Alzheimer's and Related Diseases Research Award Fund

2018-2019 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. Summaries of the final project reports submitted by investigators funded during the 2018-2019 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 **Dianne C. Daniel, PhD, and Edward M. Johnson, PhD***

Cellular Mechanisms of Pur-based Peptides for Frontotemporal Dementia

Frontotemporal Dementia (FTD) is currently an incurable disease. The most common genetic cause of FTD is a DNA sequence repeated many times in the gene C9orf72 (C9). This expanded sequence is made into RNA repeats and dipeptide repeats (DPRs), which aggregate in neurons in the brains of patients and cause them to degenerate. Pur-alpha protein, discovered in Dr. Johnson's laboratory, binds tightly to the RNA repeats and reduces nerve cell degeneration in animal models. Pur-alpha plays an essential role in RNA transport in neurons, and its sequestration by C9 repeat sequences could affect this step in RNA metabolism. The project investigators have tested TZIP, a Pur-based peptide containing a cell entry signal, as a potential therapy for this form of FTD. They identify TZIP binding to the C9 RNA repeats, including structures formed by the repeats known as G-quadruplexes, as a promising target for FTD therapy. Pur-peptide modulation of C9 repeat RNA through conformational shifts in this structure represents a new mechanism for regulation of RNA-protein binding and potentially of RNA transport. Data indicate that TZIP improves the process for removal from the cell of toxic aggregates, which can include DPRs. The investigators have shown that labeled peptide diffuses into cells of brain regions after injection into a ventricle. They have designed a virus with copies of the C9 repeat to infect mouse fetal cortical neurons as an in vitro study model. This system provides a laboratory model for testing promising peptides, which will provide the basis for a potential FTD therapy.

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

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

Although there are multiple competing theories to explain the cognitive dysfunction seen in diabetes, the investigator's lab had preliminary data establishing that the cholesterol synthetic pathway is also disrupted in the brains of diabetics and that this disruption leads to an increase in the cholesterol oxidation product, 7-ketocholesterol, a molecule also increased in AD. Their studies also demonstrated that mice with impaired astrocyte cholesterol synthesis have disrupted circadian rhythms. In this ARDRAF-funded study, it was found that: 1) 7-ketocholesterol could make the astrocyte cells of the brain, the cells responsible for most brain cholesterol synthesis, have weakened circadian rhythms and that 2) the rhythms were strengthened by the use of the hormone melatonin. These two opposing effects indicate that the site of action is a transcription factor, the retinoic acid receptor (RAR)-related orphan receptor alpha (RORα). Further, the investigators found that the circadian rhythms of mice fed a high fat diet and mice with AD both have a weakening of circadian rhythms similar to what was seen in vitro. These weakened circadian rhythms in mice coincided with an increase in brain 7-ketocholesterol, suggesting that 7-ketocholesterol is driving circadian disruptions in both AD and obesity/diabetes. With this knowledge, the investigator will use the new tools developed to pursue: 1) further direct evidence of the role of 7-ketocholesterol in the disruption of circadian rhythms in mice and 2) strategies to prevent this disruption. The goal is to eventually develop therapeutics to address circadian disruptions in patients with AD. ***(Dr. Ferris may be contacted at 412/605-8541, hf4f@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 built an interactive web application that allows Alzheimer's patients and informal 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 home and community. Currently, the FM system has collected 265 patient-months of data. These data are classified into representations that provide caregivers with crucial information about the efficacy of their caregiving and the Negative Behavioral Trends (NBTs) of their loved ones (i.e., lower than normal step counts, declining lifespace, and ragged wake-up times). The website allows caregivers to interact with their loved ones' data, and receive appropriate interventional suggestions. For instance, alerts regarding declining lifespace (a measure of the number of excursions outside the home) can result in a caregiver making more of an effort to take the loved one outside the home to interact with a more enriched environment, which has been shown to enhance functional status. Back end coding allowed the investigator to write updated code that queries the database and processes real-time data for the front end (web interface). Website coding allowed for design work to optimize what the Caregiver Portal looks like, what it shows, and how caregivers interact with the resulting data. Once the NBT algorithms were built, they were tested for false positives and negatives by running them on FM data sets. The false negative rates were under 5% because the NBTs were so dramatic, e.g., the average for the lifespace NBTs was a 45% decline.

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