

Alzheimer's and Related Diseases Research Award Fund

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**FINAL PROJECT REPORTS FROM THE  
2005-2006 ALZHEIMER'S RESEARCH AWARD FUND**

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 to stimulate innovative investigations into Alzheimer's disease (AD) and related disorders along a variety of avenues, such as the causes, epidemiology, diagnosis, and treatment of the disorder; public policy and the financing of care; and the social and psychological impacts of the disease upon the individual, family, and community.

**GMU            Jane Flinn, Ph.D. (Dept of Psychology) "The Effect of Enhanced Levels of Zinc and Iron in Drinking Water on Memory, Amyloid Configuration, and Plaque Development in Transgenic Mice"**

Alzheimer's disease is characterized by the presence in the brain of intracellular tangles and extracellular plaques containing the amyloid protein. Attention has recently focused on the role of metals in plaque formation, as amyloid binds to zinc, copper, and iron. Transgenic mouse models of AD have been developed, and brain concentrations of metals can be increased by raising animals with enhanced levels of metal in the drinking water. This study examined how elevated zinc and iron affected memory, amyloid conformation and plaque formation in a transgenic mouse model of Alzheimer's disease. Transgenic mice raised on enhanced zinc or iron showed deficits in spatial memory, when tested in the Morris water maze, compared to those raised on lab water. Spatial memory is dependent on the hippocampus, where both zinc and iron are found. The mice were also tested on a task designed to investigate their ability to consolidate memories (the Novel Object Recognition task), measuring whether they could remember that they had previously seen an object. Transgenic mice raised on excess zinc showed no preference for the novel object (which normal mice do), performing at chance level. In contrast, Tg mice raised on iron were not impaired on this task, compared to those raised on lab water. Initial analyses of metal content showed that high levels of both iron and zinc were seen in plaques. The beta pleated sheet form of amyloid, the type of amyloid found in the end stage of the disease, co-localized better with the iron than with the zinc. Since zinc has been recommended as a treatment for age related macular degeneration, and ingestion of zinc can deplete copper in the body, the investigator raised some mice with a small amount of copper added to the zinc-enhanced water. This reduced the spatial memory deficits, but did not affect memory for objects. These studies indicate that metals in drinking water can affect memory in a mouse model of Alzheimer's disease. *(Dr. Flinn can be reached at 703/993-4107)*

**GMU            Pamela M. Greenwood, Ph.D. (Department of Psychology) & Karl Fryxell, Ph.D. (Department of Molecular and Microbiology) "Use of Allelic Association to Study the Genetics of Cognitive Aging"**

Although the risk of Alzheimer's disease is thought to be influenced by several genetic factors, only one gene, APOE, has been conclusively linked to the disease. However, the APOE gene, which is neither necessary nor sufficient for Alzheimer's disease, also has a broad role in health and repair of neurons in the brain. The investigators hypothesize that genes which affect neuronal health and efficiency of neuronal communication (neurotransmission) may also affect cognitive aging. However, little work has been done to investigate the role of such genes in cognitive aging. Consequently, this research team carried out four experiments on over 400 young and old healthy people to investigate how normal variation in eight genes modulates aspects of attention, memory, and visual search. The genes were selected based on previous work, including their own previous investigations of APOE and neurotransmission genes. Analyses indicate that one neuroprotection gene (BDNF) may modulate attentional function in aging. This indicates that normal variation in neuronal plasticity may play a role in the course of cognitive aging. If confirmed, this finding will provide evidence supporting research into the role of neuronal protection genes as an important avenue for investigating risk factors related to cognitive decline in aging. *(Dr. Greenwood can be reached at 703/993-4268; Dr. Fryxell can be reached at 703/993-1069)*

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**College of Christine J. Jensen, Ph.D. and colleagues (Center for Public Policy Research)**  
**William and Mary “Promoting an Effective Partnership between Families Coping with Alzheimer’s**  
**Mary Disease and Their Healthcare Providers”**

