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).

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 (rpb1 = .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)

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)
Evidence suggests that the memory decline in AD is due to the accumulation in the brain of protein fragments called amyloid-beta (Aβ). Emerging evidence suggests that AD may also be attributed to a progressive deterioration of the capacity of mitochondria, the cell powerhouse, to produce energy in the form of adenosine triphosphate (ATP). Besides, AD development has been linked to a progressive impairment in brain’s ability to respond to insulin, known as brain insulin resistance. This study asked: “Is there any connection between the accumulation of Aβ, mitochondrial function, and insulin resistance in the AD brain?” Aβ disrupts neuronal functions by affecting mitochondrial dynamics and insulin signaling. Even though these studies have provided valuable information for understanding the molecular players involved in AD pathogenesis, the intimate molecular mechanisms involved are still poorly understood. The investigators developed a two-photon fluorescence lifetime imaging assay which allowed the detection of changes in mitochondrial activity in live cells in culture. By using human neuronal progenitors, it was found that mitochondrial activity is directly regulated by the hormone insulin and nutrients such as the amino acids arginine and leucine. This process involves a specific nutrient-mediated activation of the lysosomal associated mechanistic target of rapamycin complex1 (mTORC1). Importantly, this process was found to be blocked by Aβ. These results unveiled a novel nutrient-dependent regulation of mitochondrial activity and establishes a novel molecular link connecting insulin resistance, mitochondrial dysfunction, and AD. This pathway may represent a new treatable target for clinical applications. (Dr. Norambuena may be contacted at 434/982-5809, an2r@virginia.edu)

VA Tech Jyoti S. Savla, PhD, Karen A. Roberto, PhD, and Rosemary Blieszner, PhD*
Families in Rural Appalachia Caring for Older Relatives with Dementia

The primary aim of this study was to learn from families in Appalachia about their approaches to caregiving and uncover whether they need and use community services currently, as well as their views of formal service use. The study was employed in two phases to gather information. In Phase 1, 10 family caregivers participated in an in-person interview to provide insight about their caregiving situation, their needs, and difficulties in receiving informal and formal help. Guided by the themes of these interviews, in Phase 2 an in-depth telephone survey followed by seven daily diary interviews was administered to 39 family caregivers. Findings suggest that spousal caregivers are more reluctant to use paid services than adult children. Filial obligations and negative attitudes toward paid services contributed to the reluctance of using paid help from outsiders. However, when caregivers experienced greater burden and stress, they were more likely to use formal services. The daily diary interviews further revealed that paid services were especially beneficial in reducing caregiver’s distress on days when the person with dementia exhibited more memory and behavior problems. These results point to the circumstances under which caregivers may get relief, despite their attitudinal reluctance to use paid services. As service providers and policy analysts consider how best to meet the needs of their aging populations, these findings demonstrate the importance of considering personal values, beliefs, and community attributes of residents of rural Appalachia to ensure optimum uptake of programs and services. (Dr. Savla may be contacted at 540/231-2348, jsavla@vt.edu)

Christopher Lisa S. Webb, PhD, and Darlene A. Mitrano, PhD
Comparative Biochemical and Behavioral Analysis of the 3xTg-AD Mouse Model of University Alzheimer's Disease

This research project was designed to better define the 3xTg-AD mouse line as a valuable model of human AD by seeking answers to the following two questions: (1) Is the blood lipid profile of the 3xTg-AD mice altered as it is in humans with AD and, if so, at what point in the mouse’s lifespan does the alteration occur? and (2) Does this mouse model experience a decline in olfactory abilities similar to that seen in humans with AD? The blood biochemistry has not yet been completed on the mice; however, preliminary histology results indicate that Aβ plaques form in the olfactory bulbs of 3xTg-AD mice, but not in the (non-AD) control mice. These plaques are clearly visible by the time the mice have reached one year of age and are not present in control mice. The histology results are supported by results from behavioral testing, using a buried food test (BFT) to assess olfaction. Preliminary results from the BFT indicate that the 3xTg-AD mice have significant deficits in olfaction compared to the control mice. (Dr. Webb may be contacted at 757/594-7056, lwebb@cnu.edu; Dr. Mitrano may be contacted at 757/594-8093, darlene.mitrano@cnu.edu)