

Alzheimer's and Related Diseases Research Award Fund

2012-2013 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 2012-2013 round of competition are given below. To receive the full reports, please contact the investigators or the ARDRAF administrator, Dr. Constance Coogle (804/828-1525, ccoogle@vcu.edu).

UVA Inchan Kwon, PhD and Erik Fernandez, PhD
“Revealing the Effect of Food Dyes on Amyloid-Beta Structure-Cytotoxicity Relationships”

Modulation of amyloid-beta (A β) peptide aggregation is considered a promising therapeutic strategy to cure Alzheimer's disease (AD). Although several U.S. Food and Drug Administration (FDA)-approved drugs temporarily reduce symptoms, no treatment exists that slows or stops progression of AD. There is a need to discover more potent molecules and elucidate their relationship to AD pathology. In the search for safe, effective aggregation modulators, the investigators have examined FDA-approved food dyes and their close analogs. They previously reported that erythrosine B (ER) and brilliant blue G (BBG) reduce A β neurotoxicity by modulating A β aggregation. These exciting results suggest that ER and BBG could be promising lead compounds for AD therapy. For this project, the researchers explored the structural basis for ER and BBG (and their analogs) A β binding and the subsequent reduction of cytotoxicity. The preliminary results obtained indicate that a BBG analog, Brilliant Blue R, could be a promising candidate to proceed with *in vivo* testing in an animal model of AD. In addition, the immunoassays revealed the 10-16 amino acid sequence of the A β peptide as a potentially important binding region for aggregation modulators/inhibitors. This work could open the door for structure-based design of molecular or peptide inhibitors that specifically target the 10-16 amino acid sequence of A β . Lastly, the immunoassays described in this work provide an economical template for researchers to obtain residue level information without the need for nuclear magnetic resonance spectrometers or other costly apparatus.

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UVA Carol Manning, PhD, ABPP-CN, Steven DeKosky, MD, and Ishan C. Williams, PhD
“Vascular Risk Factors and Cognition in African Americans”

Vascular risk factors are associated with dementia. African-Americans have high rates of vascular risk factors and have high rates of dementia. However, dementia and Mild Cognitive Impairment (MCI), often a sign of early dementia, may be under-recognized in African-Americans coming in for general medical appointments. In this study, ninety-six African-Americans who were coming in to see their primary care physicians had cognitive testing immediately. None of the participants were coming to see their doctors because of cognitive complaints. Vascular risks were identified through the participants' medical records. Vascular risk factors included high blood pressure, diabetes, high cholesterol, history of stroke and cigarette smoking. Cognition was examined in relation to vascular risk factors. Concern about cognitive functioning in participants and physicians was also examined. Data revealed that vascular risks had a negative impact on cognition. According to our cognitive test results, 41% percent of our sample had MCI, despite a lack of cognitive complaints. In addition, neither the patients nor the physicians were aware of the degree of cognitive impairment. African-Americans, coming to see their primary care physicians for reasons other than memory, had high rates of cognitive impairment and vascular risk factors. Vascular risks were correlated with cognitive impairment. These findings indicate high rates of unrecognized cognitive impairment in this population and suggest that patients and physicians may be unaware of these difficulties. Lack of awareness may be secondary to limited appointment time and poor knowledge of risks for cognitive change.

Marymount University Julie D. Ries, PhD, PT
“Balance Training Program Designed for Individuals with Alzheimer’s Disease: The Effect on Balance and Falls”

Individuals with Alzheimer’s disease (IwAD) experience more frequent and more serious falls than their age-matched peers. Balance training is effective in improving balance and decreasing falls in cognitively intact older adults. This study was developed to analyze the effects of a balance training program designed specifically for IwAD, with specific guidelines for communication/interaction and deliberate structure of training sessions. Thirty participants with AD were recruited from three adult day-center programs; twenty-two of them completed at least one post-test session. Balance and mobility tests were administered immediately before and after the three-month program and again three months later. Balance training sessions were 45 minutes, twice per week and were characterized by functional, relevant activities, with considerable repetition, and with sessions consistently formatted with blocks of time dedicated to different tasks. Participants were up on their feet the majority of each session and were individually challenged as much as possible. Although most IwAD did not remember participating in the program week to week, or recognize the researchers after the three-month program, they demonstrated statistically significant improvements in balance. This finding suggests that their bodies had a “motor memory” of the training even if participants did not have a cognitive memory of it. Balance deteriorated after termination of the program, although participants did maintain some improvement three months after the training. Fewer participants experienced falls the six months following program initiation ($n = 5$) than the six months prior to initiation ($n = 9$). This upright and intensive balance training program shows promise for improving balance and potentially decreasing falls in IwAD.

