

Alzheimer's and Related Diseases Research Award Fund

2014-2015 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 2014-2015 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).

GMU Robin Couch, PhD
Neuroprotection and Alzheimer's Disease

Nerve growth factor (NGF), a protein naturally produced in the brain, is capable of preventing neuronal cell death, such as that associated with Alzheimer's disease (AD). Recent preclinical and clinical AD studies have noted a reduction in the rate of cognitive decline upon treatment with NGF. However, because NGF is unable to penetrate the blood brain barrier, current means of delivering NGF directly to the brain are highly invasive and cost prohibitive. Oral drugs capable of stimulating the upregulation of NGF in the brain are preferred. To that end, this research group has identified protein kinase C (PKC) and several of its downstream effectors as critical to the upregulation of NGF protein. They used a series of protein specific agonists and antagonists to validate select members of the PKC signal transduction pathway, thereby highlighting them as promising targets for the development of new therapeutics for the treatment of AD. (*Dr. Couch may be contacted at 703/993-4770, rcouch@gmu.edu*)

UVA Erin Pennock Foff, MD, PhD and Benjamin Purow, MD
Investigating the Role of miR-762 in Mediating Disease in C9ORF72-Based Frontotemporal Degeneration

It is known that amyotrophic lateral sclerosis and frontotemporal dementia can be caused by a common genetic mutation in the C9ORF72 gene. The investigators discovered that a particular regulatory microRNA had high predicted affinity to bind this mutation, and questioned whether inappropriate binding of that molecule could contribute to disease process. In this funded project, they were able to demonstrate that: a) the predicted microRNA shows altered activity in blood and stem cells derived from patients with the disease, b) specific genes are misregulated in the cells in a manner consistent with microRNA disruption, and c) those disruptions may be contributing to some of the known features of the disease, including excitotoxicity to glutamate. These results constitute the most critical first steps in validating the investigators' proposed mechanism's potential role in mediating part of the disease phenotype. This initial data has also contributed to a new initiative in the lab to build more sophisticated model systems using three-dimensional stem cell cultures that will better approximate normal brain structure and cellular interactions. (*Dr. Foff may be contacted at 434/243-1006, epf4b@virginia.edu; Dr. Purow may be contacted at 434/982-4415, bwp5g@virginia.edu*)

Warren Memorial Hospital Jonathan Winter, MD and J. William Kerns, MD
Pharmacologic and Non-Pharmacologic Management of Behavioral and Psychological Symptoms of Dementia (BPSD): A Mixed-Method Pilot

Because antipsychotic medications (APs) for treating the behavioral and psychological symptoms of dementia (BPSD) can cause rare severe side effects (SE), an FDA Black Box Warning (BBW) was issued to reduce their use. This mixed methods study explored why roughly 20 percent of Virginia nursing home patients still remain on APs. Quantitatively, they trended the prescribing rates of all psychotropics in Virginia's Medicaid dementia population since the FDA BBW. Not only has AP utilization not decreased, but use of alternative medications for BPSD that have not been shown to be safer or more efficacious are increasing. Qualitatively, they assessed the experiences and perceptions of POAs and nurses (caregivers) about decision-making processes concerning pharmacologic/non-pharmacologic approaches to BPSD management. Caregivers feel that non-pharmacologic strategies (NPS) can work for most BPSD, but have limits. Community POAs also feel "on their own," in developing and utilizing NPS, with little help from physicians and inadequate supporting resources. Furthermore, caregivers see pharmacologic strategies as effective, especially if the 'right' medication is used in addition to NPS. What's more, no caregiver reported ever knowingly observing the severe SE of APs described by the BBW. These severe SE of APs were rarely discussed by physicians and poorly understood by caregivers. (*The investigators may be contacted at 540/631-3700, jwinter@valleyhealthlink.com, bkerns@valleyhealthlink.com*)

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GMU Joseph J. Pancrazio, PhD

Analysis of Amyloid Beta Effects with Living Neuronal Networks

Assays based on dishes of cells offer a means of screening potential therapeutics and accelerating the drug development process. In this study, the investigator used dishes of interconnected brain cells or neurons on electrical recording devices called microelectrode arrays to examine the effects of amyloid- β 1-42 (A β 42), a biomolecule implicated in the Alzheimer's disease process. The research showed that a special form of A β , oligomeric but not the monomeric, diminishes electrical activity from the network of neurons on the microelectrode arrays. This observation is important because clinical and animal model results suggest that the neuroactive form of A β is the oligomer and so the assay method is sensitive to the pathologically relevant form of the molecule. The effects of the oligomer are persistent over a period of at least 24 hours and do not appear to be associated with cell death. In addition, the researcher demonstrated that the excitatory receptors in the brain, that are triggered by the neurotransmitter glutamate, play a role in the effects of A β 42 on neuronal network activity. Exposure to blockers of these receptors modulated the time course of A β 42 oligomer effects on the neuronal networks. Pretreatment of the neuronal networks with two model therapeutics, methylene blue and memantine, reversed the effects of oligomeric A β 42. These findings suggest that cultured neuronal networks may be a useful platform in screening potential therapeutics for A β induced changes in neurological function.

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Virginia Doris T. Zallen, PhD, Golde Holtzman, PhD, and Kye Kim, MD

Tech *Evaluation of a Web-Based Decision Aid for People Considering a Genetic Testing for Alzheimer's Risk*

This team of investigators developed an online decision-aid prototype as an educational tool to help in making decisions about whether or not to use the APOE genetic test to estimate genetic risk for Alzheimer's disease. This prototype was evaluated by over 1,200 participants in a two-part (before and after) survey-based study. Both the quantitative data (the responses to the survey questions) and qualitative data (additional written comments from the participants) reveal a high level of satisfaction with the tool as a means of providing information relevant to this decision. Using feedback obtained in response to a request for suggested improvements to the tool, the prototype was re-designed to provide a greater ease of functionality and greater accessibility on a wide variety of platforms. In addition to validating the usefulness of this tool for individual decision-making, this study identified areas which may be the subject of future consideration by the medical community and by government agencies. These areas include: a) ways of encouraging the further creation of online tools as educational aids in making genetic-testing and other health-care decisions, and b) the consideration of policies to help ensure that consumers have adequate information as they consider genetic testing for Alzheimer's disease and other disorders. The enhanced decision aid will now be made available online at no cost to the wider public.

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UVA Zhiyi Zuo, PhD

Environmental Enrichment Reduces Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction (POCD) often occurs in patients 60 years of age or older. It not only affects daily living, but also is associated with increased death after surgery. Recent studies indicate that inflammation in the brain, an abnormal process for many chronic brain diseases including Alzheimer's disease, may be involved in POCD. This investigation employed environmental enrichment (EE) to test whether that non-pharmacological intervention could reduce POCD in aged mice. The results showed that EE reduced surgery-induced learning and memory impairment. The reduced brain cell generation needed for learning and memory was also attenuated after surgery. These results provide initial evidence to suggest that improved environment after surgery may be a potential way to reduce POCD. These data should help in the design of clinical studies to test the beneficial effects of EE in humans.

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