Alzheimer's and Related Diseases Research Award Fund

2018-2019 ALZHEIMER'S RESEARCH AWARD FUND RECIPIENTS ANNOUNCED

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 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. The awards this year have been enhanced by a $50,000 donation from Mrs. Russell Sullivan of Fredericksburg, in memory of her husband who died of dementia. Sullivan awards are indicated by an asterisk (*). The ARDRAF competition is administered by the Virginia Center on Aging in the School of Allied Health Professions at Virginia Commonwealth University. Questions about the projects may be directed to the investigators or the ARDRAF administrator, Dr. Constance Coogle (ccoogle@vcu.edu).

EVMS **Dianne C. Daniel, PhD, and Edward M. Johnson, PhD***

Cellular Mechanisms of Pur-based Peptides for Frontotemporal Dementia

Frontotemporal Dementia (FTD) is the second most common cause of dementia in younger people. Up to 40% of patients with FTD have family members who have had the disease. The most common genetic cause of FTD (20% of all cases) is a repeated DNA sequence that is greatly expanded (the C9 HRE). The C9 HRE is made into toxic dipeptide repeat proteins (DPRs), which aggregate in nerve cells in the brain and cause them to degenerate. Pur-alpha, discovered by Dr. Edward Johnson's laboratory, is a major protein that binds to the C9 HRE sequence. When the amount of Pur-alpha is increased in cells or an animal model with the C9 HRE mutation, neurodegeneration is greatly reduced. Drs. Daniel and Johnson have demonstrated that Pur-alpha reduces pathological effects of the C9 HRE in lymphoblasts from patients with the C9 mutation and neuronal cells. In this study, they will test Pur-based peptides as a potential therapy for FTD caused by the C9 HRE. They will expand their findings to optimize the reduction of toxic proteins, demonstrate reduced abnormalities in cells from FTD patients, and establish the precise mechanisms at work. Results from these experiments will facilitate development of a leading candidate for therapy in FTD. ***(Dr. Daniel may be contacted at 757/446-5684, danieldc@evms.edu; Dr. Johnson may be contacted at johnson@emeritus.evms.edu)***

VCU **Joseph M. Dzierzewski, PhD***

Cognitive and Inflammatory Consequences of Sleep in Older Adults with Alzheimer's Disease and Their Caregivers

Research is needed to understand factors related to cognitive and functional decline in older adults with Alzheimer's disease (AD) in order to improve quality-of-life; decrease healthcare utilization, institutionalization, and caregiver burden; and identify potential targets for interventions. Studies of non-demented, community-dwelling older adults suggest that sleep disruption is an important risk factor for cognitive and functional decline. This work has begun to be extended to older adults with AD. Similarly, inflammation has been associated with negative health events and changes in cognitive functioning in non-demented older adults and to a lesser extent in older adults with AD. Previous studies show that sleep and inflammatory factors are related in both non-demented older adults and older adults with AD. However, studies seldom simultaneously assess sleep, inflammation, cognitive functioning, and mood in individuals with AD and rarely, if ever, extend such assessments to include the caregivers of older adults with AD. The central hypothesis of this proposal is that disturbed sleep in older adults with AD will negatively affect cognitive functioning and mood and extend to functioning in caregivers. Furthermore, the investigator will seek to demonstrate that this relationship is partially driven by chronic inflammatory responses. Understanding modifiable risks for cognitive and emotional functioning in both older adults with AD and their caregivers is critical to designing effective interventions, which is the next step in this promising line of research. ***(Dr. Dzierzewski may be contacted at 804/628-0645, dzierzewski@vcu.edu)***

UVA **Heather A. Ferris, MD, PhD***

Mechanisms of Diabetes-Mediated Increases in Alzheimer's Disease and Dementia

There are multiple competing theories to explain the cognitive dysfunction seen in diabetes, including microvascular damage, insulin resistance and advanced glycation end products. The investigator's lab has demonstrated that the cholesterol synthetic pathway is also disrupted in the brains of diabetics. This disruption leads to an increase in the cholesterol oxidation product, 7-ketocholesterol, a molecule also increased in AD. Preliminary studies show 7-ketocholesterol can alter circadian rhythms in astrocytes, the brain cells responsible for most brain cholesterol synthesis. This disruption is similar to what the investigator has shown in mice that have impaired astrocyte cholesterol synthesis. Given that circadian rhythm disruption is the most common reason for institutionalization among individuals with AD, understanding this process further is vital. This study will determine the impact of 7-ketocholesterol on the circadian rhythms of not only astrocytes, but neurons in the suprachiasmatic nucleus (the master regulator of circadian rhythms). Various agonists and antagonists will be used to determine if this disruption is occurring through the RORα receptor, as currently suspected. The research will further determine other pathways impacted by this disruption. Anticipated results have the potential to not only elucidate some of the underlying interactions between diabetes and AD, but also reveal a potentially druggable target for diabetes and AD mediated circadian rhythm defects. ***(Dr. Ferris may be contacted at 412/605-8541, hf4f@virginia.edu)***

ODU **Patrick C. Sachs, PhD, Peter A. Mollica, PhD, MB(ASCP), Robert D. Bruno, PhD, and Shu Xiao, PhD***

Investigating the Effects of Sub-Nanosecond Pulsed Electric Fields as a Potential Protein Disaggregation Agent in Huntington's Disease and Alzheimer's Disease Neurons

