



CDMRP



Department of Defense

Peer Reviewed Medical Research Program



U.S. Army Medical Research and Materiel Command



Congressionally Directed Medical Research Programs

The Congressionally Directed Medical Research Programs (CDMRP) was born in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This resulted in the initiation of a unique partnership among the public, Congress, and the military, which has persisted and grown to encompass multiple targeted programs. The CDMRP has received almost \$5.4 billion in appropriations from its inception in fiscal year 1993 (FY93) through FY09. Approximately 9,500 awards have been made across 19 different programs through FY08. Funds for the CDMRP are added by Congress to the Department of Defense (DOD) budget annually to provide support for targeted research programs focused on a variety of cancers, genetic diseases, trauma-induced problems, childhood diseases, and other areas of health interest to military personnel and their families, the veteran population, and the general public. Under the auspices of the U.S. Army Medical Research and Materiel Command (USAMRMC), the CDMRP manages these programs from receipt of funds, through competitive selection of proposals and individual project performance, to award closeout.



Peer Reviewed Medical Research Program

Since 1999, the Peer Reviewed Medical Research Program (PRMRP) has supported research across a broad range of scientific areas with an underlying goal of enhancing the health and well-being of service personnel and their families and the veteran population.

Through FY09 (excluding FY07, in which no appropriation was made), Congress has appropriated \$444.5 million (M), which has supported approximately 325 research projects. Historically, military doctors and surgeons have pioneered medical breakthroughs, such as reconstructive surgery, the use of antibiotics, and kidney dialysis, in response to warzone needs. Research supported by the PRMRP to address near-term military needs continues this tradition. As with military medical research and its applications throughout history, PRMRP-funded research has many applications to civilian needs.

Because the military also provides medical services to millions of non-deployed personnel, their dependents, military retirees, and veterans, there is also a need to support research for a wide range of medical issues that affect this population, including children and the elderly.

The PRMRP is committed to funding research that will strongly impact the development and implementation of devices, drugs, or clinical guidance that will change the face of diagnosis and treatment for a wide range of clinical applications.



"The PRMRP is a wonderful program to identify research efforts from the best scientists in the world that benefit U.S. service members."

Carl Castro, Ph.D., Colonel, U.S. Army
U.S. Army Medical Research and Materiel Command
Joint Programmatic Review Panel Member

"It was very exciting and motivating to see so many people dedicated to help find and help fund research that could help people with cancer or other serious diseases. I have seen the intense commitment that people working to battle this beast have."

Ken Youner
Action to Cure Kidney Cancer
Consumer Peer Reviewer



VISION

Identify and fund the best medical research to protect and support the warfighters, veterans and all beneficiaries and to eradicate diseases that impact these populations.

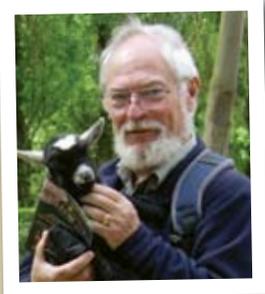
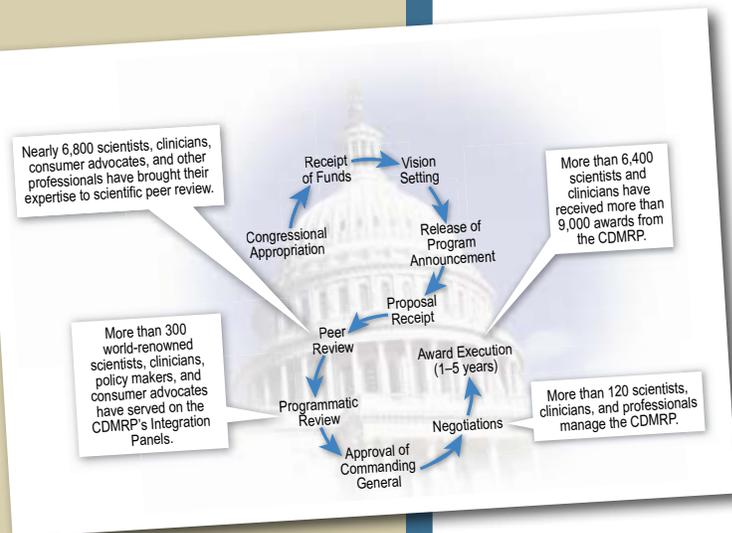
MISSION

Provide support for military health-related research of exceptional scientific merit.

Program Management

Members of Congress, consumer advocate communities, scientists and clinicians, and the DOD are working together to better understand a variety of disease processes, improve diagnostic procedures to increase accuracy and speed, and develop better therapeutic agents and devices. Congress appropriates funds and determines the topic areas for proposal solicitation.

The program management cycle includes a two-tier review process for proposal evaluation recommended by the National Academy of Sciences Institute of Medicine. The first tier of evaluation is an external scientific peer review of applications against established criteria for determining scientific merit and is conducted by members of panels composed of scientists and clinicians, who are subject matter experts, and consumers. The second tier is a programmatic review conducted by members of a Joint Programmatic Review Panel who compare submissions and make funding recommendations based on programmatic priorities, portfolio balance, scientific criteria, and mechanism-specific criteria. The Commanding General of USAMRMC issues the final approval for funding prior to award negotiations and execution of the proposed research project.



“The peer review process is so different from journal reviews because there are more inputs to the process, and the range of expertise assembled is far wider. This makes the discussions on proposals very stimulating, and one always comes away from the face-to-face sessions having learned something new. The inclusion of representatives from interest groups [consumer reviewers] is an important step forward, and they play a useful role in producing balance to the group. It makes the experts think about what they are saying more.”

John Horton, M.B.Ch.B.
World Health Organization
Scientific Peer Reviewer



“My experience with PRMRP has been very gratifying. My disease is very shame based and most people attach a stigma with addiction. The acceptance that I have experienced with the staff and scientists [of PRMRP] has been very humbling and rewarding. For an addict to come from the depths of this disease to working side by side with scientists and professionals committed to furthering the prevention and the recovery of addiction makes me realize we are not alone”

Jeannie Villarreal
Faces and Voices of Recovery
Consumer Peer Reviewer

Peer Review Panel

The PRMRP peer review panels are composed of respected scientists and clinicians with disease- or condition-specific expertise, as well as dedicated consumer advocates. Both groups work together to provide unbiased, expert advice on the scientific and technical merit of the proposals and their potential impact for patients and their families. Peer review panel members also evaluate the overall relevance of the proposals based on review criteria published for each award mechanism. Scientific reviewers for peer review are selected for their subject matter expertise. Consumer reviewers are nominated by an advocacy or support organization and are selected on the basis of their leadership skills, commitment to advocacy, and interest in science.

“I very much enjoy participating in and chairing CDMRP reviews. A truly unique [and beneficial] aspect of the PRMRP is the collaborative finalization of the reviews so that a coordinated and consistent evaluation is created for the applicant before the reviewers leave the panel meeting. I think this provides optimal feedback to the applicant on the strengths and weaknesses of the proposal.”

Kent Vrana, Ph.D.

***The Pennsylvania State University College of Medicine
Scientific Peer Reviewer***



“As a survivor, I was very happy to help provide a face to the patient population for the scientists participating on the panels. Being able to contribute as a survivor in some small way to cutting-edge research was a great experience for me.”

