Alzheimer's and Related Diseases Research Award Fund

2017-2018 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, such as 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 School of Allied Health Professions at Virginia Commonwealth University. Questions about the projects may be directed to the investigators or the ARDRAF administrator, Dr. Constance Coogle (ccoogle@vcu.edu).

VCU **Heather Lucas, PhD**

Developing an Expression Platform for Tetrameric Alpha-Synuclein to Advance Systemic Biochemical Studies

The aggregation-prone protein α-synuclein (αS) has been linked to neurodegenerative diseases such as Alzheimer's disease (AD) and, more commonly, to Parkinson's disease and Lewy Body Dementia. This protein has been suggested as a modulator of cognitive function, yet its native function and disease-related conformation remain ill-defined. New findings have indicated the presence of a native tetrameric alpha-helical conformation that is stable to aggregation. A convenient method to isolate tetrameric αS for biochemical studies has yet to be reported, even though stabilization of this aggregation-resistant conformer may represent a viable therapeutic approach. Moreover, metal dyshomeostasis has long been linked to PD, but the influence of biometals on the aggregation propensity of tetrameric αS cannot be studied systematically until a robust method of accessing the tetramer is identified. Accordingly, an expression and purification platform will be developed for tetrameric αS that exploits fusion protein technology and relies on mild isolation techniques available through affinity chromatography, rather than conventional ion exchange chromatography methods that require high salt and dilute protein conditions. This platform will extend the reach of biochemical and biophysical investigations of αS, yielding valuable insight into a key protein that lies at the crossroads of several neurodegenerative diseases and setting the stage for the identification of new targets for drug development. ***(Dr. Lucas may be contacted at 804/828-7512, hrlucas@vcu.edu)***

VA Tech **Harald Sontheimer, PhD***

Is Amyloid Toxic for Glial Cells?

It is commonly assumed that amyloid contributes to functional impairment of neurons, albeit how amyloid is toxic to brain remains unclear. While plaques are found near neurons they are often close to brain support cells called astrocytes as well as along blood vessels. The astrocytes touch blood vessels throughout the brain and have been shown to support the integrity of the blood brain barrier (BBB) that prevent entry of blood born molecules into the brain. Astrocytes also regulate blood flow by releasing vasoactive molecules. The investigator has demonstrated that vascular amyloid separates the astrocytic attachments on blood vessels called endfeet. By forming a rigid cast around arterioles and penetrating arteries, the amyloid deposits hinder the release of vasoactive molecules and impair the regulation of blood flow. This funded study will now explore whether amyloid deposits also cause local impairment of blood flow and BBB integrity. The over-arching hypothesis is that amyloid impairs astrocyte function and therefore, vessel health and local regulation of blood flow. Obviously, impairments of blood flow will starve neurons of energy and could hasten their demise, thereby explaining the progressive dementia. These studies may show a completely unexplored pharmacological target. ***(Dr. Sontheimer may be contacted at 540/526-2229, sontheimer@vt.edu)***

VCU **Xuejun Wen, MD, PhD**

An In Vitro Model for Alzheimer's Disease based upon 3D Self-Assembled Neurovascular Microtissues

Conventional model systems that rely on in vivo transgenic/lesion and cell line studies are unable to capture the complexity and biology of the human system. As a result, therapeutic strategies that are efficacious in animal models fail in pre-clinical and clinical human trials. In order to improve the translational potential of experimental studies, establishing an in vitro humanized model for AD is imperative. The investigator previously fabricated an in vitro AD tissue model based upon 3D self-assembled neurovascular microtissues of primary AD cortical neurons and glia cells that are associated with microvasculatures. This project aims to validate the model through testing of neurovasculature-delivered drugs in comparison to 2D co-culture model and in vivo profile. Once validated, the in vitro AD tissue model would offer a stable experimental framework to facilitate AD modeling, and drug discovery and testing in a dynamic, high-throughput manner. The project would also define guidelines for the development of in vitro models of the specialized neurovascular tissue environment to advance understanding of healthy states and pathologies, identifying therapeutic targets, and drug testing. ***(Dr. Wen may be contacted at 804/828-5353, xwen@vcu.edu)***

VCU-Shenandoah Family Practice Residency **Jonathan Winter, MD***

Changes in Physician Approaches to Behavioral and Psychological Symptoms of Dementia since CMS's National Partnership to Improve Dementia Care

