Commonwealth of Virginia

ALZHEIMER'S AND RELATED DISEASES RESEARCH AWARD FUND

2023-2024 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. Questions about the projects may be directed to the investigators or the ARDRAF administrator, Dr. Faika Zanjani (fzanjani@vcu.edu).

Awards Committee 2023

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, PhD
Eastern Virginia Medical School

Severn Churn, PhD
National Institute of Health

Christine Jensen, PhD
Riverside Center for Excellence in Aging and Lifelong Health

Michael Pyles, PhD
Virginia Commonwealth University

Patty Slattum, PharmD, PhD
Virginia Commonwealth University

George Worthington, MS
Virginia Department for Aging and Rehabilitative Services

Special Thanks

The Virginia Center on Aging would like to acknowledge the generous contribution of Mrs. Russell Sullivan of Fredricksburg to the ARDRAF, in memory of her husband who died of dementia.

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Commonwealth of Virginia
ALZHEIMER'S AND RELATED DISEASES RESEARCH AWARD FUND

Andres Norambuena, PhD
University of Virginia

A Novel Mechanism for Mitochondrial Metabolic Rewiring in Human Microglia and its Role in Alzheimer's disease

Dysfunction in mitochondria (the cell's powerhouse and metabolic factory) has been proposed as a key contributor to Alzheimer's disease (AD). However, the underlying molecular mechanisms explaining how a "healthy" microglia (immune cell of the central nervous system), becomes an AD one, remains poorly understood. By combining molecular studies with state-of-the-art microscopy of mitochondrial functioning, we seek to study a novel mechanistic link that could explain how human microglia dysfunction contributes to AD pathogenesis, opening the possibility to develop novel therapeutic interventions.

About Andres Norambuena, PhD

Dr. Norambuena's research aims to understand how cell surface receptors transmit signals into cells, how these signals regulate cell functions, and how they fit into the overall picture of cellular functions mediated by soluble factors, oncogenes, and other stimuli. As a postdoc in Martin Schwartz lab at UVA, he helped provide new insight into how lipid rafts behave after the loss of cell adhesion and he assisted in furthering understanding of the mechanism for a pathway that was discovered 10 years earlier, but was still not understood. While he was there, he learned that soluble forms of amyloid-β oligomers (AβOs), one the main culprits in Alzheimer's Disease, bind lipid rafts at the cell surface, potentially altering signaling at an early stage of AD pathogenesis. This issue of foundational importance to AD, motivated him to join the Bloom lab after his training with Dr. Schwartz was complete. Since then, his independent work has provided evidence that AβOs selectively disrupt normal signaling by mTORC1 by activating this multi-subunit protein kinase complex at the plasma membrane instead of at the lysosomes (Alzheimers Dement. 2017;13(2):152-167). This rudimentary event later paved the way for the discovery of a fundamental signaling pathway that regulates mitochondrial activity in neurons (EMBO J.2018;37(22). pii:e100241; Neurobiol.Dis. 2022 https://doi.org/10.1016/j.nbd.2022.105737). Dr. Norambuena's interest in molecular mechanisms of AD has recently expanded to explore mechanisms leading to mitochondrial metabolic rewiring in human neurons effected by AD. In this ARDRAF proposal, his team has joined forces with Dr. George Bloom and Dr. John Lukens, to explore if extracellular oligomeric forms of the microtubule-associated protein Tau, rewire mitochondrial metabolism using iPSC-derived human microglia. They are interested in exploring its mechanisms and contribution to AD pathogenesis.

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Commonwealth of Virginia
ALZHEIMER'S AND RELATED DISEASES RESEARCH AWARD FUND

Rebecca Heise, PhD,
and Dong Sun, MD, PhD
Virginia Commonwealth University

Probing the role of NLRP3 inflammasome on cognitive dysfunction following Acute Respiratory Distress Syndrome in an Alzheimer's disease model

