Commonwealth of Virginia
Alzheimer's and Related Diseases Research Award Fund

2024-2025 ARDRAF 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 ARDRAF is administered by the Virginia Center on Aging in the College of Health Professions at Virginia Commonwealth University.

Awards Committee 2024

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

Paul Aravich, Ph.D.
Eastern Virginia Medical School

Kimberly Battle, Ph.D., FNP-BC
VCU Health

Anne Brown, Ph.D.
Virginia Tech

Severn Churn, Ph.D.
National Institutes of Health

Christine Jensen, Ph.D.
Riverside Center for Excellence in Aging and Lifelong Health

Alicia Pickrell, Ph.D.
Virginia Tech

Laura Sands, Ph.D.
Virginia Tech

Ishan Williams, Ph.D., FGSA
University of Virginia

Jodi Winship, Ph.D, OTR/L
Richmond Aging and Engaging

George Worthington, M.S.
Virginia Department for Aging and Rehabilitative Services

Ning Zhang, Ph.D.
Virginia Commonwealth University

Mingyang Zheng, Ph.D.
Radford University

Questions about the projects may be directed to the investigators or the ARDRAF administrator, Dr. Faika Zanjani (fzanjani@vcu.edu).

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AN ARTIFICIAL INTELLIGENCE SOLUTION TO SOCIAL ISOLATION AND LONELINESS OF CAREGIVERS OF PEOPLE WITH DEMENTIA

Janusz Wojtusiak, Ph.D. - George Mason University

The unprecedented growth of Artificial Intelligence (AI) methods in recent years has opened new possibilities in providing care for people with Alzheimer's and related diseases (ADRD) and supporting their caregivers. One area of importance is social isolation and loneliness in caregivers, who often dedicate themselves to caring for loved ones affected by ADRD.

This project is intended to lay the foundation for a large study of utilizing AI methods to address social isolation and loneliness among people who care for those with AD and who are suffering from dementia. Addressing social isolation requires several steps: identification of those who are in need and who can benefit from an AI-based intervention, designing and building the system, and its dissemination and analysis.

The first part of this project serves as an independent study of how to accurately identify caregivers who are socially isolated or at risk of becoming socially isolated. That task is accomplished by applying machine learning methods to predict social isolation using three survey datasets, then transferring the models to Medicare claims, and finally, running a large-scale simulation of how at-risk caregivers can be identified.

The second part of this project will result in a framework for AI-based interventions intended for caregivers. It will be based on a detailed review of available state-of-the-art AI-based technologies that can support caregivers of people with ADRD.

Janusz Wojtusiak, Ph.D. is a professor of health informatics in George Mason University's Department of Health Administration and Policy and is the Division Director for GMU's Programs in Health Informatics. He also serves as the director of the Machine Learning and Inference Laboratory. Dr. Wojtusiak obtained an M.S. in Computer Science from Jagiellonian University and his Ph.D. in Computational Sciences and Informatics from George Mason University.

Dr. Wojtusiak's research interests include the development and use of intelligent systems in medical settings, healthcare, and health. He focuses on creating artificial intelligence methods that make sense in health applications. Some of Dr. Wojtusiak's recent research includes work on prediction of patients' functional decline over time, interpretability and transparency of machine learning methods in health, evaluation of machine learning models, prediction of movement in people with Alzheimer's Disease, temporal modeling of data, technology-based contact prediction during a pandemic, and equitable analysis of bruise images and data.

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DEVELOPING PREDICTIVE ANALYSIS FOR COGNITIVE IMPAIRMENT AND CHRONIC PAIN INTERACTIONS: A PRELIMINARY STEP TOWARDS INTEGRATED CARE

Huaiyang Zhong, Ph.D., Robert S. McNamara, Ph.D., and Jyoti Savla, Ph.D. - Virginia Tech

This study aims to improve care for older adults with cognitive impairment living in rural areas by focusing on the connection between cognitive concerns and chronic pain. Cognitive impairment can make it difficult for people to manage their daily activities and other health problems, such as chronic pain, which is common among the elderly and affects quality of life and mental health.