The primary objective of this project was to identify the needs of family caregivers and healthcare providers who care for persons with memory loss. A total of 128 caregivers completed a telephone or online survey, and 27 health care providers participated in a focus group and completed a survey. The hypothesis that primary care physicians would be more likely to provide a diagnosis of Alzheimer’s disease than a specialist was not supported. Caregivers reported their primary source of information about the disease was the doctor; however, the majority reported that the doctor provided more information about medications than about the course of the disease or available resources. Physicians and nurses reported that time to spend with patients and families and awareness of community services were their biggest challenges. These findings suggest a number of policy-related recommendations: 1) Increase awareness about the local Alzheimer’s Association among medical professionals and family caregivers; 2) Promote the provision of training programs for family caregivers and health care providers to address the identified health literacy issues and to strengthen the healthcare partnership; 3) Raise awareness of the Certificate for Added Qualifications in Geriatric Medicine (available for physicians board certified in Family Medicine and Internal Medicine) and encourage support for the Geriatric Loan Forgiveness bill; 4) Encourage greater utilization of technology among healthcare providers to track the needs of persons with dementia; and 5) Expand clinical standards to include support for the health care triad in dementia care. *(Dr. Jensen can be reached at 757/221-1971)*

**Virginia Tech Bradley G. Klein, Ph.D. (Department of Biomedical Sciences, College of**  
**Veterinary Medicine) and Jeffrey R. Bloomquist, Ph.D. (Department of**  
**Entomology) “Modulation of Cognitive Sequelae of Parkinsonism by Environmental**  
**Manganese: Implications for Dementia with Lewy Bodies”**

The principal aim of this study was to address whether environmental manganese can contribute to, or facilitate, the cognitive decline that has been observed in Parkinson’s disease. Mesocortical and nigrostriatal dopaminergic pathways are respective potential neural substrates for such behavioral deficits, in a mouse model of the Lewy body disorder. The experimental work employed the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model of the Lewy body disorder Parkinson’s disease (PD) and was directed at identifying interactions between Mn and MPTP in behavioral and dopaminergic toxicity. The investigators provided substantial evidence for Mn/MPTP interactions in dopaminergic and behavioral toxicity. They demonstrated that these interactions occur in both motor and cognitive behavior and in respective dopaminergic neural substrates of these classes of behavior (e.g. nigrostriatal and mesocortical pathways). Support was furthermore provided for differential Mn/MPTP interactions in mesocortical vs. nigrostriatal dopaminergic pathways. These results have implications with respect to the underlying mechanisms of cognitive decline in another Lewy body disorder, Dementia with Lewy Bodies, the most common form of neurodegenerative dementia after AD. *(Dr. Klein can be reached at 540/231-7398; Dr. Bloomquist can be reached at 540/231-6129)*

**UVA Michelle King, Ph.D. (Department of Biology) “Direct Interactions between A $\beta$  and**  
**Tau in Cultured Cells”**

The primary objective of this study was to characterize the relationship between pre-fibrillar  $\beta$ -amyloid and intracellular tau expression, as modeled in a cell culture system. The principal observation used initially was time-lapse photography of tau and tubulin localization following  $\beta$ -amyloid treatment. First, the investigator was able to quantify the microscopy findings by counting cells in populations treated with  $\beta$ -amyloid, and these data provided statistical significance in the initial observation. Second, the findings were confirmed by using an independent biochemical assay for tubulin. And finally, all of the findings were confirmed by microscopy and biochemistry of primary neurons treated with  $\beta$ -amyloid. A significant question regarding the signaling pathway connecting  $\beta$ -amyloid and tau still remains. While the original objectives proposed have been attempted, the research has yet to yield a potential candidate pathway. New experiments are ongoing, as this information is crucial to our understanding of the relationship between tau and  $\beta$ -amyloid and has great potential as a means for designing molecules for therapeutic intervention. *(Dr. King can be reached at 434/243-7764)*

**UVA Isaac G. Onyango, D.V.M., Ph.D. (Department of Neuroscience and Neurology)**  
**"Molecular Mechanisms of Neurodegeneration in Alzheimer's Disease"**

