compared to the young participants, older adults’ frontal cortex (e.g. left BA 10) was engaged about 300 msec earlier during memory retrieval. Our results provide new evidence that older adults engage frontal cortex earlier in time than younger adults during working memory retrieval processes. Such compensatory “detour” contributes to older adults overall slower reaction times.

Discussions

Our findings suggest that the slower reaction times observed in older adults in all cognitive tasks is not just slowed neural responses. The “general slowing” (Salthouse, 1996) is contributed by additional engagement of the frontal cortex in spatiotemporal dynamics in the aged brain. The theoretical implications of the new evidence indicate that general response slowing is beyond slowed processing speed, but also involves the early engagement of additional cortices, and hence a longer processing time in older adults’ brains compared to those in the young.
Tau mediates neurotoxicity by impeding endoplasmic reticulum function

Matthew Neal\textsuperscript{1} • Maria Bodero\textsuperscript{1} • Alexandra Neal\textsuperscript{1} • Jose F. Abisambra, PhD\textsuperscript{1,2}
\textsuperscript{1} Sanders-Brown Center on Aging, University of Kentucky • \textsuperscript{2} Physiology, University of Kentucky

\textbf{Student}

Tauopathies comprise a group of over 15 neurodegenerative diseases that are bound by a common pathological hallmark: deposits of the microtubule-associated protein tau in the brain. The most common tauopathy is Alzheimer’s disease (AD), a crippling neurodegenerative disorder that afflicts over 5.5 million Americans and 26 million individuals across the world. Since the mechanism responsible for this phenomenon remains unclear, treatment options for tauopathies are limited.

We recently uncovered that pathological tau binds to proteins on the endoplasmic reticulum (ER) membrane in AD brains. Furthermore, we found that this interaction is deleterious to cellular function and is linked to cell death. Albeit, the mechanism linking toxic tau with ER malfunction and cell death are not known.

Our goal was to identify these tau-associated ER proteins, and in doing so, design novel therapeutic strategies aimed at restoring ER function. To this end, we coupled sub-cellular fractionation of human AD brains with immuno-precipitation assays and unbiased proteomics. This strategy identified over 5,000 peptides corresponding to proteins that associated with tau. This subset of ER proteins participates in protein translation (ribosome-binding proteins), calcium storage, and vesicle sorting, among many others.

Disruption of these functions results in the chronic promotion of ER stress and the unfolded protein response, alterations of protein sorting, and inhibition of protein clearance pathways via proteosomal and autophagic routes, all of which lead to cell death. Therefore, tau-associated ER disturbance plays a role in the pathogenesis of tauopathies. Further elucidation of the consequences of tau-ER interactions will likely unveil therapeutic targets.
COMMUNITY SESSION

Location: Bluegrass Ballroom, Lexington Convention Center, 430 W Vine, Lexington, KY

8:30 am Check-in and Continental Breakfast Buffet

9:00 Welcome and Introductions
Linda J. Van Eldik, PhD
Director, Sanders-Brown Center on Aging and Alzheimer’s Disease Center
University of Kentucky

9:15 Researching Ways to Make Memories Last a Lifetime
Frank M. LaFerla, PhD
Chancellor’s Professor of Neurobiology and Behavior
Director, Institute for Brain Aging and Dementia
University of California, Irvine

10:15 Break

10:30 Sanders-Brown Center on Aging Faculty Research Highlights & Audience Q & A
Donna Wilcock, PhD  Moderator
Jose Abisambra, PhD  Brain Pathology
Gregory Jicha, MD, PhD  Clinical Trials
Brian Gold, PhD  Neuroimaging
Marie Smart, LSW  Caregiving

12:00 Closing Remarks
Linda J. Van Eldik, PhD
FRANK M. LAFERLA, PhD
University of California, Irvine

Dr. Frank LaFerla is a Chancellor’s Professor and Chair of the Department of Neurobiology and Behavior at the University of California, Irvine. He serves as the Director of the Institute for Memory Impairments and Neurological Disorders, and is also a Fellow of the Center for the Neurobiology of Learning and Memory. Dr. LaFerla received his B.S. in Biology from St. Joseph’s University in Philadelphia. His graduate training was completed at the University of Minnesota where he earned his Ph.D. in the field of virology in 1990. He subsequently was a postdoctoral fellow at the Holland Laboratory of the American Red Cross before moving to Irvine as an assistant professor in 1995.

