

Alzheimer's and Related Diseases Research Award Fund

2015-2016 FINAL PROJECT REPORT SUMMARIES

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 and is administered by the Virginia Center on Aging at Virginia Commonwealth University. The awards this year were enhanced by a \$25,000 donation from Mrs. Russell Sullivan of Fredericksburg, in memory of her husband who died of dementia. Sullivan awards are indicated by an asterisk (*). Summaries of the final project reports submitted by investigators funded during the 2015-2016 round of competition are given below. To receive the full reports, please contact the investigators or the ARDRAF administrator, Dr. Constance Coogle (ccoogle@vcu.edu).

EVMS Frank J. Castora, PhD and Randolph Coleman, PhD
Biochemical Systems Theory Modeling of Alzheimer's Disease Using Mitochondrial Genes Involved in Amyloid Precursor Protein and Tau Processing

Mitochondrial dysfunction is a critical component in the pathogenesis of Alzheimer's Disease (AD) where deficits in oxidative capacity and energy production have been reported. The investigators previously found abnormal expression of several genes critical to mitochondrial energy production in AD brains. In this study, total RNA was isolated from age-matched controls, AD and AD⁺ (AD possessing a mitochondrial DNA mutation) frozen autopsy brain samples, and the abnormal expression of 168 genes involved in mitochondrial function and energy production was assessed. A subset of mitochondrial genes was found to be critically involved in mitochondrial energy production and function in AD brains. The investigators have now begun to build a mathematical model of AD using Biochemical System Theory (BST). Through the development and application of appropriate differential equations, the flux of various metabolites and small molecules will be simulated and used to generate a testable model of mitochondrial involvement in AD pathogenesis. (*Dr. Castora may be contacted at 757/446-5657, castorfj@evms.edu; Dr. Coleman may be contacted at 757/221-2679, racole@wm.edu*)

UVA Alev Erisir, MD, PhD*
Ultrastructural Neuropathology in Transgenic Models of Alzheimer's Disease

This investigation aimed to reveal brain alterations that are too small or too subtle to be detected by the microscopic tools used for studying lesions in AD. Using transgenic mice aged between 3 and 12 months that overexpress amyloid and electron microscopy (EM), the earliest alterations in brain structure were characterized prior to the onset of cognitive decline. The brain regions known to display AD pathology were surveyed to characterize the emergence and severity of ultrastructural lesions therein. In addition, immuno-EM was used to identify when and where A β -associated neuronal deterioration started. Their systematic analyses revealed evidence of a previously unappreciated culprit for the cognitive decline that emerges before 5 months of age. Particularly, the oligodendrocytes, the cells that make myelin, become hypermotile in the presence of overexpressed amyloid. The consequence is over-myelination, or rather disruptive myelination, all across the brain. Basal forebrain and entorhinal cortex, the sites of first neurodegeneration in human AD, contained oligodendrocyte hypermotility-related pathologies at the youngest ages. Other regions displayed progressively more severe pathologies at later ages, in a spatial pattern similar to the consensus staging protocol for the neuropathologic assessment of human AD established by the National Institute on Aging and the Alzheimer's Association. By the ages when cell death is prominent, myelin outfoldings gave rise to massive bulb structures, which are transitional to neuritic plaques. These results provide insights into the mechanism and role of oligodendrocyte hypermotility that will guide future studies of AD neuropathology in the human brain. (*Dr. Erisir may be contacted at 434/243-3549, ae4h@virginia.edu*)

VCU

MaryPeace McRae, PharmD, PhD and Patricia Slattum, PharmD, PhD*
Investigating the Relationship between Benzodiazepine Medications and the Development of Blood Brain Barrier Dysfunction as Risk Factors for Alzheimer's Disease

The main focus of this project was to accumulate experimental evidence that would establish a mechanism of the observed association between benzodiazepine use and the development of AD. The goal of these studies was to investigate the effects of benzodiazepine medications on the integrity and function of the blood brain barrier (BBB). Utilizing the *in vitro* human BBB model already established in the investigator's lab, studies confirmed the hypothesis that select benzodiazepines alter measurements of barrier integrity. The ability of the barrier to maintain its selectivity was only modestly affected by the benzodiazepines, and treatment with alprazolam did not result in changes in amyloid β flux across the barrier. Further work will be conducted to examine the effects of the benzodiazepines on the expression of the transport proteins involved in amyloid beta passage across the BBB. (Dr. McRae may be contacted at 804/628-5076, mpmcr@vcu.edu; Dr. Slattum may be contacted at 804/828-6355, pwslattu@vcu.edu)

VPI & SU

Webster L. Santos, PhD and Gregorio Valdez, PhD*
Controlling Neuronal Sphingosine-1-Phosphate as Alzheimer's Disease Therapy

