Commonwealth Health Research Board
FY 2017/2018 Grant Award Abstracts

Frank Castora, Ph.D., Eastern Virginia Medical School
The role of differentially expressed mitochondrial energy production genes as regulators of amyloid precursor protein processing in Alzheimer's disease

Project Summary: Alzheimer's Disease (AD) is the most common form of dementia in the elderly and within 10 years the number of Virginians with AD will climb to 160,000. Mitochondrial dysfunction is a critical component in the pathogenesis of AD where deficits in oxidative capacity and energy production have been reported. We have recently found abnormal expression of a number of genes critical to mitochondrial biogenesis and energy production in AD brains. These genes are involved in proteosomal degradation and aggregation of Aß peptides and senile plaques, hallmark features of AD. Using biochemical systems theory (BST), we have constructed a testable mathematical model for AD. We will confirm the role of these mitochondrial proteins in Aß aggregation and AD pathogenesis using CRISPR/Cas9 gene editing technology, with the goal of identifying new targets for therapeutic interventions designed to delay or modulate the onset of AD.

Kathryn Cole, Ph.D., Christopher Newport University
Anticancer Drug Design: Structure and Function of New HDAC8-Depsipeptide Complexes

Project Summary: Histone deacetylases (HDACs) play a critical role in the regulation of many biological processes, including cell differentiation, proliferation, senescence, and apoptosis. Aberrant HDAC activity has been implicated in a number of diseases, most notably cancer, making these enzymes validated targets for drug design. Indeed, four HDAC inhibitors (HDACi) have been FDA approved for the treatment of cancer. Depsipeptides are a new class of HDACi. These molecules bind to the catalytic zinc ion and make extensive binding interactions with the mouth of the enzyme active site, making them the most potent HDACi known to date. Spiruchostatin A and its synthetic derivative, Xyzistatin, are both analogs of one of the FDA approved HDACi. The research proposed herein investigates HDAC8 inhibition by Spiruchostatin A and Xyzistatin. We propose to measure HDAC8 inhibition and determine the structures of the HDAC8-inhibitor complexes to elucidate specific binding interactions and to develop more potent, second generation inhibitors.

Nicholas Farrell, Ph.D., Virginia Commonwealth University
Targeting Triple Negative Breast Cancer

Project Summary: This proposal aims to meet the overarching challenge of eliminating the mortality associated with metastatic triple negative breast cancer. This achievement will also meet the secondary overarching challenge to revolutionize treatment regimens by developing safe and effective interventions. A major goal of cancer research is to prevent metastasis and limit the primary tumor to a relatively localized site, allowing for more effective intervention at that site. The effectiveness of chemotherapy is limited by metastasis when the tumor spreads away from the primary site of occurrence, sometimes years later. The new treatment conceptualized is based on drugs that can act on multiple levels overcoming limitations of as single-targeted drugs. Development of new medicines which may simultaneously attack a range of targets, and with potential for personalized medicine based on genetic profile, would represent a significant addition to the anti-cancer armamentarium as adjuvant therapy in triple negative breast cancer.

Commonwealth Health Research Board
FY 2017/2018 Grant Award Abstracts

Babette Fuss, Ph.D., Virginia Commonwealth University
Regulation of myelin repair: the role of the actin cytoskeleton

Project Summary: Stimulation of endogenous progenitor cells represents a promising but yet unavailable therapeutic strategy for diseases in which the central nervous system (CNS) myelin sheath is affected. The most prominent of such diseases is Multiple Sclerosis (MS) but myelin injury may also play an important role in a number of neuropsychiatric diseases. Our studies proposed here investigate a conceptually novel molecular mechanism, namely the role of a calcium/calmodulin-dependent protein kinase IIß (CaMKIIß)-actin cytoskeleton axis, in regulating myelin repair in the CNS. These studies are pioneering in the sense that actin cytoskeleton regulatory mechanisms as part of the regulation of CNS remyelination are a highly understudied area, despite known defects in such mechanisms in MS. In the long-term, we anticipate these studies to lead to the identification of novel therapeutic targets for stimulating CNS repair under pathologic conditions that involve injury to the myelin sheath.

Matthew Hartman, Ph.D., Virginia Commonwealth University
Development of an oxygen-independent strategy for targeted phototherapy of cancer

Project Summary: Patients undergoing cancer chemotherapy treatments suffer from many severe side effects that would be diminished if the anticancer drug could be activated only in the vicinity of the tumor. In this proposal, we aim to develop a technology that will enable local release of a known anticancer drug, doxorubicin, at the site of a tumor using red light. The proposal itself will involve chemical synthesis of a form of doxorubicin that is blocked from activity because it cannot enter cells. Upon illumination the blocking group will be removed and the drug will enter the cancer cells to exert its antitumor effect.