Jasan Zimmerman

***National Coalition for Cancer Survivorship
Consumer Peer Reviewer***



Joint Programmatic Review Panel

The PRMRP JPRP is composed of prominent and respected representatives of the military services, the Department of Veterans Affairs (VA), the Office of the Assistant Secretary of Defense for Health Affairs, and the Department of Health and Human Services. Members of the panel recommend the program vision statement and suggest a means to accomplish that vision through the program’s mission statement. Panel members develop investment strategies that meet the needs of the military, VA, and civilian communities. They review proposals and recommend the most programmatically relevant studies for funding.

“My total experience of participating in the PRMRP is one of humility and gratitude. That we have been honored with the opportunity to positively impact the lives of Warriors and their families through research is not taken lightly but greeted with passion and great reverence.”

DonnaMaria Jones, R.Ph., Pharm. D.

***Lieutenant Colonel, U.S. Air Force
Office of the Surgeon General***

Joint Programmatic Review Panel Member



Gregory Belenky, M.D., and Tom Balkin, Ph.D.
Walter Reed Army Institute of Research
Investigator-Initiated Research Award

Sleep loss has wide-ranging effects on neurobehavioral and cognitive performance. These effects are particularly problematic in combat environments where effective performance depends on execution of complex mental operations under stressful conditions. Dr. Belenky proposed to develop an effective sleep management system for optimizing individual mental performance. The proposed system encompassed several levels of monitoring and management ranging from a personal wrist-worn sleep/activity monitor to a mathematical performance prediction algorithm. As such, the system provides information on an individual's recent sleep/wake history and predicts performance capacity, informing the wearer and his/her chain of command of predicted military readiness—a metric that serves as an effective decision aid to military unit commanders. Dr. Belenky successfully developed an unobtrusive, wrist-worn actigraph with an embedded mathematical performance prediction algorithm for tracking activity and sleep periods. This has since been patented, licensed, and made commercially available. The system can be used to optimize the work schedule of individuals wearing the actigraph to maximize cognitive capacity during working hours and, thus, has both military and civilian applications. This work led to additional patents and is the subject of ongoing refinement and development by Dr. Belenky.



Publications:

- Balkin TJ, Bliese PD, Belenky G, et al. 2004. Comparative utility of instruments for monitoring sleepiness-related performance decrements in the operational environment. *J Sleep Res.* Sep;13(3):219-227.
- Belenky G, Wesensten NJ, Thorne DR, et al. 2003. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: A sleep dose-response study. *J Sleep Res.* Mar;12(1):1-12.

Patent:

- June 1, 2004. Patent #6,743,167. Method and system for predicting human cognitive performance using data from an actigraph.



Credits: Research Triangle Institute, d/b/a RTI International ("RTI").

Robert M. Bray, Ph.D.
Research Triangle Institute
Investigator-Initiated Research Award

Military recruits are subject to the forced abstinence of alcohol during basic and advanced training periods, but little is known about alcohol abuse among military personnel post-basic training and post-advanced training or the factors that help explain abuse, in the form of heavy episodic drinking, during post-training periods. Dr. Bray's research project was designed to investigate this phenomenon and to clarify the role of the military environment in alcohol misuse as well as the contribution of personal background and risk/protective factors that may mediate the relationship. The study examined the extent of alcohol and tobacco use

and related problems among junior enlisted personnel in the Air Force and Navy before they entered military service and after completing basic training. Results of the project provided information on the relative contribution of background factors and military service on the high rates of alcohol and tobacco use among junior enlisted personnel.

Analyses of alcohol use showed a rate of 43% heavy episodic drinking during the month prior to basic training, 16% by infrequent heavy episodic drinkers (five or more drinks per occasion at least once; four or more for women), and 27% by frequent heavy episodic drinkers (five or more drinks per occasion; four or more for women, at least once a week). Pre-basic frequent heavy episodic drinkers averaged 8 drinks per occasion and nearly 15 heavy episodic drinking days during the month. In contrast, heavy episodic drinking following basic training was substantially lower: 12% for infrequent heavy episodic drinkers and 9% for frequent heavy episodic drinkers. The rate of frequent heavy episodic drinking (27%) before joining the military was notably higher than the 18.5% among civilians in the same age group (National Survey on Drug Use and Health, Office of Applied Studies, 2006). Dr. Bray believes that this finding suggests that a disproportionate number of frequent heavy episodic drinkers may be self-selecting into the military and bringing potential drinking problems with them. Final results, supplemented with results from the 2005 Department of Defense Health Related Behaviors Survey, indicate that while the

"Findings from the present study have been helpful in providing evidence suggesting that military education, prevention, and intervention programs may be helping to keep rates of alcohol misuse lower than they were among young people prior to joining the military."

initial phases of military training sharply reduce frequent heavy episodic drinking, low post-basic training rates are likely to increase over time but probably not to pre-military levels. The study suggests that once in the military individuals learn the regulations and normative expectations about alcohol use and reduce their heavy episodic drinking habits, especially in the early days of training after the drinking ban is lifted. Expectations and norms in the military regarding frequent heavy episodic drinking likely help to prevent rates from returning to pre-service levels.

Publications:

- Bray RM, Brown JM, Pemberton MR, et al. Alcohol use after forced abstinence in basic training among United States Navy and Air Force Trainees. *Journal of Studies on Alcohol and Drugs*, in press (Jan. 2010).
- Green KJ, Hunter CM, and Bray RM. 2008. Peer and role model influences for cigarette smoking in a young adult military population. *Nicotine Tob Res* 10(10):1533-41.

- Volumetrically Controlled Manufacturing ■ Defense and Veterans Head Injury Program ■ Acute Lung Injury Research ■ Smoking Cessation ■ Alcohol Abuse Prevention Research ■ Digital Mammography Imaging ■ Sleep Management ■ Paget's Disease ■ Diabetes ■ **Militarily Relevant Disease Management** ■ Retinal Display Technology



Charles Engel, M.D.
Walter Reed Army Medical Center
Investigator-Initiated Research Award

Post-traumatic stress disorder (PTSD) is characterized by symptoms that include re-experiencing a traumatic event, avoiding reminders of the event or feeling emotionally numb, and hyperarousal. Individuals with PTSD experience psychological and physical comorbidity and consequently reduced quality of life. Overall, the effects of PTSD may have substantial economic costs to society. U.S. Army Colonel Engel proposed to clinically evaluate PTSD treatments for active-duty and veteran women, a population that had not been studied previously. He compared prolonged exposure, a form of cognitive behavioral therapy, to present-centered therapy, which is the approach used most often by VA clinicians. In prolonged exposure, a subject is asked to vividly recount a traumatic event repeatedly until the patient's emotional response decreases and to gradually confront safe but fear-evoking trauma reminders. Instead of focusing on trauma, present-centered therapy focuses on current life problems as manifestations of PTSD. In this clinical trial, 284 female veterans and active-duty personnel with PTSD were randomly assigned to receive prolonged exposure or present-centered therapy, delivered according to standard protocols in 10 weekly 90-minute sessions. Women who received prolonged exposure experienced greater reduction of PTSD symptoms than those who received present-centered therapy. The prolonged exposure group was 1.8 times more likely than the present-centered therapy group to no longer meet PTSD diagnostic criteria and 2.4 times more likely to have full remission of symptoms. The positive results achieved in this study provide evidence that prolonged exposure through repeatedly recounting a traumatic event can improve the symptoms and quality of life in female veterans and active-duty personnel suffering from this debilitating condition.

