Commonwealth Health Research Board
Abstracts for 2015/2016 Grant Awards
(July 1, 2015 to June 30, 2016)

David Archer, M.D., Eastern Virginia Medical School

Dysfunctional Hemostasis and Inflammation in Women with Uterine Myomas and Heavy Menstrual Bleeding

Project Summary: Excessive blood loss during menstruation affects 8 to 15% of women and results in iron deficiency anemia. Excessive menstrual bleeding affects women's quality of life resulting in absenteeism, decreased home and work productivity, avoidance of social and recreational activities, and diminished interest in sexual intercourse. Current medical treatments do not control the excessive blood loss for many women. Hysterectomy cures excessive bleeding, but is associated with complications, death, and for young women, loss of fertility. During normal menstruation blood clots in the broken uterine blood vessels to limit blood loss, however, excessive bleeding occurs when blood clotting becomes abnormal. The purpose of this study is to evaluate the role of local uterine inflammatory factors on the blood clotting system in women with normal and excessive menstrual bleeding. The data from this study will identify new and more effective medical treatments for excessive menstrual bleeding.

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.

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.

Elizabeth Gilbert, Ph.D., Virginia Polytechnic Institute and State University

Using anorexic and obese chickens to identify targets for appetite regulation

Project Summary: Because 30% of adults in the Commonwealth are considered obese (CDC), Virginia is in considerable need of an effective anti-eating strategy. New perspectives on appetite may come from studying the anorexic and obese concurrently and perhaps even more so from non-mammalian models. The body weight selected lines of chickens, the only model of anorexia and obesity originating from common ancestors, existing only at Virginia Tech, have been selected for either low (LWS) or high (HWS) juvenile body weight for 55 generations and are comprised of anorexic and obese individuals. The objective of this study is to identify differentially expressed proteins between juvenile LWS and HWS in the hypothalamus, a region of the brain involved in appetite regulation. Identified peptides/proteins will be evaluated as potential pharmacological targets for manipulating appetite.

Kristian Hargadon, Ph.D., Hampden-Sydney College

The Role of Melanoma-derived Factors in Suppressing the Maturation, Activation, and T Cell Stimulatory Capacity of Dendritic Cells

Project Summary: The studies proposed in this grant application are aimed at understanding melanoma-associated suppression of dendritic cells (DC), innate immune cells that function as critical regulators of anti-tumor immune responses. Gaining mechanistic insight into the basis for melanoma-mediated suppression of DC maturation and activation and understanding the role of melanoma-altered DC in the induction of tumor-associated T cell dysfunction will enhance our understanding of tumor immune escape. Such findings have the potential to identify novel targets for interfering with melanoma-associated DC dysfunction, and they are likely to suggest immunotherapeutic strategies designed to improve the functionality of endogenous tumor-associated DC *in situ*, the efficacy of exogenous DC-based anti-tumor vaccines, and the overall quality of anti-tumor T cell-mediated immune responses.

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Helen I'Anson, Ph.D., Washington and Lee University
The role of snacking in early obesity onset in children

Project Summary: Alarming data on the percentage of overweight and obese youth in Virginia (22%), suggests an urgent need to study appetite regulation in appropriate animal models. Snack foods account for up to 27% of daily caloric intake in children and contribute significantly to excess energy intake and weight gain, however, there are no animal models that study the role of snacking in obesity onset during development. The proposed project will investigate the signals and mechanisms involved in early onset of obesity due to snacking using a newly developed female rat model. Insulin sensitivity, leptin resistance and serum metabolites will be monitored during the study. Tissues associated with development of metabolic abnormalities, such as visceral adipose tissue, liver and the hypothalamus of the brain will be studied for changes in relevant proteins and neuropeptides. Our results will inform clinical studies to develop appropriate interventions during early childhood and prior to obesity onset.

