

COMMONWEALTH OF VIRGINIA

Alzheimer's and Related Diseases Research Award Fund

2022-2023 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, including 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 \$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 (*). The ARDRAF competition is administered by the Virginia Center on Aging in the College of Health Professions at Virginia Commonwealth University. Questions about the projects may be directed to the investigators or the ARDRAF administrator, Dr. L. Constance Coogle (ccoogle@vcu.edu).

EVMS Frank J. Castora, PhD and Randolph A. Coleman, PhD*

Does the AD-related T9861C mitochondrial DNA (mtDNA) mutation result in gene expression changes that can identify potential AD therapeutic targets?

Mitochondria are the energy-producing structures inside nerve cells. Evidence for the involvement of mitochondrial function in Alzheimer's Disease (AD) has accumulated over the years. Dr. Frank Castora's lab has identified a mutation in mitochondrial DNA (mtDNA) that is strongly associated with Alzheimer's disease (AD). In fact, 15% of their human AD brain samples possessed this mutation to varying degrees. This mutation affects a specific component of an essential protein complex that helps make ATP, the energy currency of brain cells. This study will examine whether this mutation changes the level of expression in other nuclear-encoded mitochondrial genes involved in various aspects of mitochondrial function. Some of these genes would be significant factors in the pathogenic networks of the AD patients. Then, in collaboration with Dr. Castora, Dr. Randolph Coleman at the College of William and Mary will incorporate groups of these negatively impacted genes of interest, along with the protein and enzyme activity values he gathers, into a new mathematical model for AD. Manipulation of this model will help filter and identify a small number of genes that may serve as therapeutic targets for AD patients possessing this mtDNA mutation. (*Dr. Castora may be contacted at (757) 446-5657, castorfj@evms.edu; Dr. Coleman may be reached at (757) 221-2679, racole@wm.edu*)

UVA Anelyssa D'Abreu, MD, PhD, MPH, and Pavel Chernyavskiy, PhD*

Does the Area Deprivation Index (ADI) influence dementia work up and diagnosis in Virginia?

The importance of geographic location as a key social determinant of health and the primary driver of geographic disparities is widely recognized across the healthcare spectrum. Understanding the influence of area-based socioeconomic disadvantage is of paramount importance when devising target initiatives to decrease disparities in dementia diagnosis. The Area Deprivation Index (ADI) provides a multidimensional metric of disadvantage by incorporating educational, housing, employment, and poverty measures derived from the American Community Survey. The ADI has been extensively studied as a valid neighborhood-disadvantage metric. The investigators intend to determine how area socioeconomic status, as measured by the ADI, influences dementia evaluation and diagnosis in Virginia. They hypothesize that those in the most disadvantaged areas do not receive proper evaluation (cognitive screening, brain imaging and routine labs), and as a consequence, receive a diagnosis of unspecified dementia. Timely and correct diagnoses of dementia and its etiology are fundamental for planning, treatment, research participation, and caregiver support. Different disease processes that lead to dementia have distinct prognosis, clinical management, social requirements and outcomes. Results of this research will inform future state, and possibly federal, policy to better address healthcare disparities and improve healthcare. (*Dr. D'Abreu may be contacted at (434) 924-8371, ad9rn@virginia.edu; Dr. Chernyavskiy may be contacted at dww4kc@virginia.edu*)

VCU Laxmikant Deshpande, PhD, and Joseph McClay, PhD*

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Assessment of Beta-site amyloid precursor protein cleaving enzyme 2 (BACE2) in a rat model of occupational-like organophosphate pesticide exposure

Epidemiological studies have reported a strong correlation between environmental and occupational exposure to pesticides and the development of AD. Experimentally, occupational-like (OP) exposure exacerbates AD neuropathology *in vitro* and accelerates cognitive deficits in transgenic AD rats. How OP exposures could elevate the risk for developing an AD-like disorder however, is entirely unknown. The amyloid precursor protein (APP)-cleaving enzyme 2 (BACE2) is naturally suppressive of amyloid β protein ($A\beta$) formation, and is thus, a deterrent to AD. The investigators' preliminary studies have shown decreased expression of BACE2 in the brains of rats exposed to an environmentally-relevant pesticide. This significant finding has not been reported before in the context of OP exposures and AD risk. The investigators will now initiate studies to assess the role of BACE2 in elevating the risk for an AD-like disorder in a rat model of OP exposure. Study results will contribute to developing scientific data that could better inform policies towards regulating OP exposure for domestic and agricultural use, considering these health risks.