"Prolonged exposure therapy for the treatment of PTSD is today a recognized standard of care; it is a recommended treatment for PTSD according to both the Institute of Medicine and the VA/DoD Clinical Practice Guideline for the management of PTSD."

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Publication:

- Schnurr, P, Friedman MJ, Engel CC, et al. 2007. Cognitive Behavioral Therapy for Posttraumatic Stress Disorder in Women, A Randomized Controlled Trial; JAMA, 297 (8): 820-30.



Ivan Vesely, Ph.D.
Los Angeles Children's Hospital
Investigator-Initiated Research Award

Physiologically accurate three-dimensional modeling of soft biological tissues is a key component of successful telemedicine and surgical simulation efforts. Modeling of these tissues is extremely challenging because of their complex nature; however, Dr. Vesely has made great strides in this research area and has developed three models that span from microstructural to phenomenological. The first is a one-dimensional model of fractional order viscoelasticity that is representative of the hierarchical nature of complex biological tissues, which have a high water content and different layers of fibrous reinforcement. The second model is a micromechanical approach to modeling these tissues that incorporates biological material and geometrical nonlinearity, a system whose output is not proportional to its input. The nonlinearity is important in modeling biological materials because their elastic stress-strain relationship is nonlinear, having a fairly elastic nature that can quickly stiffen. Finally, he developed a computationally expedient and accurate constitutive equation to capture the dispersion of collagen fibers that is typical of biological tissues in three-dimensional fiber networks. These key pieces of technology form the foundation with which to study soft tissue behavior in more detail. However, they are not yet ready for implementation into surgical simulators due to their speed. Dr. Vesely hopes to further refine these models and implement them in faster hardware and software at which time he believes they can be incorporated in real surgical training systems.

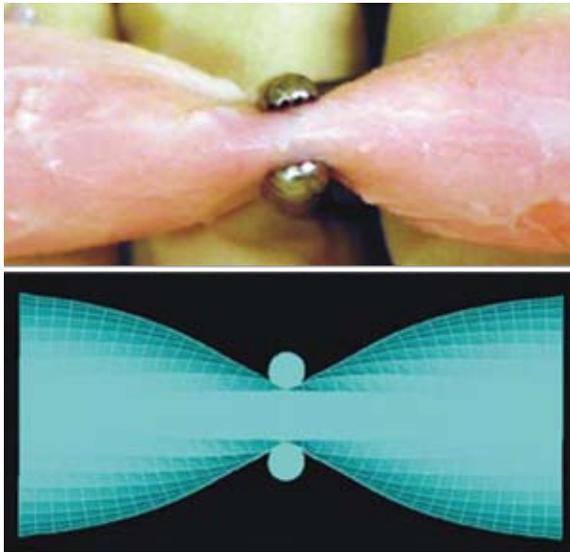
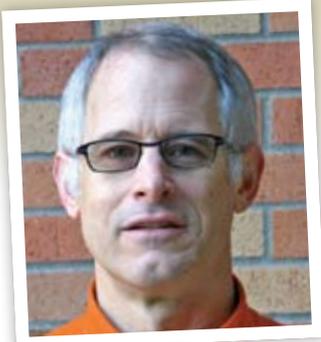


Image (top) of a pressurized segment of pig aorta being clamped with forceps, simulating one of the key features of virtual surgery training—manipulating tissues. The image on the bottom is an finite element analysis (FEA) simulation of the same condition, complete with fluid/solid interactions. By matching the deformed profiles of the FEA simulation to real experimental data of the same deformation, confidence can be had that the model matches reality. Tuning of such models can be done best through the inverse FEA methods.

Publications:

- Einstein DR, Freed AD, Stander N, et al. 2005. Inverse parameter fitting of biological tissues: A response surface approach. *Ann Biomed Eng* 33(12):1819-1830.
- Freed AD, Einstein DR, and Vesely I. 2005. Invariant formulation for dispersed transverse isotropy in aortic heart valves: An efficient means for modeling fiber splay. *Biomech Modeling Mechanobiol* 4:100-117.

- CAT Scan Technology for Lung Cancer ■ Venus 3-D Technology Program ■ Arthropod-Transmitted Infectious Diseases
- Dengue Fever Vaccine ■ Freeze Dried Platelets ■ Fungi Free (a topical anti-fungal agent effective in mitigating onychomycosis)
- Gulf War Illness Research ■ Smoking Cessation ■ Obesity-Related Disease Prevention, especially in minorities ■ Health System Information Technology ■ Remote Emergency Medicine Ultrasound ■ Molecular Biology for Cancer Research ■ Health Care Informatics ■ Vitamin D Research ■ **Medical Surgery Technology** ■ Neural Mechanisms of Chronic Fatigue Syndrome



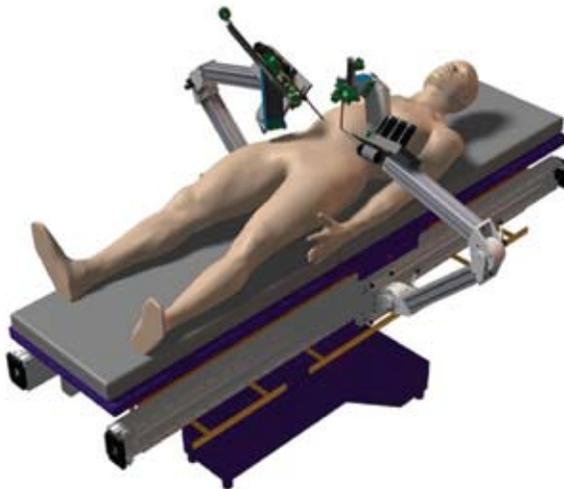
Credit: "University of Washington".

Blake Hannaford, Ph.D.
University of Washington
Investigator-Initiated Research Award

Timely access to a surgical unit is critical in emergency situations, such as those encountered on the battlefield. Unfortunately, all too often getting the wounded to the correct surgical team is problematic. Similarly, access to

"We recently completed a 24-hour experiment in which nine labs around the world adopted an Internet communication standard developed by our lab and experimentally verified all the possible interconnections between surgical control stations and surgical robots. The labs, in Europe, North America, and Asia, developed their systems independently and with totally different software architectures. However, the new communication protocol we developed was easy for them to integrate into their systems and successfully allowed teleoperation among these heterogeneous machines."

medical specialists is a global issue for individuals living in remote areas. For this reason, much work has been focused on expanding and enhancing telemedicine and telesurgery capabilities. The recent evolution of surgical robotics is the result of rapid progress in the field of robotics and telerobotics. Dr. Hannaford proposed to model, design, build, and experimentally evaluate a new surgical robot manipulator system. Through size reduction and dexterity enhancement (based on features of existing units), Dr. Hannaford envisioned a battlefield-ready telesurgery unit, which could reduce the time between injury and medical care. Dr. Hannaford began the project by evaluating the kinematics and the dynamics of surgeons performing several different minimally invasive surgical (MIS) tasks using a currently available robotic operating system in a porcine model. The resulting data were then used for the kinematic optimization of a spherical surgical robotic manipulator, which was then fitted to be teleoperated via a remote master device. Dr. Hannaford believes the surgical robotic manipulator will provide all the necessary movement degrees of freedom that manual MIS provides. The prototype surgical robot is currently undergoing further study.