Acute respiratory distress syndrome (ARDS) is commonly caused by sepsis, inhalation of harmful substances, pneumonia, and injury. ARDS has increased globally due to the COVID-19 pandemic and patients often require mechanical ventilation. However, this procedure frequently worsens the original insult and produces an exaggerated inflammatory response, potentially leading to poor outcomes. Cognitive problems are prevalent at discharge for patients who survive ARDS with mechanical ventilation and may persist for a year or longer. Aged patients are more likely to be mechanically ventilated and impacted by pre-existing dementia or Alzheimer 's disease (AD). This study will investigate the lung-brain axis in ARDS patients to find treatment targets, especially in those with AD. Our hypothesis is that inflammation in the lung-brain axis is the fundamental player in the severity of cognitive impairment and lung complications following ARDS. Literature suggests the NLRP3 inflammasome plays a role in both AD and ARDS, independently. However, the NLRP3 inflammasome has not been linked to lung-brain inflammation in aging, AD, and ARDS. We plan to examine the shared mechanism of NLRP3-related inflammation in response to lung and secondary brain injury. We will utilize a mouse model of ARDS in wild-type mice and transgenic AD mice. In Aim 1, we will assess the expression levels of NLRP3 inflammasome, pulmonary function, and cognitive function in wild type and transgenic AD mice following experimental ARDS. In Aim 2, we will examine the role of the NLRP3 inflammasome linking lung-brain inflammation in ARDS using transgenic AD mice also deficient in NLRP3 gene.

About Rebecca Heise, PhD

Dr. Heise is an Associate Professor of Biomedical Engineering and the Inez A. Caudill Jr. Distinguished Professor at Virginia Commonwealth University (VCU). She holds an affiliate appointment in the Department of Physiology and Biophysics at VCU and is a member of the Massey Cancer Center, the Institute of Engineering and Medicine, and the Center for Pharmaceutical Engineering. She earned her B.S. in chemical engineering with an additional major in Biomedical and Health Engineering from Carnegie Mellon University in 2003. She then earned her PhD in bioengineering from the University of Pittsburgh in 2008 and went on to complete her postdoctoral work in the Laboratory of Respiratory Biology at the NIEHS in Research in Triangle Park, NC. She joined the faculty of Biomedical Engineering at VCU in 2010. Dr. Heise's research focuses on pulmonary mechanobiology and regenerative medicine. She seeks to understand how the mechanical environment in the lung influences cellular behavior in health and disease with in vitro and in vivo models. Dr. Heise also researches the use of naturally-derived extracellular matrix as a biomaterial for cell and drug delivery to the lung. She has been awarded an R01 from the National Institute of Aging to study the effects of ventilator induced lung injury on inflammatory cell signaling, and she has earned a CAREER award from the National Science Foundation to study cell-ECM interactions in pulmonary fibrosis.

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ALZHEIMER'S AND RELATED DISEASES RESEARCH AWARD FUND

Natalie Dautovich, PhD, and Vivian Dzokoto, PhD

Virginia Commonwealth University

RESPECT: Restorative Practice for Black Caregivers' Stress

Black Americans are twice as likely to live with Alzheimer's disease or a related dementia as White Americans. Racial inequities in caregiving persist, with Black care partners providing significantly longer hours of care and receiving less respite than White care partners. Unfortunately, Black care partners of individuals living with dementia are at risk for a variety of negative outcomes including reduced psychological well-being, decreased quality-of-life, and poor sleep. Despite heightened stressors, Black care partners show numerous strengths such as more positive appraisals of caregiving, lower levels of psychological distress, and more positive affect in comparison with White care partners. Consequently, there is an urgent need to amplify Black care partners' strengths while addressing the stressors they face. Hence, we are proposing a randomized pilot study to test a novel investigation of breathwork as a simple, cost-effective, fast-acting, brief (five minute), accessible, and culturally-responsive approach for reducing Black caregiver stress. Across one year, we will assess the feasibility and acceptability of a one-month, recorded daily breathwork training program with 44 Black informal caregivers. We will also conduct descriptive analyses comparing the outcomes of the intervention to a waitlist control to determine if breathwork is associated with reduced stress and related outcomes commonly observed in caregivers. The study's findings will (1) support an NIH application, (2) serve as dissertation and preliminary exam data for two VCU doctoral students, (3) provide research training opportunities for VCU undergraduates, and (4) help to build community partnerships with black care partners.

About Natalie Dautovich, PhD

Dr. Natalie Dautovich is an Associate Professor of Psychology within the Counseling Program in VCU's Psychology Department. With a background in counseling, health and geropsychology, Dr. Dautovich is committed to reducing inequities by promoting better sleep health across the lifespan. She also serves as the Environmental Fellow for the National Sleep Foundation and is an Associate Editor for Sleep Health and Editor for the Journal of Behavioral Sleep Medicine. Dr. Dautovich has written over 70 peer-reviewed publications, 15 book chapters, and one book.