Dr. LaFerla has received several honors for his research accomplishments including the Ruth Salta Junior Investigator Achievement Award from the American Health Assistance Foundation, Zenith Fellows Award from the Alzheimer’s Association, UCI Chancellor’s Fellow, Distinguished Mid-career Faculty Research Award, UCI Innovation Award and the Promising Work Award from the Metropolitan Life Foundation for Medical Research. He serves on the Scientific Advisory Board for the Orange County Alzheimer’s Association and the Medical and Scientific Advisory Boards for Sonexa Therapeutics, Akeso Health Sciences, and Signum Biosciences. He is also a member of the editorial boards of three scientific journals: Current Alzheimer Research, Neurobiology of Aging, and Neurobiology of Disease.

Dr. LaFerla’s research is focused on understanding the pathogenesis of Alzheimer’s disease, the most common form of dementia among the elderly. His laboratory has developed several transgenic mouse models of neurodegenerative disorders including the first transgenic mouse model of Alzheimer’s disease that recapitulates the two major neuropathological lesions, plaques and tangles. This mouse model, referred to as the 3xTg-AD mice, has been widely distributed to researchers throughout the USA and over 20 countries throughout the world. His laboratory has used this model to understand the relationship between plaques and tangles and how each affects the development of the other, and more significantly, this model has proven to be invaluable for the pre-clinical evaluation of novel therapeutic compounds.

His research group was also among the first to show that stem cell transplantation could be useful for the treatment of cognitive dysfunction. Findings from his lab show that stem cells promote repair not via a cell replacement mechanism but by performing a “nursing” function. Work in his lab shows that the transplanted neural stem cells produce high amounts of the neurotrophic factor, BDNF, which promotes synaptogenesis. Recently, the lab was awarded $3.6 million from CIRM as part of the Early Translation Grant Program to develop an Alzheimer’s disease therapy involving human neural stem cells.

“Researching Ways to Make Memories Last a Lifetime”

In the USA, someone develops Alzheimer’s disease every 68 seconds, and as of 2013, there are over 5.5 million Americans afflicted. Unfortunately, current therapeutics provide no disease-altering effects, leaving the demand for novel therapies high. Stem cell therapy represents a unique strategy for helping to restore the neuronal and synaptic damage that ensues in Alzheimer’s disease. Our findings show that stem cells rescue behavioral deficits associated with Alzheimer’s disease pathology and focal loss of hippocampal neurons. Our data indicate that genetically-modified stem cells provide a powerful combinatorial approach to not only enhance synaptic plasticity but to also modify underlying Alzheimer’s disease pathology. Many translational issues must be overcome and will be discussed.
SPEAKER PRESENTATIONS

Sanders-Brown Center on Aging Faculty Research Highlights

Donna Wilcock, PhD, Moderator
University of Kentucky

Donna Wilcock is an Assistant Professor in the Department of Physiology and Sanders-Brown Center on Aging at the University of Kentucky. Donna has an active research program focusing on the role of inflammation in Alzheimer’s disease and vascular dementia. In particular, she studies different types of inflammation and how these different types might change the course of the disease or the way the disease is treated. Her ultimate goal is to enhance our understanding of inflammation in vascular dementia and Alzheimer’s disease so that we can better tailor treatment to the individual patient. Her research is currently funded by the National Institutes of Health, the University of Kentucky Alzheimer’s Disease Center, the University of Kentucky Clinical and Translational Science Award and Baxter Pharmaceuticals.

“Brain Pathology”

Jose Abisambra, PhD
University of Kentucky

Jose Abisambra is an Assistant Professor in the Department of Physiology and Sanders-Brown Center on Aging at the University of Kentucky. The overall objective of his research program is to investigate the molecular mechanisms by which the brain protein tau causes neurodegeneration in diseases of aging such as Alzheimer’s, and in doing so, identify novel therapeutic targets.