Publications:

- Rosen J, Lum M, Trimble D, et al. 2005. Spherical mechanism analysis of a surgical robot for minimally invasive surgery analytical and experimental approaches. *Studies in Health Technology and Informatics–Medicine Meets Virtual Reality* (MMVR05) 111:422-428.
- Rosen J, Chang L, Brown JD, et al. 2003. Minimally invasive surgery task decomposition—etymology of endoscopic suturing. In: *Studies in Health Technology and Informatics–Medicine Meets Virtual Reality* 94:295-301.

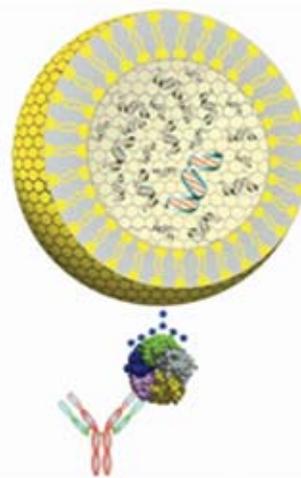


Jeffrey T. Mason, Ph.D.
Armed Forces Institute of Pathology
Investigator-Initiated Research Award

Critical to the protection against biological toxins that can be lethal at extremely low concentrations is early and rapid detection of the hazardous agents. Due to the potency of some biotoxins, such as botulinum toxin, current detection systems are often not sensitive or specific enough to perceive the biotoxins at levels that may be sufficient to cause harm. Dr. Mason proposed the development of a simple and reliable field-deployable assay system with both high specificity and sensitivity sufficient to detect less than 1 attomolar concentrations of biotoxins. Dr. Mason

developed an assay format that incorporates DNA-competent liposomes. DNA templates that will be used as surrogate markers of toxin levels are encapsulated into closed-shell liposomes containing biotoxin-specific fatty acid residues to bind the biotoxin of choice. The liposomes are placed into wells coated with antibodies that also will recognize and bind the biotoxin. Once the sample solution is added to the well the biotoxin in the sample will be captured by the biotoxin-specific antibody and will bind DNA-competent liposomes through the biotoxin-specific fatty acid residues. Because the antibodies are anchored to the wall of the well, liposomes and extraneous sample components that have not been bound by the antibody may be washed out of the well. The next step is to rupture the bound liposomes to release the encapsulated DNA. Amplification results of the released DNA templates using polymerase chain reaction (PCR) techniques will be used as surrogate markers indicating the amount of biotoxin present in the tested sample; the more liposomes bound, the more DNA released, the more toxin present in the sample. The resulting assay is called the liposome PCR (LPCR) assay. Dr. Mason can detect biological toxin concentrations lower than 1 attomolar in environmental samples, such as water, soil, and air samples, or biological specimen, such as urine. LPCR assays have been developed to detect cholera toxin, tetanus toxin, and botulinum toxin serotype A and are 100 to 1,000 times more sensitive than existing assays for these biological toxins. This assay format can measure biological toxin concentrations over a range of 5–6 orders of magnitude and is highly specific and sensitive, minimizing the potential for false-positive and negative results. Additionally, a single LPCR assay can analyze approximately 20 individual specimens in about 6 hours using instrumentation that is readily available in a large number of laboratories and in some field-based environments.

“Recently, the assay has been modified so that it can be used to detect any protein for which antibodies are available. This has greatly expanded the utility of the method, and assays to detect the HIV virus and carcinoembryonic antigen, a protein cancer biomarker, have been developed. The assay for carcinoembryonic antigen is 10,000 times more sensitive than the current clinical test for this protein.”



Pictorial representation of an immunoliposome. Shown are the bilayer (yellow), encapsulated dsDNA reporter (green with red bars), and monosialo-ganglioside GM1 receptor (blue). The immunoliposome is shown bound to a CTBS pentamer, which also is bound to a capture antibody.

Publications:

- Mason JT, Xu L, Sheng ZM, et al. 2006. A liposome-PCR assay for the ultrasensitive detection of biological toxins. *Nat Biotechnol* 24:555-557.
- Mason JT, Xu L, Sheng ZM, et al. 2006. Liposome polymerase chain reaction assay for the sub-attomolar detection of cholera toxin and botulinum neurotoxin type A. *Nat Protoc* 1(4):2003-2011.

Patent:

- September 1, 2009. Patent 7,582,430 Immunoliposome-nucleic acid amplification (ILNAA) assay.



Thomas J. Inzana, Ph.D.
Virginia Polytechnic Institute and State University
Investigator-Initiated Research Award

Francisella tularensis is a bacterium that causes tularemia, also known as “rabbit fever,” in humans and animals. Due to its ease of dispersion, its ability to survive for long periods in the environment under harsh conditions, and the fact that as few as 10 organisms can cause human disease, *F. tularensis* has been classified by the Centers for Disease Control and Prevention as a Category A bioterrorism agent that is likely to pose a national security risk. However, there is no vaccine currently available for protection against this infection. Relatively little is known about the

properties of *F. tularensis* that contribute to its virulence. It has been reported that a capsule-deficient mutant of the *F. tularensis* live vaccine strain (LVS) is less virulent than its parent strain, suggesting that a capsule encasing the bacterium is a potential virulence factor in *F. tularensis* pathogenesis.

“A photonic biosensor has been developed to detect *F. tularensis*, and is being revised to optimize sensitivity. A highly protective complemented mutant of a Type A strain has been developed, which will be tested in non-human primates and further characterized. A capsule-like complex (CLC) and the genes for the polysaccharide component of this CLC have been identified. Mutants of type A strains are being developed to evaluate as vaccine candidates.”

Dr. Inzana designed experiments to further examine the characteristics of the *F. tularensis* bacterial capsule, believing that it is a critical component of the bacterium in regard to resistance to host defenses, and in the future development of diagnostic tests and vaccines. While screening for mutants deficient in capsule, mutants of LVS and a clinical Type A isolate were identified that lacked the O-antigen of the lipopolysaccharide (LPS). Complete loss of O-antigen from the bacteria alters the surface phenotype and abrogates virulence in *F. tularensis*. However, it also compromises the induction of full protective immunity against *F. tularensis* infection in mice. When the mutation in the Type A strain was complemented, production of O-antigen was restored, but the complemented strain was still attenuated. Intradermal immunization of mice with this complemented strain resulted in protection against challenge with a high dose ($>10^5$ bacteria) of the virulent Type A strain. Although the basis for the attenuation in the complemented strain is not understood, studies are continuing on the molecular mechanism of the attenuation, and the level of attenuation and protection in nonhuman primates. Continued studies on the capsule have resulted in the isolation of a capsule-like complex (CLC) that is upregulated following passage of the bacteria in defined medium and culture for several days at lower temperature. It is possible that this CLC is the glycocalyx of a bacterial biofilm. The genes that encode for the proteins that synthesize the polysaccharide component of this CLC have been identified and several mutants generated. Mutations in the CLC polysaccharide locus are currently being made in Type A strains. In addition, O-antigen and CLC mutants are being combined with LPS-protein and CLC-protein conjugates, respectively, to determine the level of protective immunity such combinations can provide. Dr. Inzana is hopeful that conjugation of these polysaccharide components to the proper protein will induce a cellular immune response, which is required for protective immunity against tularemia. Furthermore, photonic nanoparticle biosensors have been developed to detect the LPS antigen and DNA targets, which can discriminate between Type A and B strains.

