Commonwealth Health Research Board
Abstracts for 2011/2012 Grant Awards (July 1, 2011 to June 30, 2012)

Justin R. Anderson, Ph.D.
Radford University
Characterization of La Crosse virus receptors in mosquito tissues
[second year of a two-year grant awarded in FY 2010/2011]

Project Summary: La Crosse virus is transmitted by mosquitoes and causes a potentially severe encephalitis, primarily in children; Virginia has reported 17 cases in the past decade. This project has two main goals: to isolate and characterize the receptor(s) the virus uses to establish an infection of the mosquito host, and to identify genetic differences in the receptor between mosquitoes that can become infected and those that cannot. We will isolate the receptor protein and sequence the gene coding for the receptor in two transmitting mosquitoes. We will then isolate the same gene from non-transmitting mosquitoes to characterize genetic mutations responsible for virus binding. Our results will lead to the development of new methods to prevent transmission of La Crosse and other viruses, either through vaccine development or by genetically modifying the mosquito host. This is a collaborative effort between researchers at Radford University and Virginia Tech.

John Harrington, M.D.
Children's Hospital of The King's Daughters [CHKD]
Treatment of Behavior Disorders among School-Aged Children with Autism Spectrum Disorders [ASD]
[second year of a two-year grant awarded in FY 2010/2011]

Project Summary: This study will evaluate the efficacy of Parent-Child Interaction Therapy (PCIT) among school-aged children (5-12 years old) with ASD and behavior problems. Research demonstrates that this family-centered behavior therapy for disruptive behavior disorders significantly improves the child's behavior by changing the child-parent interaction, and the results generalize to the school environment. Due to the prevalence of behavior problems among children with ASD, novel treatments are needed to improve quality of life and academic success. We will evaluate the effectiveness of PCIT in reducing disruptive behavior and improving compliance during parent child interactions based on observed disruptive behavior during parent child interactions, parent- and teacher-reported disruptive behavior, and parent stress. Both Child and Parent-level outcomes will be examined at the pretest, during treatment, posttest, and 3 month follow-up. Findings will provide preliminary evidence to support a larger program of research into the treatment of behavioral problems among children with ASD.

Molly Hughes, M.D., Ph.D.
University of Virginia
Development of Novel Antimicrobial Agents for Multi-Drug Resistant Bacterial Pathogens

Project Summary: Since 1996, there has been a dramatic and alarming increase in the incidence of multi-drug resistant (MDR) Gram-negative bacteria, such as *Klebsiella pneumoniae*, causing human infections such as bloodstream infections and pneumonias. Multi-drug resistance among Gram-negative bacteria denotes resistance to three or more major classes of antibiotics. This increase in MDR Gram-negative bacteria has been recognized throughout the world and within the United States, including the Commonwealth of Virginia. Given the exceedingly few to no therapeutic options currently available, new strategies are urgently needed to fight these bacterial pathogens. We have been studying chemokines, which are proteins produced by cells of the human immune system in response to infections. Certain chemokines have demonstrated antibacterial activity against both Gram-negative bacteria (*Escherichia coli*) and Gram–positive bacteria (*Listeria monocytogenes*). Given our

experience working with the chemokines, we propose to study and develop these chemokines as novel antimicrobial agents against MDR Gram-negative bacterial pathogens.

Kylene Kehn-Hall, Ph.D.
George Mason University
BTK induction by HIV: Implications for Therapeutics

Project Summary: HIV-1 is the cause of the Acquired Immunodeficiency Syndrome (AIDS), a destructive disease of the immune system. Worldwide estimates of individuals infected with HIV-1 are 40 million and increasing. The 2008 estimate indicated that there are over 20,000 people living with HIV/AIDS in Virginia. Breakthroughs in treatment have been able to delay the onset of AIDS. The existence of a latent reservoir means that the virus can never truly be eliminated. In addition, current therapies for HIV-1 (HAART) can promote resistant strains of the virus. Therefore, there is a critical need for new targets for HIV therapy, which will not develop resistance. Therapeutics targeted against non-essential host proteins hold great promise to limit resistance. Our research is aimed at understanding the therapeutic potential of targeting Bruton's Tyrosine Kinase (BTK) in HIV-1 infected cells. Studying BTK could potentially lead to new treatment options for HIV/AIDS.

