Commonwealth Health Research Board
Abstracts for 2010/2011 Grant Awards (July 1, 2010 to June 30, 2011)

Anne B. Allison, Ph.D.
Mary Baldwin College
The Role of Arf6 in Directing Intracellular Traffic in Breast Cancer

Project Summary: Virginia has one of the highest rates of breast cancer mortality in the country. The proposed research investigates how an important regulatory molecule, Arf6, affects breast cancer pathogenesis. Normally, Arf6 regulates transport within the cell. Utilizing powerful quantitative approaches such as flow cytometry and deconvolution microscopy, we will analyze how Arf6 regulates the trafficking of two proteins with established roles in cancer progression, β1 integrin and EGFR. This research will determine how these trafficking processes malfunction in aggressive breast cancers and has the potential to instruct current therapeutic strategies. Results from this study will enhance our understanding of fundamental cell biology as well as breast cancer research.

Justin R. Anderson, Ph.D.
Radford University
Characterization of La Crosse virus receptors in mosquito tissues

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.

Mark L. Gabriele, Ph.D.
James Madison University
Establishing complex auditory circuits: Molecular mechanisms and functional implications for treating the hearing impaired
[second year of a two-year grant awarded in FY 2009/2010]

Project Summary: Hearing, performed by the auditory system, is one of our two most important senses and is critical for speech and language acquisition. Despite the significant incidence of hearing loss and new treatment strategies (e.g. cochlear and auditory brainstem implants), fundamental questions concerning the development, organization, and maintenance of auditory connections persist unaddressed and therefore unanswered. We hypothesize that a family of signaling molecules (Eph receptors and ephrins) are partly responsible for establishing functional circuits in the developing auditory system. In collaboration with the Department of Communication Sciences and Disorders at JMU and the Center for Developmental Biology at The University of Texas Southwestern Medical Center, we propose to determine the role of Eph/ephrin interactions in constructing frequency-mapped auditory circuits. An understanding of early auditory system circuit formation mechanisms will necessarily guide new design paradigms for treating the hearing impaired and their most appropriate means for intervention.

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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]

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.

Mary Jayne Kennedy, Pharm.D.
Virginia Commonwealth University
Evaluation of mitochondrial gene sequence variants as biomarkers of aminoglycoside-induced renal injury in newborn infants

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.

Woong-Ki Kim, Ph.D.
Eastern Virginia Medical School
Targeting of CD16+ Monocytes in HIV NeuroAIDS
[second year of a two-year grant awarded in FY 2009/2010]

Project Summary: The HIV epidemic is still raging in the United States, and the State of Virginia is not immune to this threat. Virginia State ranks 12th in number of reported AIDS cases in the country, and currently 18,425 persons are estimated to be living with HIV and AIDS in Virginia. While deaths associated with HIV infection have decreased thanks to effective antiretroviral treatment, dementia developed in HIV-infected patients continues to increase because individuals are living longer. Recent reports provide evidence that CD16+ monocytes, a type of white blood cells, emerge during HIV infection and that these cells correlate with cognitive impairment and HIV-associated dementia. To directly assess a pathogenic role of these cells, we propose the selective depletion of CD16+ monocytes with anti-CD16 antibody treatment in our well-characterized monkey model of HIV CNS

disease. Our novel approach to selectively target CD16+ monocytes could lead to an effective immunotherapy for HAD.

Jennifer Stewart, Ph.D.
Virginia Commonwealth University
Generation of Mice Deficient in Vesicular Monoamine Transporter-1: Potential Links to Schizophrenia

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

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

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.

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