Publications:

- Li J, Ryder C, Mandal M, et al. 2007. Attenuation and protective efficacy of an O-antigen-deficient mutant of *Francisella tularensis* LVS. *Microbiol* 153:3141-3153.
- Inzana TJ, Glindemann G, and Snider G. 2004. Characterization of a wildtype strain of *Francisella tularensis* isolated from a cat. *J. Vet. Diagn. Invest.* 16:374-81.

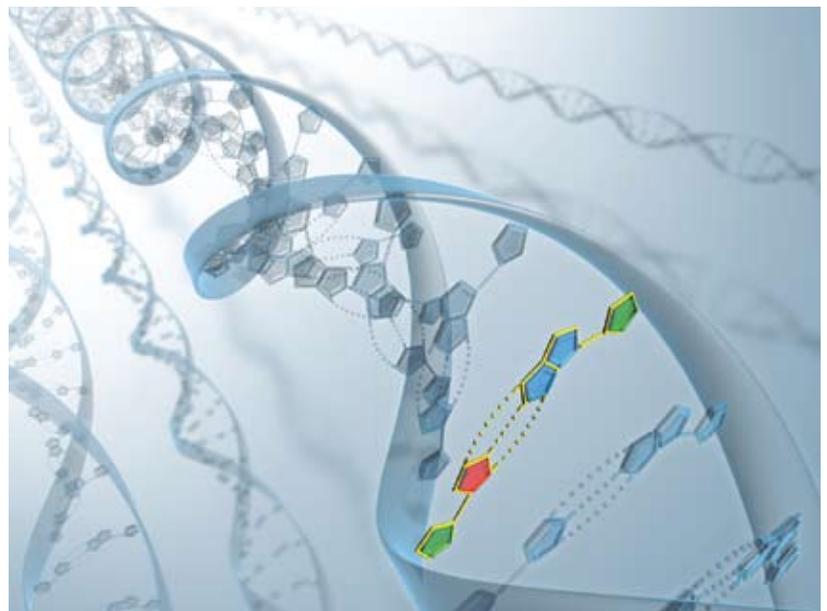


John Harmon, M.D.
Johns Hopkins University
Investigator-Initiated Research Award

Wound healing is a controlled, coordinated response to tissue injury leading to scar tissue formation. Growth factors are the key players in stimulating the wound repair process by signaling activation of cellular proliferation, stimulating migration of cells into the wound site, or synthesis of structural elements of the extracellular matrix. However, in infection and sepsis, both of which are often associated with war wounds, normal healing processes are disrupted, leading to a delayed

wound closure that can be devastating. Unfortunately, topical application of growth factors for managing healing in infection and sepsis shows limited success due to rapid degradation of growth factors by tissue proteases, enzymes that break down proteins. The use of DNA plasmid therapy, a form of delivery of therapeutic genes, has not been clinically acceptable due to its low efficiency. Thus, Dr. Harmon proposed to develop a more effective bioengineered gene therapy system that delivers growth factor plasmid DNA into wounds and promotes the healing process. A novel in vivo electroporation procedure, which increases the electrical conductivity and permeability of the cell plasma membrane, was optimized to enhance cutaneous DNA delivery and gene expression at the wound site and proved to be much more efficient than methods used previously. The procedure was successfully tested in a battlefield-simulated rat model of impaired wound healing using DNA encoding keratinocyte growth factor (KGF), a growth factor important for cell proliferation. Dr. Harmon showed that animals injected with KGF DNA at the wound border, with subsequently applied multiple short electroporative pulses, significantly improved the rate and quality of wound healing by day 12 as compared to the controls, which received KGF DNA only.

"We have ongoing preclinical trials as well as favorable biodistribution and toxicity testing."



Publications:

- Ferguson M, Byrnes CK, Sun E, et al. 2005. Wound healing enhancement: Electroporation to address a classic problem of military medicine. *World J Surg* 29:S55-S59.
- Marti GP, Lin MP, Qaiser R, et al. 2004. KGF-1 plasmid delivered with electroporation accelerates wound closure in diabetic mice. *J Am Coll Surg* 199:S59.

- Military-Relevant Disease and Injury ■ Army Nutrition Research ■ Blood-Related Cancer Research ■ Volume Angio CAT Research
- Social Work Research ■ Miniature Renal Assist Devices ■ Bone-Related Disease Research ■ Natural Toxin Detection Technology
- Cell Response to Anti-Cancer Agents ■ Mt. Sinai Cancer Research Program ■ Smoking Cessation ■ Casualty Care Research Center
- Chiropractic Care ■ Neuroscience Research ■ **Anti-Diarrhea Supplement** ■ Providence Cancer Center



Stephen Savarino, M.D., M.P.H.
Naval Medical Research Center
New Program Project Award

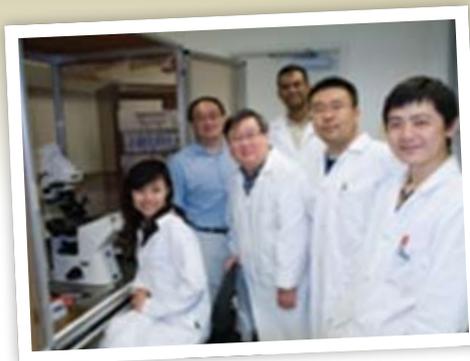
Diarrhea represents a significant health threat for both military and civilian travelers to developing countries. The military requirement for a solution to this problem is becoming even more acute as U.S. fighting forces have been increasingly concentrated in developing areas of the world. Diarrheal diseases exact a significant cost in terms of lost duty and effectiveness for our military and can have a debilitating impact on travelers. There is currently no licensed drug or biologic that provides a safe, effective mode of prevention, leaving an important deficiency in military

and travel medicine. Navy Captain Savarino and his team at the Naval Medical Research Center, collaborating with researchers at Johns Hopkins University and ImmuCell Corporation, identified the protein components of colonization factors (CFs) on the surface of the enterotoxigenic *Escherichia coli* (ETEC) organism that cause it to attach to the gut, which leads to disease. IgG antibodies were developed that could prophylactically treat diarrhea caused by ETEC. The research team used bovine milk (colostrum) to produce a volume of antibodies to these so-called intestinal adhesins and conducted a pilot trial to test the preventive power of the antibodies compared to a placebo preparation. Two different antibodies showed significant protection compared to the placebo controls.

“Scientifically, the research done under this program project demonstrated that this type of adhesive protein component of bacterial fimbriae is a protective antigen. This is the first time that this has ever been demonstrated in human studies for any such proteins of this class.”

To continue testing the efficacy of different antibodies, CAPT Savarino needed to develop a human challenge model of diarrhea with two different strains of ETEC, one producing the CF called CS17 and another CF, CS19. A CS17-ETEC challenge model was successfully developed and subsequently used to test a second round of bovine colostrum antibody preparations. While two different CS19-ETEC strains were evaluated in volunteers at increasing doses, the one strain that caused disease fell short of the target attack rate of 80% at the highest dose tested in these studies. Interestingly, for both the CS17-producing and CS19-producing ETEC types, the group’s findings for the first time offer clear evidence of the importance of these CFs in human disease. In this regard, CAPT Savarino and his multidisciplinary research team have made significant strides toward development of new tools for the testing of travelers’ diarrhea prevention strategies. Moreover, this team has clearly established proof-of-principle for the preventive efficacy of an anti-adhesin immunoprophylactic treatment based on cow’s milk against a significant health hazard for both military and civilian populations.