Mary Jayne Kennedy, Pharm.D.
Virginia Commonwealth University
Evaluation of mitochondrial gene sequence variants as biomarkers of aminoglycoside-induced renal injury in newborn infants
[second year of a two-year grant awarded in FY 2010/2011]

Project Summary: Aminoglycoside (AG) antibiotics are commonly used to treat infections in newborns. Despite their effectiveness, AGs can have harmful effects on the kidney. Approximately 7% of AG-treated infants develop kidney damage. This damage may affect kidney development and cause permanent structural/functional changes especially in premature infants whose kidneys continue developing after birth. Given the potential consequences, it is important to identify infants predisposed to injury before treatment is started so that alternate antibiotics can be used. Screening tools, however, are currently unavailable. Genetics are important in determining susceptibility to AG-induced hearing loss and it is possible that genetics may also influence susceptibility to AG-induced kidney injury. Therefore, the objective of this proposal is to investigate associations between genetics and AG-induced kidney damage. Ultimately, we may be able to reduce the number of AG-treated patients (adult and pediatric) who develop injury and improve the risk:benefit ratio of antibiotic treatment in Commonwealth citizens.

Frank Lattanzio, Ph.D.
Eastern Virginia Medical School
Development of a well tolerated, anti-angiogenic agent to treat drug resistant cancers

Project Summary: Cancer, in its many forms, is one of the two leading killers of all adult Virginians. For a solid tumor to survive, it must establish a network of functional blood vessels (angiogenesis). Halting this angiogenesis would control the progression of the disease. A number of agents directly or indirectly can stop angiogenesis, but all to date are non-specific and cause systemic toxicity and/or have limited efficacy. We have found an ophthalmological agent that specifically halts abnormal blood vessel growth without side effects in several ocular disease animal models and has the potential to serve as an anti-cancer drug that targets the tumor's blood vessels with minimal systemic toxicity, with a specific ability to treat tubulin-drug resistant tumors. We propose to evaluate this agent's *in vitro* and

in vivo characteristics in treating cancer. In addition, the agent may also serve as a biomarker to detect the presence of tumor-related blood vessels.

Masoud Manjili, Ph.D.
Virginia Commonwealth University
Sequential common gamma chain cytokines can expand tumor antigen-reactive T cells that are resistant to cancer-associated immune suppression & generate long-lasting memory responses against HER02/neu

Project Summary: Biological therapy for breast cancer by means of lymphocytes has had striking success against melanoma, but it has had only limited efficacy against breast cancer. This has been because of two main obstacles: 1) breast cancer increases a type of cells called myeloid-derived suppressor cells (MDSC) that suppress lymphocytes against the tumors; 2) even if MDSC are eliminated by other therapies, lymphocytes that are being used for the treatment cannot generate long-lasting memory against cancers. We have recently developed a protocol for growing lymphocytes in the culture such that they become resistant to immune suppressor cells and at the same time generate long-lasting memory against breast cancer. This treatment protocol was 100% successful in animal models. Such striking observation prompted us to test the efficacy of this protocol on the blood of breast cancer patients outside of patients' body before initiating a phase I/II clinical trial in breast cancer patients.