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VCU Vladimir Sidorov, PhD
“Identification and Characterization of nAChRs Clustered in Cell Membrane Lipid Rafts Using Novel Patching Technique with Chemically Modified Electrodes”

Neuronal nicotinic acetylcholine receptors (nAChRs) are critical to cell functioning and essential in the development of Alzheimer’s disease. The function of alpha4beta2 and alpha7 subtypes of nAChRs is regulated by association of the receptors with rigid areas of neuronal membranes, known as lipid rafts. The overall goal of this project is to develop a novel technique that allows identification and characterization of the functional properties of nAChRs based on selective patching of the raft and fluid areas of cell membranes with a chemically modified borosilicate electrode. During this initial stage of the investigation, a robust chemical procedure for surface modification of borosilicate electrodes was developed for use in the planned electrophysiological experiments. The procedure allows tethering of a synthetic macromolecule, cyclen 2, which serves as a selective binding agent for the fluorescent dye pyranine. The binding phenomenon is readily observed due to the fluorescence quenching. In order to utilize these electrodes, a series of lipid conjugates with pyranine have been synthesized. The confocal microscopy imaging experiments revealed that the cholesterol-pyranine conjugates rapidly partition into the dynamic areas of cell membranes consistent with the ordered domains (rafts). While being in a rapid lateral motion, the fluorescently labeled cholesterol remained fully accessible for interactions with cyclen 2 attached to the glass surface. Future undertakings will test the hypothesis that the functional behavior of nAChRs is directly affected by their localization in the ordered membrane domains. Such characterization of nAChRs docked in the raft areas of membranes may lead to better understanding of key factors in the development of Alzheimer’s disease as well as to the methods for treatment of this condition.

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Ferrum College **Megan M. St. Peters, PhD**
“Who Forgot the Hippocampus? Potential Involvement in the Neural Circuitry of Attentional Control”

The ability to focus on important stimuli and ignore irrelevant stimuli in our environment is essential to the “top down” control of attention. It is suggested that the memory of what is important in an environment is essential to this top-down control, and recent research suggests that attentional impairments may precede or largely contribute to the memory problems associated with dementia of the Alzheimer’s type (DAT). Yet studies examining the brain pathways involved in attention have failed to examine the role of the hippocampus, a brain region commonly associated with memory loss and DAT. The current pilot study tested a rodent model with cholinergic deafferentation of the hippocampus in an operant sustained attention task. Task parameters enabled the introduction of irrelevant distractors in order to assess top down control of attention. Although there was a relatively small sample size ($n = 6$ per group), the data suggest no effect of lesion. However, several parameters (toxin site location, concentration, and task) can be further explored in future research to better understand the potential neural interplay between memory and attention.

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VCU **Dong Sun, MD, PhD**
“Excessive Inflammation in Aging Population Following Brain Injury Impairs Hippocampal Neurogenesis and Cognitive Function: Implication for AD”

Recent evidence suggests that impaired neurogenesis in the hippocampus is a critical event and may underlie cognitive deficits in AD. Aging and traumatic brain injury (TBI) are the leading risk factors in the development of AD. This project tested the hypothesis that under neuropathological conditions, aging produces excessive inflammatory responses which impair hippocampal neurogenesis and cognitive function. In Aim 1, serum and brain tissue homogenates from young and aged rats at different time points following TBI were assayed to measure the expression levels of 24 cytokines/chemokines. Another group of animals was used to assess the level of hippocampal neurogenesis. In Aim 2, minocycline and 7,8-DHF were used to target neuroinflammation and neurogenesis for improved cognitive function in animals following TBI. At the early time point, several pro-inflammatory cytokines/chemokines were expressed at high levels in both serum and brain, and the aged animals had a higher expression compared to their younger counterparts. At 3 days post-TBI when the inflammatory mediators were expressed at high levels, a decreased number of newly generated neurons were found in the injured aged brains as compared to age matched sham controls or their younger counterparts. Short term minocycline treatment at the acute stage post-injury significantly attenuated TBI-induced inflammatory cell responses in the brain and the production of several pro-inflammatory cytokines particularly in the aged rats. The administration of 7,8-DHF at the same stage improved cognitive function. These studies suggest that targeting inflammation and neurogenesis may have therapeutic potential to improve cognitive recovery in aging populations.

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