Sphingosine-1-phosphate has been shown to be a potent lipid signaling molecule that protects neurons from dying as a result of biological insults. Six synthetic small molecules designed to specifically inhibit the activity of one or both of the sphingosine kinases (SphK1 & SphK2) were tested on hippocampal neurons cultured under conditions that mimic the stress environment in brain regions affected by AD. Three compounds showed promise for preventing pathophysiological changes in hippocampal neurons and thus promoting their long-term survival in culture. In addition, neurons treated with one of these contained more synaptic-like structures, indicating that inhibiting these kinases either promotes the formation of new synapses or stabilizes and prevents the loss of already existing synapses. The investigators are currently determining the optimal dose for the designed compound, and testing the therapeutic benefit on cortical neurons. The data obtained should serve as the basis for developing treatments for AD. (Dr. Santos may be contacted at 540/231-5742, santosw@vt.edu; Dr. Valdez may be contacted at 540/526-2076, gvaldez1@vtc.vt.edu)

GMU

Catherine J. Tompkins, PhD and colleagues*
Individuals with Dementia at Adult Day Health Care Centers: Examining the Effects of Individualized Music on Mood and Agitation

The Music and Memory Program© is an international program that brings personalized music selections into the lives of people with dementia. A mixed method, six-week quasi-experimental two-group design was implemented to examine the effects of linking individualized treatment goals to strategic music implementation on behavioral and emotional functioning in a sample of older adults with dementia participating in five different adult day health care centers. The results demonstrated a positive change in mood and a decrease in agitation for the intervention group participants based on behavioral observations. This research will increase understanding of a non-pharmacological, situation-specific individualized music intervention that can be used by formal and informal caregivers to impact the behavior of individuals with AD. (Dr. Tompkins may be contacted at 703/993-2838, ctompkin@gmu.edu)

VPI & SU Bin Xu, PhD, David Bevan, PhD and Ling Wu, MD, PhD*

Molecular Mechanisms of Amylin as a Novel Contributor to Alzheimer's Disease

Epidemiological studies have shown a link between type 2 diabetes (T2D) and the risk for AD. A feature common to both diseases is the formation of amyloid peptide aggregates. The peptide associated with AD is amyloid beta ($A\beta$), and for T2D, it is amylin. Amylin can possibly travel to the brain, and aggregate themselves into amylin amyloids, or combine with $A\beta$, to form amylin/ $A\beta$ -crossed amyloids. This project applied an interdisciplinary approach involving cellular, biochemical, biophysical, and computational methods to define the amylin amyloid species, establish cell-based neurotoxicity assays, and assess amylin/ $A\beta$ -crossed amyloid formation and toxicity. The investigators were able to define three amylin amyloid species that have distinct sizes and shapes. They further defined how amylin forms amyloid and fibril using multiple biochemical and biophysical methods. They established cell-based functional assays that can be used to assess amylin-induced neurotoxicity. Two compounds used in Alternative and Complementary Medicine to treat diabetes, inflammation and neuroprotection were found to potently inhibit amylin-induced neurotoxicity. Mechanistic insights were provided through detailed and comprehensive cellular, biochemical, and computational simulation studies. These results serve as the basis for a future comprehensive research program to elucidate molecular events that contribute to AD as well as to devise potential treatment strategies. (*Dr. Xu may be contacted at 540/231-1449, binxu@vt.edu; Dr. Bevan may be contacted at 540/231-5040, drbevan@vt.edu; Dr. Wu may be contacted at 540/231-8442, wul3@vt.edu*)

2014-2015 DELAYED FINAL PROJECT REPORT

UVA Roberto Fernandez-Romero MD, MPH, PhD

The Neurophysiology of Driving Impairments in Early Alzheimer's Disease

Getting lost in familiar surroundings, wandering, and unsafe driving are some of the most debilitating early symptoms of AD and represent a major safety concern. These visual-spatial impairments have been associated with a decreased capacity to perceive optic flow, the pattern of visual-motion that is naturally observed during common tasks like ambulation or vehicular driving. Using an electroencephalographic technique known as event related potentials (ERPs), the investigators recorded specific brainwaves that are generated by optic flow and found significant differences between AD patients and controls. In this study they combined ERPs with a virtual reality driving test to explore the links between decreased brain responsiveness and driving capacity in a group of 19 patients with early stage AD and 18 cognitively normal elderly controls. Only one patient passed the driving test and only one control subject failed it. A comparison of test scores showed highly significant differences between the two groups, supporting the utility of virtual reality in the assessment of driving capacity. The researchers also found statistically significant differences in the magnitude of ERPs, with AD subjects showing smaller responses that were also linked to poor driving scores and impaired cognitive tests. These results have several implications; the differences in response magnitude between groups and their association to cognitive scores support the potential utility of ERPs as early markers of Alzheimer's. Furthermore, the association between ERPs and driving score supports the notion that impaired perception of optic flow is partly responsible for impaired driving capacity and suggests that ERPs may serve as screening tools. Future studies with larger samples will be necessary to generalize these findings and establish normal parameters. Longitudinal studies will also explore the use of optic flow ERPs as markers of disease progression. (*Dr. Fernandez-Romero may be contacted at 434/ 243-5611, rf6u@virginia.edu*)