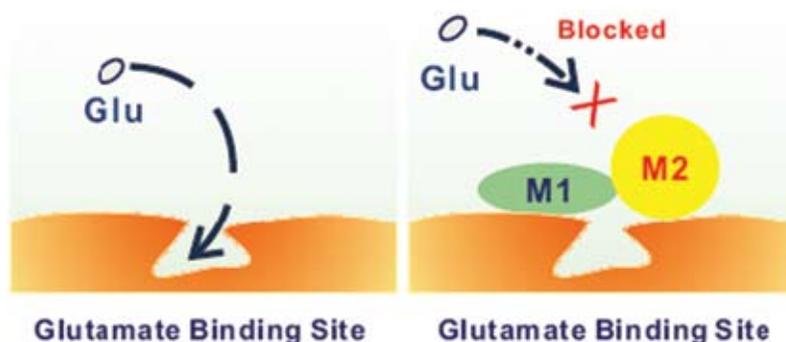
Li Niu, Ph.D.
State University of New York at Albany
Investigator-Initiated Research Award

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal neurodegenerative disorder in which, for reasons that are not well understood, the nerve cells of the brain and spinal cord that control voluntary muscle movement gradually deteriorate.

There is no known

therapy to effectively halt the progression of ALS. Studies have shown that men and women who have served in the U.S. military are 60% more likely than civilians to develop a fatal muscle-wasting disease such as ALS. Mechanistically, excitotoxicity or overstimulation of glutamate receptors, resulting in an exaggerated influx of calcium and cell death, is thought to be one of the leading causes of ALS. Dr. Niu is targeting the excitotoxicity pathway in the hope of developing drugs for treating ALS patients. He and his team focused on GluR2Qflip, a key α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit that controls the amount of calcium ions that enter neurons. The rationale for this choice is that riluzole, the only therapeutic drug available for ALS patients, is an inhibitor of presynaptic release of glutamate, the natural neurotransmitter that activates the glutamate receptors. When glutamate receptors are excessively active, a higher level of calcium will flux into the cells, and intracellular calcium overload is toxic to cells. In keeping with this rationale, a number of investigators believed that targeting postsynaptic AMPA receptors by using inhibitors was a logical step toward developing an effective drug for ALS. However, water solubility of almost all existing, small-molecule inhibitors has been historically problematic. In a novel approach, Dr. Niu has been pursuing identification of potent, water-soluble inhibitors called RNA aptamers, which directly inhibit AMPA receptor function. To date, his research group has identified two aptamer classes that inhibit the GluR2Qflip activity with nanomolar potency. Dr. Niu believes that these RNA aptamers represent novel and promising lead compounds for drug development for an effective ALS therapy.

"Our aptamers represent a new class of drugs and will allow us to rigorously test the hypothesis of excitotoxicity in neurodegeneration and in ALS. Practically it would offer a new drug for ALS therapy."



Publications:

- Huang Z, Pei WM, Han Y, et al. 2009. One RNA aptamer sequence, two structures: A collaborating pair that inhibits AMPA receptors. *Nucleic Acids Research* 37:4022-4032.
- Pei W, Huang Z, Niu L, et al. 2007. GluR3 flip and flop: Differences in channel opening kinetics. *Biochemistry* 46:2027-2036.

Patent:

- October 13, 2009. Patent 7,601,823. Nucleic acid inhibitors of glutamate receptors.

- Pseudofolliculitis Barbae ■ Anti-Diarrhea Supplement ■ Smoking Cessation ■ Epilepsy Research ■ Geneware Rapid Vaccine Development ■ Interventional Cardiovascular Magnetic Resonance Imaging Technologies ■ Muscle Function Research ■ Malaria Vaccine Initiative ■ Osteoporosis and Bone Related Disease Research ■ Paget's Disease ■ Amyotrophic Lateral Sclerosis
- **Limb Loss and Paralysis Research** ■ Providence Cancer Research Project



Credits: Courtesy of the Louis Stokes Cleveland Department of Veterans Affairs Medical Center

Ronald Triolo, Ph.D. Case Western Reserve University Investigator-Initiated Research Award

Lack of mobility and limited accessibility remain serious problems for veterans with spinal cord injury despite advances in medical management and the passage of the Americans with Disabilities Act. In addition to restricting physical access to many environments and

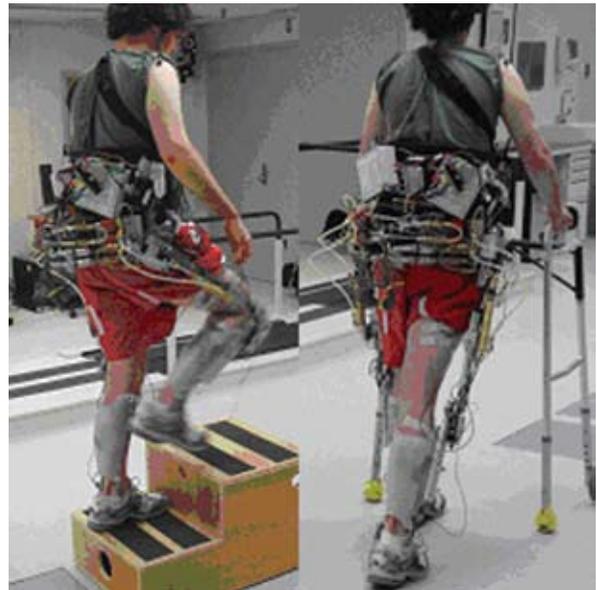
"This project will contribute significantly to the intrinsic autonomy of individuals with paralysis by providing a novel means to exercise, negotiate uneven terrain, and overcome the physical barriers to personal, professional, and social opportunities, and life experiences. Military personnel rendered wheelchair dependent due to paralyzing injuries sustained from blast or other orthopaedic trauma will benefit directly from this research."

life opportunities, immobility and wheelchair dependence cause degenerative changes in the bones, joints, heart, lungs, and skin.

Dr. Triolo and his research team have developed a prototype hybrid neuroprosthesis that enhances personal mobility for paraplegics that may one day provide them the means to stand, walk, and even exercise while simultaneously preventing or reversing the deleterious effects of paralysis.

This neuroprosthesis incorporates real-time control coordinated with exoskeletal bracing and implanted functional electrical stimulation (FES) to simulate natural movement. It has joints that unlock during movement powered by contractions, through FES, of the otherwise paralyzed muscles and then lock again to rest the muscles during phases when joint angles do not change. The controller structure includes a gait event detector, which coordinates the actions of controllers for the trunk, hip, knee, and ankle with FES to adjust the stimulation delivered to each muscle, producing feedback for a more normal gait.

Some of the new technology employed in the prototype includes a variable constraint hip mechanism (VCHM) designed to maintain posture while allowing for uninhibited sagittal hip movement. The VCHM provides good hip and trunk stability and erect posture without interfering with functional lower extremity dynamic movements during walking and stair climbing. The hydraulic knee mechanism has been redesigned for added strength and versatility and is being performance tested. The trunk support provides variable firmness in different planes of support. It stiffens more while the user is standing or walking but disengages during sitting to provide unencumbered motion and more comfort. The neuroprosthesis is now undergoing human testing in both paraplegic and able-bodied subjects in a pilot study.



