Commonwealth Health Research Board
Abstracts for 2009/2010 Grant Awards (July 1, 2009 to June 30, 2010)

Mark L. Gabriele, Ph.D.
James Madison University
Establishing complex auditory circuits: Molecular mechanisms and functional implications for treating the hearing impaired

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.

John A. Hossack, Ph.D.
University of Virginia
Ultrasound-Triggered Release of Rapamycin from Microbubbles to Treat In-Stent Restenosis
(second year of a two-year grant awarded in FY 2008/2009)

Project Summary: Atherosclerosis, or closure of a blood vessel, leads to heart attack and accounts for more than 50% of deaths in Virginia. Current treatment of a diseased vessel is performed by deploying a metal stent to reopen the vessel. Unfortunately, due to complex cellular processes, sustaining a vessel's increased internal diameter for >6 months proves challenging. Even when the most advanced stents are used, the cells in the vessel proliferate resulting in vessel re-closure, and subsequent cardiac events. We address this critical problem by developing a new method to deliver a drug to suppress cellular proliferation. We will integrate ultrasound imaging with means of delivering antiproliferation drugs loaded into FDA-approved microbubbles. Following deployment of the metal stent, the drug-loaded microbubbles are perfused through the artery and focused ultrasound is used to rupture the bubbles and deliver the drug through the otherwise unbreachable cell membrane, increasing dose and thus preventing vessel reclosure.

Molly A. Hughes, M.D., Ph.D.
University of Virginia
Interaction of Host Chemokines with Pathogenic Bacteria: A Novel Antimicrobial Strategy
(second year of a two-year grant awarded in FY 2008/2009)

Project Summary: Chemokines are small proteins that are produced in response to a variety of infections and are involved in the host inflammatory response. We have found that three related chemokines called MIG, IP-10, and ITAC, exhibit antimicrobial effects on the spores and vegetative cells of the bacterium, *Bacillus anthracis*. Thus, these naturally occurring immune mediators may function as host antimicrobial agents in addition to their known function of recruiting white blood cells and other inflammatory cells to the site of infection to fight an invading pathogen. This would represent a novel mechanism by which the host combats pathogenic bacteria. By understanding the mechanisms by which chemokines inhibit *B. anthracis*, and given the increasing incidence of antibiotic-resistance amongst bacteria globally with the relative scarcity of new classes of antibiotics to counter the

emergence of resistance, this project may open up new therapeutic strategies for use against a broad range of pathogens.

Woong-Ki Kim, Ph.D.
Eastern Virginia Medical School
Targeting of CD16+ Monocytes in HIV NeuroAIDS

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.

Robert L. McKown, Ph.D.
James Madison University
Development of Novel Diagnostics and Treatments for Ocular Diseases
(second year of a two-year grant awarded in FY 2008/2009)

Project Summary: Lacritin is a human tear protein that stimulates tear secretion and promotes new cell growth. Recombinant lacritin is currently in preclinical animal studies as a new therapeutic to treat dry eye. It was recently discovered that recombinant variants of lacritin exhibit a potent antibacterial activity offering a new line of defense for the prevention and treatment of bacterial keratitis. We hypothesize that lacritin is a natural protector of the ocular surface and that topical application of human recombinant lacritin may promote wound healing and be an effective treatment for dry eye and bacterial ocular diseases. In collaboration with the University of Virginia, Eastern Virginia Medical School, and Walter Reed Army Medical Center Washington D.C., we propose to develop the first clinical immunoassay for human tear lacritin and pursue the development of recombinant lacritin as a novel therapeutic for wound healing and the treatment of ocular diseases.

Ke Sheng, Ph.D.
University of Virginia
Radiosensitization by Quantum Dot/Photofrin Conjugates
(second year of a two-year grant awarded in FY 2008/2009)

Project Summary: Cancers beginning or spreading to the liver or lungs are frequently lethal. Tumors too large for surgical removal are treated with radiation, however, killing these large tumors with radiation alone is limited by radiation damage to normal liver and lung tissue. Drugs that increase radiation cell killing are called radiosensitizers. We developed a novel radiosensitizer by chemically combining or conjugating a nanoparticle called a Quantum Dot, which creates light when exposed to radiation, to a drug called Photofrin, which is a photosensitizer that uses light energy to make oxygen chemically reactive resulting in cell death. This radiosensitizer kills 34% more tumor cells in cell culture studies than radiation alone. We propose to purify the conjugate, determine the optimal dose for radiosensitization in cell culture, and then determine the biodistribution, metabolism, toxicity, and efficacy of killing tumors in mice as a necessary step towards clinical development for human use.

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James E. Turner, Ph.D.
Virginia Military Institute

Estrogen's Role in Protecting the Cardiovascular System from Damage and Degenerative Diseases

(second year of a two-year grant awarded in FY 2008/2009)

Project Summary: There is an abundance of molecular, cellular, biochemical, animal model and human patient literature to support the concept that estrogen impacts the cardiovascular system in significant ways. Yet, in the face of all this evidence investigators and clinicians alike were puzzled by the fact that the recent Women's Health Initiative (WHI) trials involving hormone replacement therapy (HRT) were halted before they were completed due to complications involving an increased risk of stroke and lack of cardiovascular protection. More recent studies state that additional basic and mechanistic estrogen research has to be pursued to better understand how to best target estrogen for optimal cardiovascular effects. To help address this staggering cardiovascular health challenge, we propose to investigate the mechanisms by which estrogen enhances the health and development of heart muscle and blood vessel function after the trauma of estrogen loss, using the zebrafish 'listless' model of congestive heart failure.

Roshna Wunderlich, Ph.D.
James Madison University

Etiology of Gender Differences in Overuse Injuries: The Interaction of Hormones, Ligament Laxity and Footwear

(second year of a two-year grant awarded in FY 2008/2009)

Project Summary: Overuse injuries constitute a considerable portion of injuries in athletes and military recruits and cause extensive occupation-specific problems. Overuse/stress injuries are more frequently observed in women. As the number of girls and women in high-level sport and the military continues to increase, it is essential to address the roles of anatomy, physiology and biomechanics in presenting a different suite of injuries in males and females. This study takes advantage of a multidisciplinary team from 2 Virginia universities to examine this gender imbalance in overuse injuries. We use biomechanical and immunological techniques to examine specific hypotheses relating hormone levels, ligament laxity, foot shape and footwear to shock attenuation and plantar pressure distribution in a group of male and female collegiate athletes. Insight into the etiology of overuse injuries through a multidisciplinary examination of the relationships among hormonal fluctuations, anatomy and biomechanics is fundamental to the prevention of this complex problem.