After CMS's 2012 initiative to reduce 'inappropriate' antipsychotic use in nursing homes, such prescribing decreased 27% in 4 years. Excluded from this calculation however were anti psychotics 'appropriately' prescribed for schizophrenia, Tourette's, and Huntington's. Over this same period, CMS described a greater than 20 percent increase in the reporting of these diagnoses. In addition, since the initiative's debut CMS has been careful to trend the prescribing of other psychiatric medications commonly used for dementia symptoms including anxiolytics, antidepressants, and sedative-hypnotics to ensure that medication substitution is not occurring as the use of anti-psychotics decreases. The investigator's previously funded ARDRAF study hinted that the use of other risky medications also used off-label for dementia symptoms in nursing homes (i.e., lithium and anticonvulsant mood stabilizers) have increased since 2012. Because utilization of these is not being trended by CMS, this study will retrospectively query de-identified data from the VA Department of Medical Assistance Service for rates of these diagnoses and medications since 2011. The objective is to better clarify how reactionary changes in diagnosing and prescribing distort the apparent reduction in pharmacologic solutions to dementia symptoms since CMS's 2012 National Initiative. ***(Dr. Winter may be contacted at 540/631-3700, jwinter@valleyhealthlink.com)***

VA Tech **Ling Wu, MD, PhD and Bin Xu, PhD***

Drug Repurposing for Tau Aggregation Inhibitors as Neuroprotective Agents for Alzheimer's Disease

AD is characterized by the accumulation of two types of abnormal structures, extracellular amyloid plaques and intraneuronal neurofibrillary tangles in brain. Small, soluble oligomers of the neuron-specific, axon-enriched, microtubule-associated protein, tau, the building blocks of the tangles, represent the most toxic molecular species in AD pathogenesis. Moreover, toxic, misfolded oligomers of both Aβ and tau self-propagate by prion-like processes, whereby their direct contact with normally folded counterparts catalyzes the latter's conversion into toxic, misfolded forms. This project will screen repurposed drugs from an NIH Clinical Collection library of 700 small molecules and identify compounds that can block tau oligomer formation and protect neurons from tau-induced cytotoxicity. Further tests will establish whether validated lead compounds from the screens and additional in vitro assays can protect cultured neurons from the adverse effects of extracellular tau oligomers.

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VCU **Shijun Zhang, PhD***

Development of NLRP3 Inflammation Inhibitors for AD

Neuroinflammation has been recognized as an essential player in the pathogenesis of AD, especially for the late-onset AD. Inflammasomes have been recently identified as multi protein complexes that tightly regulate the innate immune response and the production of pro-inflammatory cytokines, and the NLRP3 inflammasome is the most extensively studied and widely implicated. The NLRP3 inflammasome regulates the production of interleukins (IL-1ß and IL-18) and has been indicated as having a critical role in the pathogenesis of AD. The investigator recently developed small molecule NLRP3 inhibitors and one lead compound was identified with in vivo efficacy to reduce AD pathology and to improve memory functions. The goal of this study is to develop more potent analogs based on the newly identified lead structure. The results will significantly facilitate development of more potent inflammasome inhibitors as potential disease-modifying agents for AD.

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UVA **Zhiyi Zuo, MD, PhD***

Empathic transfer of postoperative cognitive dysfunction

Caregiving spouses of patients with dementia have an increased chance of suffering from dementia. Although the mechanism of this phenomenon is not clear, increased stress due to caregiving and similar living environments are thought to contribute to it. Postoperative cognitive dysfunction (POCD) is a relatively new but well-documented clinical entity that affects patients after heart and non-heart surgeries. POCD not only affects patients' daily activity but also predicts high mortality. Recent studies from the investigator's laboratory and others have indicated that inflammation in the brain, an abnormal process for many chronic brain diseases including Alzheimer's disease, may be involved in POCD. Preliminary data showed that mice living in the same cage with mice that have surgery also develop neuroinflammation and POCD. In this project, the investigator will determine how this empathic transfer works and which brain regions are activated in the cage-mates of the mice with surgery. These studies have a significant implication for bystander health and will help us understand how caregiving spouses of patients with dementia may develop dementia as well.

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2017-2018 ARDRAF Awards Committee

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