This project will analyze electronic health records to predict who might be at risk of chronic pain related to cognitive impairment. This innovative approach aims to better incorporate pain management into care for those with cognitive difficulties. Additionally, the project will investigate the reverse relationship: identifying individuals with chronic pain who might be at risk of developing cognitive impairment and integrating cognitive evaluation into pain management plans for older adults.

By focusing on both cognitive impairment and chronic pain, this project seeks to provide a fresh perspective on patient care. Advanced data analysis techniques will help overcome the challenges of current diagnostic methods, which are often time-consuming and require specialized skills. The ultimate goal is to provide healthcare professionals with accurate and efficient tools for early identification and combined management of these conditions. In turn, these methods hold the potential to improve the lives of older adults and help healthcare systems better address the complex needs of this vulnerable population.

Huaiyang Zhong, Ph.D. conducts research focused on developing models to inform medical and health policy decision-making. His prior work on infectious disease control, including HIV, HCV, and COVID, has enabled him to collaborate extensively with both governmental and non-governmental agencies. These collaborations aimed to design and assess health policies in several countries, including Ghana, Rwanda, Uganda, Moldova, and Uruguay. Recently, he had the privilege of working alongside the White House, the Congressional Budget Office, and NIH leaders to draft the US HCV elimination program.

Shifting his focus to chronic conditions, Dr. Zhong's new area of research examines the intersection of cognitive impairment and chronic pain among older adults. His project aims to enhance care for older adults with cognitive impairment in rural areas by exploring the relationship between cognitive impairment and chronic pain. By developing predictive models using machine learning, his work seeks to improve integrated care strategies and ultimately enhance the quality of life for this vulnerable population.

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DEFINING THE HIPPOCAMPAL MOLECULAR-PHYSIOLOGICAL-COGNITIVE AXIS DYSFUNCTION UNDERLYING THE EPISODIC MEMORY LOSS IN ALZHEIMER'S DISEASE

Theodore Dumas, Ph.D. - George Mason University

Alzheimer's disease (AD) is a neurodegenerative disease of aging that destroys brain structures required for memory storage and retrieval, including the hippocampus. AD occurrence rates are predicted to double by 2060 highlighting the need for better therapies.

The episodic memory loss seen in early-stage AD patients and in multiple mouse models of AD is associated with disturbances in hippocampal neuronal network activity. Expression of neurotransmitter receptors that regulate experience-dependent changes in hippocampal network activity. NMDA receptors are reduced in animal models of AD and restoration ameliorates the pathological changes in hippocampal network activity. However, NMDA receptors produce at least two separate signals, the relative contributions of which to hippocampal network activity have not been investigated.

Utilizing transgenic mice that express mutated NMDA receptors, we discovered that ion channel signaling subserves learning ability while direct interaction with other synaptic proteins facilitates long-term memory retrieval. Thus, we hypothesize that the NMDA receptor direct protein signaling that improves memory retrieval also positively modulates hippocampal network activity.

To test this, we will examine hippocampal network activity in middle-aged transgenic mice expressing mutated NMDA receptors while these animals engage in a spatial memory task. We predict that, relative to wild-type littermates, mutations to direct protein signaling will enhance long-term spatial memory performance and augment hippocampal network activity during successful long-term memory trials. Positive findings would point to NMDA receptor direct protein signaling as a critical therapeutic target in AD and may result in the creation of far more effective treatments and potential cures.

Theodore Dumas, Ph.D., is an Associate Professor of Cognitive and Behavioral Neuroscience in the Psychology Department and the Doctoral Program Director for the Interdisciplinary Program in Neurosciences at George Mason University. He has published fifty journal articles, numerous book chapters, and one book. Dr. Dumas is an award-winning educator who delivers seminars to health professionals on a national circuit and has been funded as Principal Investigator three times by the National Institutes of Health and as a Co-Investigator on other federally funded projects (Department of Defense). Dr. Dumas is dedicated to treating psychiatric diseases and improving mental health.

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UNDERSTANDING THE CONTRIBUTION OF CHOLESTEROL TO NEUROINFLAMMATION AND ALZHEIMER'S DISEASE.

