# Commonwealth Health Research Board
# Abstracts for 2008/2009 Grant Awards (July 1, 2008 to June 30, 2009)

**Dianne Daniel, Ph.D.**
**Eastern Virginia Medical School**
***MCM7 and MCM8 in the Control of DNA Replication in Ovarian Cancer***
(second year of a two-year grant awarded in FY 2007/2008)

**Project Summary**: In the United States and in Virginia, ovarian cancer has the highest mortality rate of gynecologic malignancies and, for women, ranks the fifth most common cancer. At diagnosis most tumors have spread beyond the ovary. A hallmark of this cancer is the loss of control of cell proliferation. Mini-chromosome maintenance (MCM) proteins have been identified as essential for licensing the DNA for duplication in a controlled manner as the cell proliferates. Several MCM family members have been implicated as markers for epithelial-derived cancers. In 2003, we discovered a new family member, MCM8. In ovarian cancer, variation in MCM8 and elevated expression of MCM7 may be preferential indicators of tumor progression. This study of MCM7 and MCM8 will help elucidate the relationship between control of DNA replication and tumor progression in ovarian cancer.

**Joanna Goldberg, Ph.D.**
**University of Virginia**
***A novel vaccine approach to combat pathogenic bacteria: a focus on the category B biothreat agents causing meliodiosis and glanders***
(second year of a two-year grant awarded in FY 2007/2008)

**Project summary**: The need to have reliable and adaptable strategies of response in place to combat bacterial pathogens is more critical than ever before. *Burkholderia mallei* and *Burkholderia pseudomallei* are category B select biothreat agents that are responsible for glanders and meliodiosis, respectively. These are both highly virulent organisms, and would pose serious health threats, if intentionally released; there are currently no approved vaccines available for either of these pathogens. The ability of these bacteria to be weaponized as well as the increased travel of our military personnel and tourists to endemic sites prompts us to develop a vaccine to protect our citizens from these agents. The long-term goal of this project is to develop effective vaccines for these infectious agents as well as validate our approach to potentially combat any pathogenic bacteria, including hospital and community acquired antibiotic resistant bacteria, and disease-causing bacteria in contaminated foods.

**John A. Hossack, Ph.D.**
**University of Virginia**
***Ultrasound-Triggered Release of Rapamycin from Microbubbles to Treat In-Stent Restenosis***

**Brief 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.

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**Molly A. Hughes, M.D., Ph.D.**
**University of Virginia**
***Interaction of Host Chemokines with Pathogenic Bacteria: A Novel Antimicrobial Strategy***

**Brief 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.

**Frank A. Lattanzio Jr., Ph.D.**
**Eastern Virginia Medical School**
***Novel diagnostic methods and neuroprotective effects of synthetic cannabinoids in the treatment of glaucoma***

**Brief summary:** Glaucoma is the second leading cause of blindness in America. Traditionally, treatment offered by ophthalmologists to the glaucoma sufferer focuses upon reduction of intraocular pressure (IOP). Even with normal pressures, some patients may have progressive vision loss, indicative of so-called low-tension glaucoma. At this stage of detection, retinal cells have been irreversibly lost. We propose to use electroretinograms to find an earlier indication of the presence of the disease, when the cells can be spared through appropriate pharmacological interventions. To improve glaucoma treatment, we are studying the ability of new, novel drugs based on endogenous cannabinoids to protect the retina and optic nerve as well to lower IOP. We concentrate on topical application of these new drugs directly to the eye to avoid adverse effects on the rest of the body. The outcome of this research may have profound effects upon the way ophthalmologists detect, understand and treat glaucoma.

**Robert L. McKown, Ph.D.**
**James Madison University**
***Development of Novel Diagnostics and Treatments for Ocular Diseases***

**Brief 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.

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**Daniel E. Nixon, D.O., Ph.D.**
**Virginia Commonwealth University**
***The effects of recombinant interleukin-2 on gut mucosal immune integrity in patients infected with HIV***

**Brief summary:** HIV infection results in early and extensive intestinal "gut" mucosal inflammation and gut immune system ("T-cell") depletion. This permits toxic bacterial products including lipopolysaccharide (LPS) to "leak" into the blood circulation. Circulating LPS leads to harmful levels of systemic T-cell "hyper"- activation, resulting in accelerated total body T-cell destruction and progression to AIDS. Given subcutaneously, "recombinant interleukin-2" (rIL-2) has been shown to reduce T-cell hyperactivation. We hypothesize that the drug may mediate this effect in part by restoring special "regulatory" T-cells that both increase the number of gut T-cells and reduce gut mucosal inflammation. We intend to prove this by measuring a reduction in LPS and inflammation biomarkers using stored serum samples from a large rIL-2 study that VCU previously participated in. Demonstration that rIL-2 can reverse gut T-cell and mucosa damage caused by HIV could significantly impact the way we treat persons afflicted with this virus.

**Ke Sheng, Ph.D.**
**University of Virginia**
***Radiosensitization by Quantum Dot/Photofrin Conjugates***

**Brief 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.

**James E. Turner, Ph.D.**
**Virginia Military Institute**
***Estrogen's Role in Protecting the Cardiovascular System from Damage and Degenerative Diseases***

**Brief 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 proposed 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.
**Jason Rife, Ph.D.**

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**Virginia Commonwealth University**
***Arm/Rmt ribosomal methylation and antibiotic resistance***
(second year of a two-year grant awarded in FY 2007/2008)

**Project Summary**: Widespread antibiotic resistance now severely limits treatment options, particularly in patients hospitalized with life-threatening conditions such as burns and cystic fibrosis. The opportunistic gram-negative pathogens, such as *Pseudomonas aeruginosa and E. coli*, are commonly treated with aminoglycoside (AG) antibiotics. A recently discovered, new form of AG resistance in these pathogens has now rendered even front-line AGs, such as amikacin, clinically useless. This new resistance is conferred by a plasmid-borne gene, called *arm* or *rmt*, which codes for an RNA methylase enzyme that modifies the bacterial ribosome at the site where AGs bind. This new form of AG resistance presents challenges to circumvention that have not previously been confronted. The goal of this proposal is to fully characterize this newly discovered methylase enzyme at the molecular level. Data from our studies will be used for the design and discovery of inhibitor drugs that will neutralize this resistance mechanism and assure the continued effectiveness of AGs.

**Terrie Rife, Ph.D.**
**James Madison University**
***Understanding Transcriptional Changes of Nitric Oxide Synthase I Leading to Diabetes***
(second year of a two-year grant awarded in FY 2007/2008)

**Project Summary**: Decreased levels of the enzyme, Nitric Oxide Synthase 1(NOS1) due to diet may play a role in the increased susceptibility of obese individuals to diabetes type-2. Reduced production of NOS1 decreases glucose absorption and elevates blood glucose. Cultured rat brain and muscle tissues will be used to provide insights into which of NOS1's twelve promoters are responsible for the lowered NOS1 found in diabetics. Cultured tissue will be treated with insulin and advanced glycolation end stage products which are increased in type-2 diabetics. Secondly, rats fed high fat and carbohydrate diets that lead to the development of diabetes type-2 symptoms will be examined to understand what changes in NOS1 protein and mRNA expression occur during the development of the disease. These studies will lead to a better understanding of why obese individuals are more susceptible than the normal population to the development of diabetes type-2.

**Roshna Wunderlich, Ph.D.**
**James Madison University**
***Etiology of Gender Differences in Overuse Injuries: The Interaction of Hormones, Ligament Laxity and Footwear***

**Brief 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.