Courtesy of the Louis Stokes Cleveland Department of Veterans Affairs Medical Center

Publications:

- Kobetic R, To CS, Schnellenberger JR. 2009. Development of a hybrid orthosis for standing, walking, and stair climbing after spinal cord injury. *J Rehabil Res Dev* 46(3):447-62.
- Kern N, Majewski T, Triolo R, et al. 2009. A locking compliant device inspired by the anatomy of the spine. *ASME Journal of Mechanical Design*. 131(1):014501-3.



Horace DeLisser, M.D.
University of Pennsylvania
Investigator-Initiated Research Award

Disparate processes ranging from wound healing to tumor growth rely on the formation of new blood vessels, a process known as angiogenesis. Impaired angiogenesis can lead to delayed wound healing whereas excessive angiogenesis contributes to the growth and spread of tumors. Therefore, correct regulation of angiogenesis is critical, and a better understanding of angiogenesis is crucial for treating a variety of diseases and disorders. Platelet endothelial cell adhesion molecule-1 (PECAM-1) is a transmembrane glycoprotein expressed on endothelial cells (ECs)

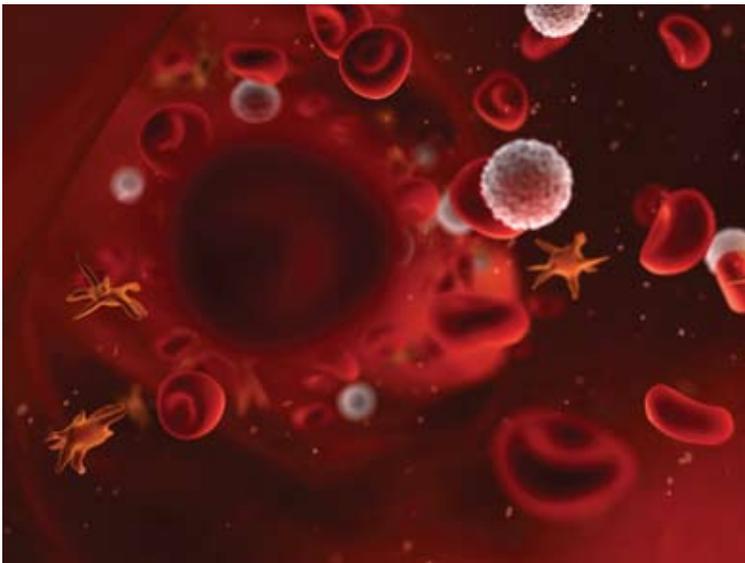
that line the circulatory microvessels and that are the central cellular actors during angiogenesis. However, the precise role of PECAM-1 during angiogenesis is not fully understood. During in vivo angiogenesis, endothelial PECAM-1 interacts

with proteins it recognizes (ligands); this initiates intracellular signaling cascades that facilitate EC motility without which angiogenesis cannot occur. Dr. DeLisser believed that these PECAM-1-dependent ligand interactions trigger PECAM-1 activation and subsequent association with the signaling molecule SHP-2. This process, in turn, was theorized to facilitate the recruitment of SHP-2 to the membrane surface where SHP-2

mediates cellular activities that enhance EC motility. Dr. DeLisser has found that administration of an anti-PECAM-1 antibody or the loss of PECAM-1 inhibits EC migration and blood vessel formation in animal models of angiogenesis. This effect occurs without impacting cellular proliferation

“The formation and continued presence of blood vessels are critical to the growth and spread of tumors. Consequently, the specific targeting of the blood vasculature already has and will be more so in the future an active area on investigation for novel anti-cancer therapy. Anti-PECAM-1 therapy may thus one day be part of the treatment of tumors.”

or survival. He therefore believes that, based on these ongoing studies and other results, therapy targeted at PECAM-1 is likely to be well tolerated. However, given the important role of PECAM-1 in the recruitment of white blood cells into sites of infection or injury, Dr. DeLisser believes that only human clinical trials will serve to establish the ultimate safety of anti-PECAM-1 therapy.



Publications:

- Cao G, Fehrenbach ML, and Williams JT. 2009. Angiogenesis in platelet endothelial cell adhesion molecule-1-null mice. *Am J Pathol* 175(2):903-915.
- Cao G, Savani RC, Fehrenbach M, et al. 2006. Involvement of endothelial CD44 during in vivo angiogenesis. *Am J Pathol* 169(5):325-336.

- Alcoholism Research ■ Social Work Research ■ Anti-Radiation Drug Development ■ Obesity Research ■ Volume Angio CAT Research ■ Chronic Pain Research ■ Duchenne's Disease Research ■ Amyotrophic Lateral Sclerosis ■ Acellular Human Tissue Matrix Research ■ Conjugate Vaccines to Prevent Shigellosis ■ Orthopaedic Extremity Trauma Research ■ Epilepsy Research ■ **Diabetes Research** ■ Blood-Related Cancer Research



Pere Puigserver, Ph.D.
Dana-Farber Cancer Institute/Harvard Medical School
Investigator-Initiated Research Award

Homeostatic mechanisms function to maintain a narrow range of blood glucose levels in response to hormones released within the body as well as nutrients ingested. However, these tightly regulated mechanisms can become dysregulated through a variety of factors. For example, high stress and intense exercise conditions combined with food deprivation make Soldiers very vulnerable to changes in blood glucose levels. Additionally, glucose homeostasis is highly dysregulated in metabolic diseases, such

as obesity and diabetes, which are on the rise in many populations. Due to the widespread, negative impact of glucose homeostasis dysregulation, Dr. Puigserver proposed to study a biochemical process that controls blood glucose levels through the control of hepatic glucose synthesis. Specifically, Dr. Puigserver wished to decipher how two proteins, CCDC101 and

WDR18, regulate the key metabolic transcriptional coactivator PGC-1 α . Research results have demonstrated that CCDC101 and WDR18 are part of the PGC-1 α transcriptional complex. Furthermore, he found that WDR18 indirectly regulates PGC-1 α activation through effects on GCN5 acetyl transferase that acetylates PGC-1 α . Although WDR18 is required for the maximum transcriptional activity and expression of gluconeogenic genes (which leads to increased blood glucose levels), the expression of hepatic glycolytic genes, which leads to decreased blood glucose levels, is not affected by expression of WDR18. However, expression of a PGC-1 α mutant that is not sensitive to nutrient-dependent

activation demonstrated an overexpression of gluconeogenesis and glycolytic genes, supporting the hypothesis that PGC-1 α activation through acetylation is key to controlling glucose and lipid metabolism. Dr. Puigserver continues his research, hoping to identify therapeutical targets that can be used to prevent glucose and lipid dysregulation in human patients.

“Our long term [goal] is to provide the molecular basis of how nutrient status and physical activity controls transcriptional complexes that directly impinge on key metabolic pathways. Importantly, these nutrient and energy pathways are operating in normal physiology but become dysregulated in age-associated diseases including metabolic diseases.”



Publications:

- Canto C, Gerhart-Hines Z, Feige JN, et al. 2009. AMPK regulates energy expenditure by modulating NAD⁺ metabolism and SIRT1 activity. *Nature* 458:1056-60.
- Coste A, Louet JF, Lagouge M, et al. 2008. The genetic ablation of SRC-3 protects against obesity and improves insulin sensitivity by reducing the acetylation of PGC-1 α . *Proc Natl Acad Sci USA* 105(44):17187-17192.



Photographer: Mr. David Miles, Audio-Visual Department, WRAIR

Ai Lin, Ph.D.