Dr. Abisambra’s joined the faculty at the SBCoA in March 2013. He says that one of the most attractive things about UK and the SBCoA is the ease of collaboration among top-notch researchers: “The UK and the SBCoA have recruited some of the most influential experts in their respective fields. Collaboration in a multidisciplinary arena is both encouraged and welcomed.”

Dr. Abisambra’s efforts are to investigate what makes tau become toxic and cause disease, and in doing so, identify novel strategies to combat tau aberrancy. Tau toxicity participates in at least 17 neurodegenerative disorders called tauopathies, and the mechanisms leading to tau toxicity are unknown. Tauopathies, the most common of which is Alzheimer’s, remain cureless. By successfully discovering a target for treating tauopathies, Dr. Abisambra hopes to positively impact the quality of life of victims who succumb to all tauopathies. The Alzheimer’s Association, the CurePSP Foundation, and the National Institutes of Health support his work.
**“Neuroimaging”**

Brian Gold, PhD  
University of Kentucky

Brian Gold is an Associate Professor in the Department of Anatomy and Neurobiology and Sanders-Brown Center on Aging. The broad aim of Dr. Gold’s research is to differentiate neurocognitive changes associated with normal aging from those associated with early Alzheimer’s disease.

One theme of his research involves identifying brain imaging patterns ‘biomarkers’ that may predict the likelihood of future Alzheimer’s disease in cognitively normal seniors. Dr. Gold is also interested in understanding how certain lifestyle variables (e.g., exercise, cognitive stimulation) may slow cognitive decline and brain aging. Growing data show that certain factors appear to improve the brain’s ability to cope with age-related neurodegenerative changes. A greater understanding about these potential ‘cognitive reserve’ variables may help promote healthier lifestyles in aging and improve the sensitivity of early dementia diagnosis. Dr. Gold’s research is funded by the National Institutes of Health. He currently serves on several journal editorial boards and scientific advisory committees related to dementia research and prevention. Dr. Gold is also a dedicated teacher, serving as a core faculty member for Medical Neuroscience, and a mentor for postdocs and students at all levels.

**“Clinical Trials”**

Gregory A. Jicha, MD, PhD  
University of Kentucky

Greg Jicha is a Professor in the Department of Neurology and Sanders-Brown Center on Aging at the University of Kentucky. Dr. Jicha serves as an Associate Director and is the Director of the Clinical Core of the UK NIA-funded Alzheimer’s Disease Center. He also serves as the Medical Director for Kentucky TeleCare and directs the Telemedicine Cognitive Clinic at UK, designed to reach out to rural populations across KY for both clinical and research-related activities in the area of AD and related disorders.

Dr. Jicha holds the Robert T & Nyles Y McCowan Endowed Chair in Alzheimer’s Research at UK. His current research interests lie in the areas of mild cognitive impairment, clinico-pathological correlations in early preclinical disease states, vascular contributions to dementia, and clinical trials of disease modifying therapies for various dementia states. He is the principal investigator at UK for the National Alzheimer’s Disease Cooperative Study Group and also serves on the Clinical Task Force and Steering Committee for the National Institute on Aging Alzheimer’s Disease Center Program.

**“Caregiving”**

Marie Smart, LSW  
University of Kentucky

Marie Smart has been working as a health and family care professional since 1972, specializing in the care of the frail elderly since 1982. She is an Alzheimer’s Care Specialist with the University of Kentucky Sanders-Brown Center on Aging Alzheimer’s Disease Center, where she assists with clinical assessments on the Healthy Brain Aging Volunteers. In addition, she provides education, training and support to professional and family caregivers and serves as staff support in clinical settings.

Ms. Smart has extensive experience in the clinical assessment of persons with Alzheimer’s and related disorders, family assessment, care planning, support, and training of professional and family caregivers on topics related to dementia and caregiving. She is a member of the Quality Assurance Review Team for The Breckinridge, an Alzheimer’s Residence in Lexington, and is Vice Chair of Christian Care Communities Board. Ms. Smart is a graduate of King College in Bristol, TN.
The Sanders-Brown Center on Aging (SBCoA) was established in 1979, and received funding as one of the original ten National Institutes of Health Alzheimer’s Disease Centers in 1985. Internationally acclaimed, the SBCoA is recognized for its contributions to the fight against brain diseases that are associated with aging.