Jia-Qiang He, Ph.D., Virginia Polytechnic Institute and State University
Biodegradable Microcapsules Containing Stem Cell Derived-Biological Pacemaker to Treat Mice with Bradycardia

Project Summary: Cardiovascular disease is one of the most prevalent and chronic illnesses in Virginia. In 2011, ~5.9% (~365,842) of Virginians was diagnosed with cardiovascular diseases, which was responsible for 13,332 deaths in our State (www.vahealth.org). Despite a better understanding of the systemic nature of cardiac arrhythmia and improved application of implantable electronic pacemaker devices, there are significant side effects associated with electronic pacemaker devices and no effective permanent means of treating these diseases. The proposed stem cell-derived beating biological pacemakers in combination with microencapsulation techniques are a highly innovative regenerative medicine strategy for the treatment of cardiac arrhythmias. Successful completion of the proposed study will establish the fundamental basis for stem cell/biomaterial-based personalized regenerative medicine to treat cardiovascular diseases and the approach can be potentially transferred to remedy other types of disorders, such as traumatic brain injury, thus offering enormous therapeutic potential for patients.

Commonwealth Health Research Board
FY 2017/2018 Grant Award Abstracts

Masahiro Sakagami, Ph.D., Virginia Commonwealth University

A salvianolic acid B-derivative: HIF1a/STAT3-directed VEGF stimulation for lung repair in emphysema

Project Summary: Emphysema progressively destroys lung's alveolar structures, leading to death, yet remains incurable, as no drug can repair its damaged lungs. With a new pathobiologic concept of epigenetic "vascular endothelial growth factor (VEGF) deficiency" that impairs adaptive angiogenesis/vasculogenesis and induces apoptosis in emphysematous lungs, we hypothesize that a methyl ester of salvianolic acid B derivative [**SMND309-ME**] is a novel dual-mechanistic VEGF-stimulating molecule for lung repair to reverse emphysema through modulation of upstream transcription factors, hypoxia-inducible factor-1*a* (HIF1*a*) and signal transducer and activator of transcription 3 (STAT3). This 2-year project will therefore examine SMND309-ME's HIF1*a*/STAT3-mediated 1) VEGF stimulation, 2) anti-apoptopsis, 3) promoted cell proliferation, migration and differentiation, and 4) functional and lung morphological recovery using in vitro lung cell (**Aim 1**) and in vivo animal (**Aim 2**) systems. Successful completion will offer SMND309-ME as a novel drug candidate and prove its HIF1*a*/STAT3-directed VEG stimulation strategy for lung repair to reverse emphysema.

Weibin Shi, Ph.D., University of Virginia

Characterization of reticulocalbin 2 as a major gene contributing to atherosclerosis

Project Summary: Atherosclerosis is the primary cause of heart attack and stroke. Inflammatory responses initiated by oxidation of LDL (bad cholesterol) trapped in the arterial wall are a central feature of atherosclerosis, but no effective medicines are available to intervene the inflammatory process due to lack of appropriate targets. Using mouse strains, we identified a major locus, Ath29, on chromosome 9 for atherosclerosis. Combined genetic and genome-wide gene expression analysis pinned Rcn2 down as a promising candidate for Ath29. RNA interference uncovered a crucial role for Rcn2 in both basal and oxidized lipid-induced inflammatory gene production in arterial wall cells.
Objective: Test the hypothesis that Rcn2 is a major gene contributing to atherosclerosis. **Approach:** We will make and characterize arterial cell-specific knockout mice to define the role of Rcn2 in atherosclerosis and arterial inflammatory responses.
Impact: Successful completion of this aim may derive a novel therapeutic target for treatment of atherosclerosis.

Erdem Topsakal, Ph.D., Virginia Commonwealth University

Implantable Biosensors for Long-Term Continuous Glucose Monitoring

Project Summary: Our goal is to design and implement subcutaneous, ultra-sensitive, miniature ZnO-based sensors for long-term continuous glucose monitoring. Owing to their direct contact with the interstitial fluid and excellent biocompatibility, these sensors will remain in the body fully functional for up to a year or more without any adverse effects. Moreover, these sensors will offer very high sensitivities (<< 1 *u*g/dL) compared to the current sensors (Enlite ™, Medtronic). The prolonged lifetime will eliminate frequent sensor replacement and increase the quality of lives of those living with Diabetes Mellitus. The proposed technology, based on patterned surfaces and nanostructures that significantly enhance sensitivity due to large surface-to-volume ratio, would allow miniaturization of sensing devices, thereby eliminating the extreme discomfort associated with the current bulky sensor technologies. To achieve our goal, we will explore different crystal orientations and forms, surface morphologies, and structures of ZnO for engineering sensors with controlled biodegradation and desired longevity.

Commonwealth Health Research Board
FY 2017/2018 Grant Award Abstracts

Bin Xu, Ph.D., Virginia Polytechnic Institute and State University

Molecular mechanisms of amylin as a novel contributor to Alzheimer's disease

Project Summary: Epidemiological studies have shown close link between obesity-related type 2 diabetes and the risk for Alzheimer's disease, but as yet the biological processes connecting these two diseases are not understood. Very recently studies have demonstrated that amylin peptides, typically formed in the pancreas, can possibly travel to the brain where they can form aggregates termed amylin amyloids. The link between the two diseases serves as the basis for the research outlined in this proposal. In particular, we will apply an interdisciplinary approach involving cellular, biochemical, animal model, medicinal chemistry, and computational methods to perform mechanistic studies of amylin amyloid-induced toxicity towards human neurons and toxicity inhibition by rationally designed small molecule inhibitors in cells and in an animal model. The outcomes from this project will serve as basis for a major research program to elucidate molecular connections between diabetes and Alzheimer's disease as well as to devise potential treatment strategies.