Aylin Rizki, Ph.D.
Virginia Commonwealth University
The role of MRE11/RAD50/NBS1 in ER/PR/HER2 Negative Breast Pre-Cancer Progression

Project Summary: Breast pre-cancers become life-threatening when they recur as invasive cancers that can spread to essential organs such as bone, lung, and brain. 10 – 30% of patients with pre-cancers progress and develop invasive cancers. Currently, our ability to predict which pre-cancers will progress is very limited. Here we propose to study the role that the MRE11/RAD50/NBS1 (MRN) complex plays in this progression. The project is based on our previous observations suggesting that MRN suppresses invasion in an estrogen receptor (ER)/progesterone receptor (PR)/Human Epidermal growth factor Receptor 2 (HER2) negative subset of breast cancers in addition to its well-known roles in genome stability. We will study the functional relationship between the MRN complex and ER/PR/HER2 in pre-invasive to invasion transition, and determine how well the expression of these proteins correlate with risk of pre-cancer to invasive cancer progression.

Jennifer Stewart, Ph.D.
Virginia Commonwealth University
Generation of Mice Deficient in Vesicular Monoamine Transporter-1: Potential Links to Schizophrenia
[second year of a two-year grant awarded in FY 2010/2011]

Project Summary: Schizophrenia is a disabling, chronic psychiatric disorder that is challenging to manage and costly. Although schizophrenia manifests in adults, it is thought to originate during early neural development. The human gene coding for vesicular monoamine transporter-1 (VMAT-1) recently advanced to the #2 position on the Schizophrenia Gene Database list of the most strongly associated genes linked to schizophrenia; however, the role of VMAT-1 gene mutations in schizophrenia is not known. Preliminary work has confirmed VMAT-1 gene expression in the brains of mice, indicating the mouse is a valid model for VMAT1 studies. The aims of the present study are to determine (1) both

behavioral and physiological effects of VMAT-1 gene knock-out (VMAT-1 deficiency) in mice and (2) effects of specific human VMAT-1 gene mutations on VMAT-1 transport activity in cultured cells. These studies represent an important first step in elucidating the role of VMAT-1 in schizophrenia.

Claretta J. Sullivan, Ph.D.
Eastern Virginia Medical School
Atomic force microscopy in sepsis research: A new look at bacterial membrane vesicles
[second year of a two-year grant awarded in FY 2010/2011]

Project Summary: Lipopolysaccharide (LPS), a molecule on the surface of bacteria, triggers the physiologic response that leads to sepsis. It is generally assumed that because LPS is attached to the bacteria, eliminating the bacteria will also eliminate the LPS. Recent reports that gram-negative bacteria produce membrane vesicles (MVs) ranging from 50-250nm in diameter which contain LPS raises questions about their role in disease. MVs are too small to detect in most filter-based diagnostic assays. Since they do not have the ability to divide, they are also not detectable in culture-based assays. Atomic force microscopy is emerging as an important tool in microbiology for high resolution imaging and nanomanipulation. The study of bacterial membrane vesicles is an opportunity to apply the technique in sepsis research for the first time. We propose novel experiments to investigate vesiculation as it occurs in individual bacteria and also to assess the impact of MVs on endothelial cells.

Arthur Weltman, Ph.D.
University of Virginia
Effects of exercise intensity on postprandial glucose disposal and endothelial function in pre-diabetic adults
[second year of a two-year grant awarded in FY 2010/2011]

Project Summary: Pre-diabetes affects 57 million U.S. adults and is associated with increased risk of cardiovascular disease. Pre-diabetics frequently experience exacerbated glycemic responses to a meal (postprandial hyperglycemia; PPH). High sustained blood glucose levels from a meal result in damaging free radical production, inflammation, and impairments in blood vessel function and for these reasons PPH has been linked to atherosclerosis. Aerobic exercise performed prior to a meal represents a viable and cost-effective approach to reducing the impact of PPH. Our lab has preliminary data to show that exercise, particularly high intensity exercise, results in lower blood glucose levels and improved blood vessel function in the post-exercise period. This study will examine the effects of acute exercise at varying intensity prior to a meal on blood glucose control and blood vessel function in pre-diabetics. The results of this study will help develop clinical exercise guidelines specific to this population.