**Our vision:** The University of Kentucky Sanders-Brown Center on Aging will be recognized locally and nationally as a premier, vitally productive and innovative aging center that effectively translates research findings into interventions and information that will benefit older adults.

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**ALZHEIMER’S DISEASE FACTS**

- Someone in the US develops Alzheimer’s disease every 68 seconds.
- Alzheimer’s disease is the 6th leading cause of death across all ages in the USA, and the 5th leading cause of death for those aged 65 and older.
- In 2010, 80,000 people in Kentucky were living with Alzheimer’s disease.
- An estimated 5.2 million persons in the U.S. have Alzheimer’s disease.
- By 2050, as many as 16 million Americans will have Alzheimer’s disease, and a new case will be diagnosed every 33 seconds.

“I spent more than 50 years in health care and know the difference that research has made in our lives.” – Mrs. Doris Engles (with her husband Morris), one of our healthy research volunteers, describes why she supports the Sanders-Brown Center on Aging, through active research involvement.

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University of Kentucky • Sanders-Brown Center on Aging • (859) 323-6040 • www.centeronaging.uky.edu
More than 100 faculty and staff pursuing the following areas of research:

- Basic and clinical research in Alzheimer’s disease
- Neurodegenerative disorders
- Stroke
- Normal brain aging

A global pioneer in Alzheimer’s disease research, the Center has over thirty years of published work and 700 study volunteers (some with the disease and some without). These individuals are studied over time and plan to donate their brains upon death. Our cutting-edge research focuses on identifying problems as early as possible, before memory loss develops, so that Alzheimer’s disease can be prevented or delayed.

The ultimate goal of the Center on Aging is to catalyze innovative and outstanding brain research while ensuring a more rapid rate of progress toward new therapies to delay or prevent age-related brain diseases such as Alzheimer’s disease, so that our volunteers, patients and caregivers become the beneficiaries of our advances in knowledge.

Unless science finds a way to slow the progression of this devastating disease, the United States will see a nearly 50 percent increase in the number of victims by 2030. In addition to the direct impact on the patient, Alzheimer’s disease also affects the lives of family members and friends.

The Center is directed by Linda J. Van Eldik, PhD, Professor, Department of Anatomy and Neurobiology. Associate Director is Stephen W. Scheff, PhD, Professor, Department of Anatomy and Neurobiology.

- Alzheimer’s disease is the leading cause of dementia, and affects 1 in 8 people aged 65 and older.
- In 2012, over 15 million Americans provided unpaid care for a person with Alzheimer’s or other dementias—care valued at >$200 billion.
- No cure or preventive measure currently exists for Alzheimer’s disease, but a number of promising therapies are being developed and tested, including several at the University of Kentucky.
- By investing in the development of therapies now, we can save billions of dollars and heartache in the future. You can help through financial donations, or by participating in one of our research programs.

From the 2013 Alzheimer’s Association Facts and Figures publication.

Please help us today in our fight against Alzheimer’s disease. For more information on research, clinical trials and ways to get involved, contact us at 859-323-6040 or visit our website www.centeronaging@uky.edu
WILLIAM R. MARKESBERY, MD (1932-2010)

The Markesbery Symposium on Aging and Dementia is named in honor of William R. Markesbery, MD, a gifted scientist and internationally recognized neurologist and neuropathologist. Dr. Markesbery’s creativity and commitment to aging research provided the impetus for the University of Kentucky to establish the Sanders-Brown Center on Aging in 1979 and name him as the first director. He held that position until his death in January 2010.

In 1985, Bill Markesbery became the director of the Alzheimer’s Disease Research Center, one of the original 10 National Institute on Aging (NIA)-funded centers in the United States, with a primary focus on neuropathology. After more than 25 years, the Alzheimer’s Disease Center continues to be funded by NIA, a remarkable achievement that demonstrates the strength and caliber of this program. During his academic career, Dr. Markesbery published more than 400 scientific papers and was one of the world’s leading experts on Alzheimer’s disease and oxidative stress. He will always be remembered as a compassionate and caring physician, a brilliant researcher, and an inspirational leader.