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VCU ***Kirsty Dixon, PhD****

Understanding TBI as a risk factor in the development of Alzheimer's disease

Traumatic brain injury (TBI) is a known risk factor for the later development of AD, with both disorders sharing symptoms and pathophysiology. Inflammation underlies both traumatic brain injury (TBI) and AD and levels of a key inflammatory cytokine, Tumor Necrosis Factor (TNF), and its receptor, TNFR1, are increased in the brain following both TBI and AD. This increase may be responsible for promoting AD pathology by stimulating the production of extracellular β -amyloid levels, that eventually form the hallmark plaques and neurofibrillary tangles indicative of AD. Interestingly, while TBI exacerbates hippocampal dendritic spine plasticity (spine loss and aberrant morphology), resulting in cognitive impairment and depressive-like behavior, this may not be driven by β -amyloid levels. Therefore there is a critical need to understand the relationship between TBI and AD, and their synergistic impact on mechanisms underlying cognitive decline. This study aims to determine how TBI-induced soluble TNF/TNFR1 activity promotes AD pathology and cognitive decline. To achieve this aim, the investigators will test a 'second generation' biologic (known as XPro1595) that selectively inhibits soluble TNF/TNFR1 activity, in 3xTg-AD transgenic mice that have undergone a TBI.

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GMU ***Hyun Kang, PhD, MA, Emily S. Ihara, PhD, MSW, FGSA, and Catherine J. Tompkins, PhD, MSW***

Stronger Memory (Phase II): Experiences of older adults and caregivers in an intervention program for cognitive impairment

Research indicates that social engagement, particularly in groups, has a positive effect on cognition. This project is a partnership between George Mason University's Department of Social Work and Goodwin House, Inc., a nonprofit continuing care retirement community. The StrongerMemory program is an intervention that incorporates a series of practices to benefit cognition. The investigators will evaluate the impact of a group social engagement intervention while participants complete the 12-week StrongerMemory program. They will compare participants that engage in weekly sessions to discuss the StrongerMemory exercises for 12 weeks with those who don't participate in the social facilitation intervention. It's hypothesized that this social engagement intervention will potentiate the cognitive, behavioral, and emotional outcomes resulting from the StrongerMemory exercises.

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Marymount University Julie D. Ries, PhD, PT Patricia C. Heyn, PhD, FGSA, FACRM, Uma Kelekar, PhD, Rita Wong, EdD, PT, and Catherine Diaz-Asper, PhD*
Remote online administration of Otago Exercise Program for Individuals with Dementia and their Care Partners: A Feasibility Study

Individuals with dementia (IwDs) fall more and are more seriously injured in falls than their age-matched, cognitively intact peers. An accessible and sustainable fall prevention program would be of great value. Using remote technology has become commonplace during the COVID-19 pandemic, and Marymount University's new Center for Optimal Aging plans to use this technology to bring a web-based version of a well-established and accepted evidence-based fall prevention intervention, the Otago Exercise Program, into the homes of IwDs and their care partners. Remote administration could overcome substantial barriers to program access. The investigators will determine the viability of this option by assessing program functionality, utility, and effectiveness. Feasibility will be evaluated by using components of the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance). The results will guide and inform adaptations of future remote training efforts for IwD, with implications at the individual, family, and societal levels. **(Dr. Ries and colleagues may be contacted at 703-284-5983; jries@marymount.edu)**

2022-2023 ARDRAF Awards Committee

The Virginia Center on Aging acknowledges the dedicated work of this independent review panel of subject matter experts and gratefully thanks them for contributing their time and expertise.

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