Heather Ferris, M.D., Ph.D. - University of Virginia

Cholesterol accumulation in the brain has been implicated in neuroinflammation and the development of Alzheimer's disease (AD). Placing mice on a high fat diet induces activation of microglia in the brain and exacerbates pathology in AD models. In addition, human studies find that having elevated serum cholesterol or obesity in midlife are risk factors for AD. In order to better design therapies to prevent AD, a clearer understanding of the connection between obesity and hyperlipidemia in the periphery and cholesterol accumulation and inflammation in the brain is needed. Cholesterol is carried by lipoprotein particles, which do not readily cross the blood brain barrier. Thus, it is unclear how peripheral cholesterol influences neuroinflammation and AD.

Astrocytes are the main source of cholesterol in the brain. In addition to producing the cholesterol, they also make the majority of ApoE in order to transport the cholesterol between cells. We previously made a mouse model in which we knocked out SREBP2, the major regulator of the cholesterol synthesis pathway, from astrocytes. These mice have impaired astrocyte cholesterol synthesis. When we bred these mice to a model of AD we completely prevented the formation of amyloid plaques and microglia activation. We will use our SREBP2 knockout model to understand if astrocyte-derived cholesterol is also necessary for high fat diet-induced neuroinflammation.

- **Aim 1.** Test if astrocyte-derived cholesterol is required for high fat diet-induced microglia activation.
- **Aim 2.** Test if overproduction of astrocyte-derived cholesterol is sufficient to drive microglia activation in an isoform specific manner.

Heather Ferris, M.D., Ph.D., is an Associate Professor in the Departments of Medicine and Neuroscience at the University of Virginia. She earned a BA in Chemistry and a BS in Biochemistry from the College of Charleston in 1998. She then attended the University of Virginia, earning her MD and a PhD in Molecular Physiology and Biological Physics. This was followed by a residency at the University of Pittsburgh Medical Center in Internal Medicine and an Endocrinology fellowship at the Beth Israel Deaconess/ Joslin Diabetes Center in Boston.

Dr. Ferris spent five years as an instructor at Harvard Medical School/Joslin Diabetes Center before returning to the University of Virginia in 2017. She now cares for older Virginians with diabetes and directs a research lab focused on understanding how metabolism impacts the risk of developing dementia.

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UNDERSTANDING HOW APOE4 EXACERBATES TRAUMATIC BRAIN INJURY PATHOLOGY TO ACCELERATE THE DEVELOPMENT OF ALZHEIMER'S DISEASE

Kirsty Dixon, Ph.D. - Virginia Commonwealth University

Traumatic brain injury (TBI) affects 1.5 million people annually in the United States with individuals frequently enduring physical, cognitive, and/or psychological impairments. Both TBI and APOE4 are known risk factors for later development of Alzheimer's disease (AD) with both disorders sharing symptoms and pathophysiology. Unfortunately, there is a lack of understanding of the relationship between TBI and AD, let alone how APOE4 may exacerbate these outcomes.

Inflammation is known to play a key role in the underlying pathology of TBI, AD, and APOE4 with numerous studies focusing on a key inflammatory cytokine known as Tumor Necrosis Factor (TNF) and its receptor TNFR1. It has been known for some time that TBI promotes an inflammatory response within the brain that includes an acute upregulation of TNF to activate TNFR1 which causes poor hippocampal pathology to impair functional outcomes (including cognitive impairment).

Under normal physiological conditions a second receptor known as LRP1 can promote TNFR1 trafficking away from the cell membrane, but this is prevented following the binding of APOE4 to LRP1, resulting in the sustained presence of membranous TNFR1. Therefore, an injury-induced upregulation of TNF/TNFR1 levels, combined with the presence of APOE4 protein, likely promotes sustained TNFR1 activity, which may then enhance the development of AD pathology, as well as injury-induced outcomes such as impaired synaptic function and WM pathology.

With that in mind, this study aims to determine how APOE4/LRP1 activity regulates TBI-induced solTNF/TNFR1 activity to drive the production of AD pathology, with associated cognitive decline.

Kirsty Dixon, Ph.D., directs the VCU Department of Surgery Neurotrauma Repair Laboratory using federal, state and local funds investigating how the brain's inflammatory response to injury and disease promotes aberrant brain pathophysiology, including understanding how traumatic brain injury is a risk factor for Alzheimer's disease. Understanding this basic pathology can lead to the development of clinically relevant therapies to improve an individual's quality of life.