Alzheimer's and Related Diseases Research Award Fund

2016-2017 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 2016-2017 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).

UVA **Matthew J. Barrett, MD, MSc, Jason Druzgal, MD, PhD, and Scott Sperling, PsyD**

Nucleus Basalis of Meynert Degeneration in Parkinson Disease Cognition

Dementia in Parkinson disease (PD) is a major source of morbidity. Degeneration of the nucleus basalis of Meynert (NBM) contributes to dementia in PD via loss of cholinergic innervation to the neocortex. The NBM has been identified as a potential intervention point to treat dementia in PD, and deep brain stimulation has been proposed as a potential therapy. As a preliminary step toward testing this therapy in PD, we determined whether MRI measures of NBM volume correlate with cognition in PD. Because it is difficult to accurately measure the NBM using MRI, we measured cholinergic nucleus 4 (Ch4) of the basal forebrain, which includes the NBM, using available cytoarchitectonic maps. The investigators found that reduced Ch4 density was associated with worse global cognition and worse performance on measures of attention, processing speed, and visuospatial function in early-stage and late-stage PD cohorts. The finding of a significant association between Ch4 density and cognitive measures in an early-stage PD cohort supports an early intervention targeting this region to prevent future degeneration. The investigation to identify a genetic marker as a predictor of Ch4 density continues, but preliminary data indicate there is no relationship between the *APOE* e4 allele, a risk factor for Alzheimer disease, and Ch4 density. The results provide evidence that reduced Ch4 density identifies more advanced PD, i.e., more advanced extra-nigral pathology. Future research will investigate whether Ch4 density may serve as a surrogate biomarker in PD. ***(Dr. Barrett may be contacted at 434/243-2012, mjb5t@virginia.edu; Dr. Druzgal may be contacted at 434/982-1736, tjd4m@virginia.edu; Dr. Sperling may be contacted at 434/982-1012, sas7yr@virginia.edu)***

VCU **Jennifer Inker, MBA, MS, Tracey Gendron, PhD, and J. James Cotter, PhD***

Use of Antipsychotic Medications by Residents with Dementia in Assisted Living Facilities

The aims of this research project were to: 1) establish a baseline rate of off-label antipsychotic medication use in residents with dementia but without a serious mental illness (SMI) in Virginia's assisted living facilities (ALFs); 2) explore what ALF characteristics correlate with the off-label use of antipsychotic medications; and 3) investigate reasons why antipsychotic medications are used off-label in ALF residents with dementia but not SMI. With oversight from an interdisciplinary, interagency research advisory committee, VCU used a mixed methods approach with a quantitative survey followed by a qualitative phase involving face-to-face interviews with administrators, directors of nursing, registered medication aides, and certified nursing aides in three ALFs. Fifty-five ALFs returned completed surveys (11.7%). The mean percentage of residents with a diagnosis of dementia but not SMI who were prescribed at least one antipsychotic medication was 40.3% (SD = 30.4), a level considerably higher than the estimated rate nationally (22%) and in Virginia nursing facilities (15.8%). For-profit status was the only significant correlation detected ($rpbi$ = .355, $p < .009$) with off-label antipsychotic medication use, with higher rates in for-profit ALFs (48.72 ± 30.1) than non-profit ALFs (26.6 ± 26.2). Interviews revealed that ALF staff are resourceful in responding to the needs of individuals living with dementia, but could benefit from guiding protocols, policies, procedures, training, and access to behavioral health specialists. ***(Ms. Inker may be contacted at 804/828-1565, inkerjl@vcu.edu)***

William & Mary **Oliver Kerscher, PhD, and Munira Basrai, PhD***

STUbL-Dependent Clearance of Transcriptionally-Active, Aggregate-Prone Proteins from the Nucleus

Altered gene expression is a hallmark of neurodegenerative disorders including Huntington's Disease. The main goal of this study was to investigate if STUbLs, a unique class of enzymes involved in targeted protein degradation, can prevent the abnormal transcriptional activity associated with a mutant, aggregation-prone fragment of huntingtin (mHtt), the causative agent of Huntington's disease. Specifically, as part of this project the investigators examined: 1) the physical interaction of STUbLs with mHtt, 2) the effect that STUbLs have on the transcriptional activity of mHtt in a tissue culture model of Huntington's disease, and 3) whether these enzymes counteract the abnormal transcriptional activity of mHtt on a genome-wide scale. It was found that increasing the levels of STUbLs reduces the chromatin association of mHtt aggregates. Furthermore, STUBLs specifically reduced mHtt-induced transcription in unique reporter gene assays. Whole-genome mRNA sequencing of mHtt-expressing cells, with and without STUbLs, were also completed. As a next step, bioinformatic analysis of these transcriptome data will be used to identify the endogenous gene targets of chromatin associated mHtt. Overall, the results are consistent with the investigators' model that STUbLs may be neuro-protective and the exciting new finding that enhanced STUbL expression levels can reduce the chromatin association and abnormal transcriptional activity of mHtt. These results implicate RNF4, an enzyme involved in targeted protein degradation, as an important player and potential therapeutic target for Huntington's Disease.***(Dr. Kerscher may be contacted at 757/221-2229, opkers@wm.edu; Dr. Basrai may be contacted at 301/402-2552, basraim@nih.gov)***

VCU **Rory McQuiston, PhD***

AAV-Induced Tau Pathophysiology in Interneurons of the Mouse Hippocampus

The tau protein has been implicated in Alzheimer's disease (AD) in which its transcortical spread follows Braak staging. There is substantial evidence indicating that spread of the disease involves pathogenic tau transmission between connected neurons, suggesting that soluble oligomers of tau contribute significantly to the disease. Neurodegeneration in AD is initially observed in layer 2 entorhinal cortex projection neurons and then spreads to the hippocampus and other regions of the temporal cortex. To investigate how neural networks may be impaired at the initial stages of the disease, we investigated the effect of pathogenic tau expression in medial entorhinal cortical neurons (MEC). The results of these studies have provided two important insights. First, using our adeno-associated viral approach to express pathogenic tau variants in cell types of interest, we could rapidly assess the impact of pathogenic tau expression on neurons and synapses in a time period of weeks. This provided a superior model compared to transgenic models in which months to years are required to assess pathogenic molecular dysfunction. Second, our data, for the first time, has shown that the effect of pathogenic tau expression on synaptic transmission depends on the identity of the postsynaptic partner. More specifically, the same presynaptic input (MEC LII) can be selectively altered when contacting a specific cell type (DGCs) but not on other neurons (PV interneurons) of the same brain region. Thus, the data highlight the need to examine the impact that pathogenic molecules associated with AD have on different subtypes of cells and synapses in the central nervous system. Such studies may identify novel potential therapeutic targets at varying stages of the disease. ***(Dr. McQuiston may be contacted at 804/828-1573, amcquiston@vcu.edu)***