Commonwealth Health Research Board
Abstracts for 2016/2017 Grant Awards
(July 1, 2016 to June 30, 2017)

Robert Bruno, Ph.D., Old Dominion University
Chimeric mammary models for elucidating microenvironment contributions to tumor suppression and promotion

Project Summary: To reach the goal of eradicating breast cancer, we must focus on both treatment and prevention of the disease. Current understanding of tumorigenesis is as a multi-step process, requiring both mutations and non-mutating promotional influences. Current evidence suggests cells capable of making tumors exist within normal adult breast tissue but are suppressed by the normal, healthy microenvironment. Therefore, understanding the mutations that lead to cancer, while important, fails to fully explain why breast tumors develop. This proposal seeks to understand how normal mammary tissues are able to control the tumorigenic potential of mutated cells, and how these cells sometimes overcome this suppression to form breast tumors. Understanding these processes can lead to new diagnostic methods for detecting BC at its earliest stages, as well as new therapeutic strategies aimed at helping the body suppress and/or eliminate these potentially dangerous cells.

Anca Dobrian, Ph.D., Eastern Virginia Medical School
Is Twist-1 endothelial-derived microparticles a key link between obesity and cancer?

Project Summary: Obesity is a serious problem, heightening the risk for several illnesses including development of cancer. It has been estimated that 20% of all cancers are caused by excess weight. While a variety of metabolic factors and inflammatory molecules originating in the obese visceral adipose tissue have been proposed a the culprit for supporting survival and adaptation of malignant cells, the mechanism explaining this relationship is not clearly established. In this application we propose that the inflammatory milieu in obese adipose tissue leads to formation by vascular endothelial cells of microparticles, which carry to proximal tissues Twist-1, a key oncogene associated with aggressive epithelial cancers and resistance to chemotherapy. Targeting obese adipose tissue endothelium to prevent microparticle-mediated Twist-1 delivery to epithelial tumors may provide a conceptually new therapeutic approach to control metastasis and chemo-resistance in obesity-related cancers. The incidence of such cancers is estimated to triple in Virginia by 2030.

Alan Ealy, Ph.D., Virginia Polytechnic Institute and State University
Fetal Outcomes from Maternal Obesity Around the Time of Conception

Project Summary: The prevalence and severity of obesity in the United States has caused a severe rise in the incidence of premature death occurring from several obesity-related diseases (*e.g.* diabetes, hypertension). Unfortunately, the adverse health consequences of obesity are being passed on to our children and to their children. Children born from obese mothers have an increased risk for obesity. They also are at a higher risk for diabetes, hypertension, dementia and other diseases as adults regardless of whether they are overweight. Causative factors and potential treatments of these problems are not known. The overall goal of this work is to better define when during early pregnancy these adverse responses to maternal obesity occur. These findings will provide crucial new information that may be used by researchers, clinicians, and dieticians to curve the severity of the developmental problems resulting from intrauterine exposure to obesity.

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Raymond Enke, Ph.D., James Madison University

Molecular and bioinformatic analysis of epigenetic gene regulation in the normal and diseased retina: Characterizing pathways for diagnosing and treating macular degeneration

Project Summary: Sight, as interpreted by our visual system, is our most important sense and is critical for deciphering our surrounding environment. Though visual impairment is a significant public health problem in the US and worldwide, fundamental questions concerning dysfunction of the visual system remain unaddressed. We hypothesize that a mechanism of gene regulation largely unexplored in retinal neurons (epigenetic modification of genomic DNA) has a large contribution to the pathogenesis of blinding retinal diseases such as age-related macular degeneration (AMD). To test this hypothesis, our interdisciplinary and multi-institutional research team will characterize molecular mechanisms shaping the onset and progression of AMD in human ocular tissue. This study will advance our understanding of epigenetic gene regulation in the diseased retina and will be applied to develop hypotheses aimed at better understanding, diagnosing, and treating AMD.

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.

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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.

Dong Sun, M.D., Ph.D., Virginia Commonwealth University

Targeting NLRP3 inflammasomes to treat traumatic brain injury with a novel pharmacological inhibitor

Project Summary: Traumatic brain injury (TBI) is a major health problem. Currently, there is no effective treatment. Following TBI neuroinflammation is a prominent event that significantly exacerbates brain tissue damage causing functional deficits, thus targeting neuroinflammation is a promising treatment for TBI. Recent studies have found that NLRP3 inflammasome is associated to exacerbation of tissue damage following TBI. Therefore, molecules that inhibit formation of NLRP3 inflammasome represent a novel strategy for TBI treatment. Recently, we have developed NLRP3 inflammasome inhibitor, 16673-34-0. Our preliminary data have demonstrated that 16673-34-0 can reduce cortical brain tissue damage and neuronal cell loss in a TBI animal model suggesting its therapeutic potential. In this proposal, we will investigate the efficacy of 16673-34-0 and its molecular mechanisms for TBI. We hypothesize that NLRP3 inflammasome plays an important role in the progression of brain tissue damage following TBI; targeting NLRP3 inflammasome with 16673-34-0 will have therapeutic effect.

David Taylor-Fishwick, Ph.D., Eastern Virginia Medical School

New Drug Target for Diabetes

Project Summary: In Virginia, 9% of the adult population has diagnosed diabetes. Diabetes care consumes over $5,000,000,000 per year. A further 6% of Virginians have undiagnosed pre-diabetes. There is no cure for diabetes and available treatments are largely palliative. An urgent need exists for therapies that will halt or reverse diabetes progression. Dysfunction of insulin-producing beta cells is central to the development of diabetes. Cellular stress in response to inflammation drives beta cell dysfunction. Our recent studies have pioneered identification of a cellular enzyme in beta cells that mediates dysfunction. Applying a selective inhibitor of this enzyme in pilot studies protects beta cell function. The development and validation experiments proposed in this application are expected to generate the data to leverage significant federal funding to maximize the therapeutic potential from this discovery. The resulting successful progression to a diabetes therapy would have significant health benefits to citizens of Virginia.

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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.

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.