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ALZHEIMER'S AND RELATED DISEASES RESEARCH AWARD FUND

Megumi Inoue, PhD, MSW, RN, Michelle Hand, PhD, and Naoru Koizumi, PhD

George Mason University

Group Digital Gaming: Experiences of Older Adults Living with Dementia in an Activity for Cognitive Impairment

Slowing the progression of dementia as well as maintaining good behavioral and psychological symptoms are important aspects of life for people living with dementia and their caregivers. This study will use a group-based digital gaming system called Obie Technology as an intervention for individuals living with dementia at a local adult day health center. This gaming system aims to promote movement, stimulate cognitive activity, and encourage social interactions. A mixed methods approach with a pretest and posttest design will be employed to examine the effects of the intervention on cognitive function, mood, and behaviors in individuals with early or moderate-level dementia. The study will involve 40 participants from the adult day health center, who will engage in the intervention twice a week for 45 minutes over a period of 20 weeks. Standardized measurements will be used to assess participants' mood, behavior, and cognitive function at the baseline, the end of week 10, and the end of the intervention period. The intervention sessions will be observed, and direct feedback will be collected from the participants. Additionally, focus groups will be conducted to gather perspectives from their family members regarding the impact of the intervention. The aim of this study is to establish preliminary evidence through a small-scale intervention study that values the direct input of individuals living with dementia and their caregivers, regarding the potential impacts and appropriateness of this state-of-the-art, forward-thinking technology.

About Megumi Inoue, PhD

Dr. Megumi Inoue is an Associate Professor in the Department of Social Work at George Mason University. Her research is focused primarily on older adults with declining health who are vulnerable to losing autonomy and dignity. When older adults' physical and/or cognitive abilities are significantly deteriorated, their right to make decisions and right to be treated with respect are easily threatened. Her research seeks ways to avoid these unfortunate situations and to support vulnerable older adults. Dr. Inoue brings her extensive clinical experience as a social worker and a registered nurse to her understanding of these research areas.

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Commonwealth of Virginia

ALZHEIMER'S AND RELATED DISEASES RESEARCH AWARD FUND

Rebecca Haberman, PhD

Mary Baldwin University

Neuronal characterization of entorhinal circuits activated in resilience to age-dependent memory decline

Despite the increased identification of a variety of risk factors for Alzheimer's Disease (AD), age remains one of the most predictive components of AD risk assessment. Yet the underlying molecular and cellular brain alterations that accrue with age and contribute to risk are much less understood. The relationship between age and dementia is confounded by the observation that many older individuals maintain healthy cognitive function throughout life, including memory function. By understanding the cellular underpinnings of healthy aging, we can better construct therapies that treat or prevent disease. Healthy, aged Long Evans rats have been established as a model for the range of cognitive outcomes experienced by older people, and includes a population of aged rats that maintain memory function on par with young adult rats. Recent work has identified a set of brain regions critical for memory function and recruited during a cue mismatch memory task in aged rats with preserved memory. This aged brain activation pattern differs from that of young rats, even though behavioral performance on the task is equivalent. The proposed research aims to expand on these findings by identifying the specific cells activated with the cue mismatch task, beginning at young ages and then moving on to explore rats at older ages. The experiments will focus on the entorhinal cortex, a brain region that exhibits vulnerability to neurodegeneration in AD and exhibits differential activation in young and aged rats with equivalent memory task performance. Studying individuals over the aging process provides insight into the development of the brain state(s) associated with preserved memory with potential to improve both prevention and treatment of age-related memory loss and AD.

About Rebecca Haberman, PhD

Rebecca Parsons Haberman earned her BS in Psychology from Duke University and a PhD in Neurobiology from University of North Carolina, Chapel Hill. Her research during these years spanned a variety of topics from development of the olfactory system, to gene expression regulation in sea urchin embryos, to the use of viruses to mitigate seizure activity in epilepsy disorders. After obtaining her PhD, Dr Haberman spent 18 years as research faculty at Johns Hopkins University, investigating brain aging and Alzheimer's disease in rodent models with Dr Michela Gallagher. This research identified age-dependent brain mechanisms that heighten brain vulnerability to neurodegenerative diseases such as Alzheimer's disease. This research also examined brain mechanisms of resilience, or the ability to stave off memory loss and neurodegenerative processes at older ages. Based on this work, a potential Alzheimer's Disease preventative therapy is currently in clinical trial (hope4mci.org). Her current research interests extend from this work, investigating the changing role of specific sets of vulnerable neurons throughout the lifespan. By characterizing the aging of neurons that are initially targeted by neurodegenerative pathology, she hopes to identify life events or conditions that lead to resilient or degenerative phenotypes. In 2020, Dr Haberman made a career change to teaching, a lifelong dream, and joined the biology faculty at Mary Baldwin University. With this move, Dr Haberman hopes to make a positive impact on students, sharing her knowledge and enthusiasm for all things scientific. Here she continues research on memory and aging, hoping to engage and inspire the next generation of scientists.

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