Both AD and Huntington's disease (HD) are marked by protein aggregates that accumulate around or within cells. Mitigation of these amyloid proteins is a major focus for the development of novel therapies. Application of electric fields has been shown to have disruptive effects on protein-protein interactions found within disease aggregates. However, this effect has not been tested in cell or animal experiments. One of the central challenges is penetrating the cell with sufficient energy to alter cellular structures while simultaneously avoiding cell damage. Picosecond pulsed electric fields (psPEF) are a new potential technique because their duration and power delivery is insufficient to cause membrane damage, but sufficient to impact the interior portions of the cell. In this study the investigators will use the psPEF exposure system they have developed to experimentally determine the effects that controlled psPEF have on pathological intracellular and extracellular protein aggregates characteristic of neurodegenerative diseases. They will expose induced pluripotent stem cells derived from the neuronal cells of patients with HD and familial AD to various electric field intensities and pulsing protocols. It is hypothesized that sub-nanosecond pulsed electric fields can interrupt the aggregative properties of pathological amyloids in HD and AD neurons. ***(Dr. Sachs may be contacted at 757/683-7090, psachs@odu.edu; Dr. Mollica may be contacted at 757/749-0090, pmollica@odu.edu; Dr. Bruno may be contacted at 757/683-7091, rbruno@odu.edu; Dr. Xiao may be contacted at 757/683-2408, SXiao@odu.edu)***

VA Tech **Webster Santos, PhD, and Kyle Hoehn, PhD**

Novel Small Molecule Mitochondrial Uncouplers as Therapeutics for Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by selective dopaminergic neuronal loss in the substantia nigra. The precise pathological trigger of sporadic PD remains unknown, but there is compelling evidence that dysfunctional mitochondria and resulting reactive species production have a causal role in PD pathogenesis. The process of mitochondrial uncoupling is one mechanism known to decrease mitochondrial reactive species production and protect neurons from cell death. In this project, we will test whether mitochondrial uncouplers will be efficacious in reducing reactive oxygen species levels and protect neurons from insults. Through a medicinal chemistry campaign and biochemical characterization in primary cultured neurons, we will investigate the therapeutic potential of mitochondrial uncouplers as neuroprotective agents.

(Dr. Santos may be contacted at 540/231-5742, santosw@vt.edu; Dr. Hoehn may be contacted at 434/924-2577, klh8st@virginia.edu)

Randolph College **A. Katrin Schenk, PhD**

Interactive Caregiver Portal for the Visualization of Activity and Location Data in an Alzheimer's Population

The investigator will build an interactive web application that allows Alzheimer's caregivers to visualize and interact with data collected by a Functional Monitoring (FM) system. The FM system uses ubiquitous computing devices (e.g., cellphones and smartwatches) to continuously collect patient location and activity data in the community. As of today, the FM system has collected 234 patient-months of data. These data can be classified into representations of important behaviors and can provide caregivers with crucial information about the efficacy of their caregiving and the health of their loved one. Making these data easy to understand and manipulate is critical for site development, so the research will incorporate an informational component that will help caregivers understand how to use their loved one's data to provide better caregiving and keep them informed of any changes in health status. Caregiver interviews will test the usability and design of the application, which will then be deployed to one beta test caregiver to track and verify detection of negative behavioral trends. (***Dr. Schenk may be contacted at 434/947-8489, kschenk@randolphcollege.edu)***

GMU **Janusz Wojtusiak, PhD and Catherine Tompkins, PhD**

Analysis of Wandering Patterns of Individuals with Alzheimer's Disease

A significant number of people with dementia are at risk of wandering and possibly getting lost. These individuals may also get hurt, cause distress to families and caregivers, and require costly search parties. Commercial technologies including GPS trackers, geo-fences, and other monitoring devices focused on older adult users can help locate the missing and, in turn, reduce potential injuries, as well as stress to the families. GPS trackers also provide detailed location data that can be used to: (1) build models capable of predicting likely areas in which searching for the missing needs to be done, and possibly (2) track progression of the disease. The new-found availability of such data opened the possibility for analytics and pattern detection impossible in the past, thus allowing for new research direction into AD and its progression. This study will focus on collecting initial tracking data for people with AD using GPS trackers, along with their medical history and sociodemographic data. The data will then be used to test the feasibility of finding patterns of movement and getting lost. ***(Dr. Wojtusiak may be contacted at 703/993-4148, jwojtusi@gmu.edu; Dr. Tompkins may be contacted at 703/993-2838 ctompkin@gmu.edu)***

2018-2019 ARDRAF Awards Committee

Paul Aravich, Ph.D.
Eastern Virginia Medical School
Severn B. Churn, PhD
Virginia Commonwealth University
Jorge A. Cortina, MD, DFAPA
UniCare Health Plan of West Virginia
Leslie Davidson, OTR/L, PhD, FAOTA
The George Washington University
Christine J. Jensen, PhD
Riverside Center for Excellence in Aging and Lifelong Health
Hamid Okhravi, MD
Eastern Virginia Medical School
Mikell Paige, PhD
George Mason University
Linda Phillips, Ph.D.
Virginia Commonwealth University
Beverly A. Rzigalinzki, PhD
Edward Via College of Osteopathic Medicine
Patricia A. Trimmer, PhD
Virginia Commonwealth University
Gregorio Valdez, PhD
Virginia Tech Carilion Research Institute
Ning Zhang, PhD
Virginia Commonwealth University
Shijun Zhang, PhD
Virginia Commonwealth University