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The University of Kansas Alzheimer's Disease Center is pleased to announce the 2011-2012 Pilot Project Program awardees. The KU ADC, along with the support of the Landon Center on Aging, will fund 4 research projects that have been judged to have significant potential for impact in their field and translation to external funding. Twenty exceptional projects were submitted in response to this inaugural request for applications. Below are excerpts from the 4 funded projects.

Janna Harris, PhD and William Brooks PhD – KUMC Hoglund Brain Imaging Center

Considerable evidence demonstrates that recovery and outcomes after a traumatic brain injury (TBI) are worse in elderly than in younger patients. Moreover, results from our laboratory and others suggest that specific injury mechanisms are altered with age. We believe that mechanism-specific biomarkers visible on proton magnetic resonance spectroscopy (1H-MRS) represent a promising novel approach for elucidating mechanisms of TBI and for translating treatments from pre-clinical to clinical trials. Our current goal is 1) to determine the magnitude and time course of the metabolic and behavioral effects of TBI in an aged animal model, and 2) determine whether TBI in aged animals is sensitive to neuroprotective treatment with cyclosporine A (CsA).

Robyn Honea, DPhil -KUMC Dept. of Neurology

Complex genetic and environmental mechanisms contribute to late-onset Alzheimer's disease and the most consistently identified risk factor for AD is family history of dementia. Moreover, maternal transmission of AD is significantly more frequent than paternal transmission. We and others have recently linked maternal transmission of risk for AD to several brain imaging phenotypes. However, the patterns of transmission and biological mechanisms through which a family history of late-onset AD (LOAD) confers risk to offspring are not fully known. There is growing evidence that the mechanism for this maternal inheritance pattern may be related to transmission through mitochondrial DNA (mtDNA) alterations. Our overall goal is to test whether there is a relationship between mitochondrial sequence polymorphisms and imaging markers of risk AD. To do this, we will test for associations between brain imaging endophenotypes and mitochondrial haplogroups derived from 138 mitochondrial polymorphisms in two large datasets with imaging, genetic, and behavioral data which, to our knowledge, has never been done.

Gang Hu, PhD – KU Higuchi Bioscience Center

In this study, we will identify the role of amyloid binding alcohol dehydrogenase (ABAD) and amyloid in changing lipid and fatty acid metabolism in Alzheimer's disease and show for the first time that there is a link between mechanisms that influence the function of mitochondria (i.e. increases in ABAD and A β) and changes in lipid metabolism. We will identify how they are linked and identified a new phenomenon that occurs within mitochondria and is potentially controlled by the binding of A β to ABAD. Specifically, we will identify the role of ABAD in A β -mediated changes in lipid metabolism relevant to the pathogenesis of AD using novel transgenic mice to determine the effect of ABAD on A β -induced lipid metabolism. The outcomes of this project will have a significant impact on the AD research field, in particular synaptic mitochondria

and lipid metabolism.

Chad Slawson, PhD – KUMC Dept. of Biochemistry and Molecular Biology

The objective of this study is to understand function of the O-GlcNAc cycling enzymes during mitochondrial impairment and Alzheimer's progression. This research is driven by the hypothesis that the O-GlcNAc cycling enzymes protect against mitochondrial impairment and that alterations in O-GlcNAc signaling promote Alzheimer's development. Support for this hypothesis comes from past work. A splice variant of O-GlcNAc transferase (OGT) localizes to mitochondria, increased mitochondrial O-GlcNAcylation impairs function and promotes apoptosis. The rationale behind this research is that once we understand the interplay between O-GlcNAcylation and mitochondrial regulation, then we can better understand the biology behind the etiology of Alzheimer's disease. The regulation of biological processes by O-GlcNAcylation is a novel approach in understanding disease progress. We believe the research proposed in this application is innovative because it will address the involvement of O-GlcNAc signaling in the regulation of Alzheimer's mitochondria.