Two cellular models of Alzheimer's disease (AD), the transmitochondrial cellular hybrid (cybrid) cell model of sporadic AD (sAD) and the SH-SY5Y cells bearing familial AD (FAD) presenilin1 mutations, over produce amyloid-beta peptide (A $\beta$ ) similar to patients. A $\beta$  requires functional mitochondria to induce cell toxicity, and the survival of neurons in AD is likely regulated by the integration of a complex network of intracellular and extracellular signals. The mitogen-activated protein kinase (MAPK) superfamily comprises the c-Jun NH2-terminal kinase (JNK), p38 MAPK, and the classical MAPK, extracellular signal-regulated kinase (ERK). This study characterized intracellular responses to oxidative stress, beginning with how oxidative stress alters activities of the apoptosis signal-regulating Kinase 1 (ASK-1) or MAPK kinase 4 (MEKK4), and how these upstream "sensors" regulate downstream, pro-apoptotic effector kinases (p 38 MAPK, JNK). Cybrids representing sAD were compared to SH-SY5Y cells expressing PS1M146L mutations as a model of FAD and A $\beta$ <sub>(1-42)</sub> treated control (CTL) cybrids. The investigator found that in all three cell models of AD, A $\beta$  mediated depletion of glutathione (GSH) enhances oxidative stress and seemingly drives the activation of p38MAPK and JNK, in the face of a weak and ineffective ERK and phosphatidylinositol 3-kinase stimulated Akt (PI-3K/Akt) activation, resulting in reduced viability. The upstream regulators are distinct with the FAD utilizing ASK-1 as the primary regulator of the cell death, whereas in the cell models of sAD, both ASK-1 and MEKK4 seem to be key regulators of neuronal vulnerability. Activation of the PI3K/Akt signal transduction system by both *N*-acetylcysteine (NAC) and nerve growth factor (NGF) enhances viability and protects against oxidant injury. Insight gained from these investigations into the signal transduction cascades activated in these cell models provide specific mechanistic insights that will lead to improved approaches to manage the oxidative stress burden in AD brain. (*Dr. Onyango can be reached at 434/243-9268*)

**UVA Heidi Scrable, Ph.D. (Department of Neuroscience)**  
**"Gene Expression Changes in the Aging HPF Axis"**

Weight loss is common in patients with AD, and often occurs before the onset of dementia. Serum levels of leptin, which correlate with levels of adiposity, have been found to fluctuate with weight in both patients with AD and age-matched controls. However, the diurnal fluctuations of leptin, which depend on levels of adrenal glucocorticoids, specifically cortisol, are altered in AD. It has been suggested that uncoupling of leptin and glucocorticoid fluctuations might underlie the weight loss observed in many patients with AD. In mouse models of AD, administration of leptin has been shown to reduce the production of the pathological A $\beta$  fragment of amyloid precursor protein (APP) in the brain. The preliminary experiments in this study addressed the relationship between the adipocyte-derived hormone, leptin and APP. The investigator previously developed a line of transgenic mice (p44), with altered insulin-like growth factor-1 (IGF-1) signaling, that present several hallmarks of AD and undergo accelerated aging, including premature accumulation of ceramide in the brain and reduced serum leptin. Hyperactivation of the IGF-1 receptor in these mice is accompanied by parallel changes in the cascade of events that results in the production of A $\beta$ . This study investigated the hypothesis that the hypothalamic-pituitary-fat cell (HPF) axis that controls metabolic pathways and maintains efficient use of energy, also plays a major role in the pathogenesis of AD. The investigator used microarray analysis to examine age-associated changes in adipocyte-specific gene expression in the p44 mice, and identified the JAK/STAT pathway as a key metabolic pathway altered in mice with accelerated aging and early onset AD-like changes in the brain. This opens up a novel pathway for possible intervention therapy in the treatment of AD and other age-associated disorders affecting brain function. The results provide a global picture of how perturbations in endocrine pathways originating in the periphery, for example, in the adipocyte, can contribute to degeneration of the brain in AD. (*Dr. Scrable can be reached at 434/982-1416*)