Deborah Kelly, Ph.D., Virginia Polytechnic Institute and State University
BRCA1-directed Transcriptional Regulation in Hereditary Breast Cancer

Project Summary: Today, women diagnosed with breast cancer have a higher chance of survival than ever before especially when detected early. However, triple negative breast cancer threatens the lives of many young women in Virginia. This form of breast cancer is extremely aggressive, more likely to recur and presents major challenges for treatment. Treatment options are limited and there is currently no known cure. We will investigate the actions of a prime culprit implicated in causing the disease, the protein factor, BRCA1. We will determine, in 3D, how BRCA1 interacts with other complex proteins poised on DNA to induce cancer. Having a 3D model to understand unique protein-DNA properties will greatly contribute to the design of new drugs that interfere with cancer-causing processes. We expect this will lead to new treatment options aimed at combating triple negative breast cancer and enhancing clinical outcomes.

Dongfeng Pan, Ph.D., University of Virginia
Tumor-targeted Delivery of Farnesylthiosalicylic Acid (FTS)

Project Summary: **Objective:** Enhancing anti-cancer efficacy of farnesylthiosalicylic acid (FTS) by targeted delivery. **Introduction:** FTS is promising candidate drug for breast cancer patients with resistant disease. However, its clinical efficacy is limited due to the poor pharmacokinetics and bioavailability. We have conjugated FTS with a small molecule tumor-targeting carrier. The conjugate exhibited improved inhibition efficacy against endocrine-resistance cancer cells compared to FTS and demonstrated highly targeted uptake into mouse xenografts. In this application we will validate its therapeutic efficacy in a preclinical setting. **Hypothesis:** Tumor-targeted delivery would enhance anti-cancer therapeutic efficacy of FTS. **Methods:** The parameters of pharmacokinetics, pharmacodynamics, and toxicity in animal model will be comprehensively studied and validated using live animal imaging and other relevant techniques. **Impact:** If succeeded, it will provide a new effective treatment for patients with relapse breast cancer from primary endocrine therapy. Furthermore, the same mechanism holds the potential for targeted delivery of other chemotherapy drugs.

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Tushar Shah, M.D., M.P.H., Eastern Virginia Medical School

Role of Novel Complement inhibitor in improving neurological outcomes in an animal model of Neonatal Hypoxic Ischemic Encephalopathy

Project Summary: Hypoxic-ischemic encephalopathy (HIE) is a condition in which brain damage is caused due to birth asphyxia or oxygen deprivation around the time of birth. HIE is a major contributor to the infant mortality rate in Virginia. The complement system, a critical part of inflammatory tissue damage, plays a major role in HIE. Several clinical trials have shown that reducing body temperature (hypothermia) improves survival and neurological outcomes in infants with HIE. Our bench-top experiments suggest that hypothermia increases complement activation, likely attenuating the benefits of hypothermia. Our lab has developed a compound (Peptide inhibitor of C1, PIC1) that blocks the complement system and potentially reduces brain damage due to complement activation. Our experiments aim to test PIC1 in newborn rats and demonstrate decreased brain damage. Our long-term goal is to develop PIC1 as an intervention to decrease mortality and improve neurological outcomes in infants with HIE.

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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Judith Voynow, M.D., Virginia Commonwealth University

Inhaled 2-O, 3-O desulfated heparin is a multifunctional anti-inflammatory therapy for cystic fibrosis lung disease

Project Summary: Cystic fibrosis (CF) is an inherited disease that causes abnormal airway mucus and recurrent bronchitis resulting in lung failure and death. A major cause of lung injury in CF is the high concentration in the airways of neutrophil elastase (NE), a product of white blood cells that degrades proteins. There are currently no effective anti-NE therapies to prevent the relentless progression of CF lung disease. Although heparin is an effective anti-NE and anti-inflammatory drug, it cannot be used in CF due to the risk of lung bleeding. A modified heparin, 2-O,3-O- desulfated heparin (ODSH), does not cause increased bleeding, yet maintains robust anti-NE and anti-inflammatory properties. **Therefore, we propose that ODSH will be an effective inhaled therapy to prevent progression of CF lung disease.** The CHRB proposal will generate critical preliminary data to test this hypothesis and to support preclinical toxicology for an FDA investigational New Drug application.