Walter Reed Army Institute of Research Advanced Technology Development Award

Every year about two billion individuals are exposed to malaria—with 300 to 500 million new cases of infection reported each year worldwide—resulting in the deaths of approximately 1.5 million to 3 million people annually. The number of cases and subsequent deaths are expected to increase globally due to a lack of access to effective drugs and to increasing malaria-acquired drug resistance to the existing treatment options, such as chloroquine and pyrimethamine. Dr. Lin chose to optimize imidazolidinedione (IZ) derivatives that are orally active with potential curative and prophylactic activity against the parasite that causes malaria. Medicinal

chemistry efforts are focused on the synthesis of chemically and/or metabolically stable IZ derivatives in a search for compounds with a longer plasma half-life than the lead agents. Preliminary work produced new IZ derivatives with longer plasma half-life and greater effectiveness in mouse and Rhesus monkey models than the parent compound itself. Further studies indicated the new IZ compounds are non-toxic and may be effective in fighting certain malaria-causing organisms. Dr. Lin plans

to further enhance the oral activity of these compounds and to expand the range of parasites affected by the compounds to encompass both blood- and liver-stage malaria.

“The project will lead to the discovery of a new, potent, and safe antimalarial drug to protect and/or treat the civilians traveling to or U.S. Armed Forces deployed to the malaria-endemic regions.”



Photographer: Mr. David Miles, Audio-Visual Department, WRAIR

Publications:

- Sathunuru R, Melendez V, Kozar MP, et al. 2008. A facile one pot synthesis of 2, 4-diamino-6-substituted s-triazine derivatives. *J Heterocycl Chem* 45:1673-1678.
- Guan J, Wang X, Smith K, et al. 2007. Malaria causal prophylactic activity of imidazolidinedione derivatives. *J Med Chem* 50:6226-6231.

Patent:

- September 5, 2006. Patent 7,101,902. 2-Guanidinylimidazolidinedione compounds and methods of making and using thereof.

■ Osteoporosis and Bone-Related Diseases ■ Post-Traumatic Stress Disorders ■ Blood-Related Cancer Research such as Leukemia, Lymphoma, and Multiple Myeloma ■ Childhood Asthma ■ Chronic Pain and Fatigue Research ■ Advanced Proteomics ■ Drug Abuse
 ■ Duchenne's Disease Research ■ Diabetes Research ■ Autoimmune Diseases such as Scleroderma and Sjogren's Syndrome
 ■ Polycystic Kidney Disease ■ Childhood Cancer Research ■ Fibromyalgia ■ Human Performance Optimization ■ Interstitial Cystitis Syndrome ■ **Autism** ■ Lupus Research



Mark Tommerdahl, Ph.D.
University of North Carolina at Chapel Hill
Investigator-Initiated Research Award

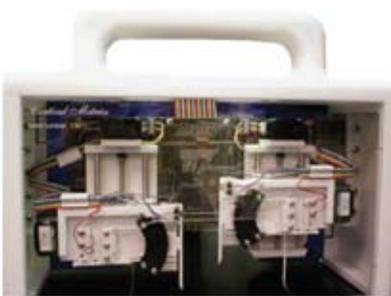
A number of neurological disorders including autism have been identified as, or are predicted to be, associated with abnormal connectivity between brain regions. Although the incidence of autism is on the rise, knowledge about the underlying mechanisms of this disorder is incomplete. Further, developing animal models in which to investigate the neurobiological deficits

associated with autism is difficult as there are very few objective metrics of the performance of human subjects with autism that can guide animal model development. As such, Dr. Tommerdahl is focusing on generating novel measures that reflect differences in underlying cortical circuitry between control subjects and those with autism to obtain objective metrics that will facilitate the development of innovative animal models of autism. To accomplish this, Dr. Tommerdahl has designed and fabricated a portable two-point tactile diagnostic stimulator that can be used for the assessment of cortical health in subjects with autism. The new device, known as the Cortical Metrics stimulator (CM-1), consists of two independently controlled stimulators therefore allowing stimuli to be delivered simultaneously to two distinct sites at different amplitudes, frequencies, and/or phases. In addition, the CM-1 automatically detects the skin surface, which provides a more efficient stimulus delivery.

"We have found that the device developed is very useful with other clinical populations (e.g., fibromyalgia, TMJD, migraine, TBI/concussion, etc.) and are starting to get some interesting pilot data. Our measures of neuroadaptation seem to be very sensitive to overall CNS health and we hope to be able to extend our work to other areas, particularly TBI, as the measures that we have developed appear to be very reliable and very sensitive to changes that are difficult, if not impossible, to detect with currently available methods."

associated with autism is difficult as there are very few objective metrics of the performance of human subjects with autism that can guide animal model development. As such, Dr. Tommerdahl is focusing on generating novel measures that reflect differences in underlying cortical circuitry between control subjects and those with autism to obtain objective metrics that will facilitate the development of innovative animal models of autism. To accomplish this, Dr. Tommerdahl has designed and fabricated a portable two-point tactile diagnostic stimulator that can be used for the assessment of cortical health in subjects with autism. The new device, known as the Cortical Metrics stimulator (CM-1), consists of two independently controlled stimulators therefore allowing stimuli to be delivered simultaneously to two distinct sites at different amplitudes, frequencies, and/or phases. In addition, the CM-1 automatically detects the skin surface, which provides a more efficient stimulus delivery.

To date, protocols for the operation of the CM-1, such as the two-alternative, forced-choice tracking procedure, have also been developed to facilitate investigations of spatial discrimination in human subjects. Assessment of the amplitude discriminative capacity of human subjects between two stimuli positioned at near-adjacent skin sites demonstrates that the performance of the amplitude discrimination task was significantly degraded when stimuli were delivered simultaneously and were near a subject's two-point limen (threshold). Subjects were, however, able to correctly discriminate between the amplitudes of the two stimuli when delivered sequentially at all inter-probe distances (including those within the two-point limen). In addition, studies focusing on the impact of local cortical-cortical connectivity on information processing in autism have been initiated. In these, the temporal order judgment (TOJ) and temporal discriminative threshold were assessed in 10 adult autism subjects and 10 healthy control subjects in the absence and presence of synchronized conditioning vibrotactile stimuli. Data from this study indicate that delivery of simultaneous and synchronized vibrotactile stimuli to near-adjacent skin sites decreases a healthy subject's ability to determine temporal order whereas autistic subjects do not demonstrate such a decreased capacity in TOJ in the presence of synchronized conditioning stimuli.



Publications:

- Tannan V, Holden JK, Zhang Z, et al. 2008. Perceptual metrics of individuals with autism provide evidence for disinhibition. *Autism Res* 1(4):223-230.
- Tommerdahl M, Tannan V, Holden JK, et al. 2008. Absence of stimulus-driven synchronization effects on sensory perception in autism: Evidence for local underconnectivity? *Behav Brain Funct* 4:19.

- Mental Health Resiliency ■ Radioprotectants ■ Paget's Disease ■ Military Relevant Disease Management ■ Efficacy and Subsequent Clinical Guidelines for the Use of Probenecid or Other Drugs to Decrease Dosage Requirements of Oseltamivir Phosphate for the Treatment of Influenza ■ Alcoholism Research ■ Pulmonary Hypertension ■ Respiratory Infection including associated respiratory disease ■ Kidney Cancer Research ■ **Eye and Vision Research** ■ Social Work Research



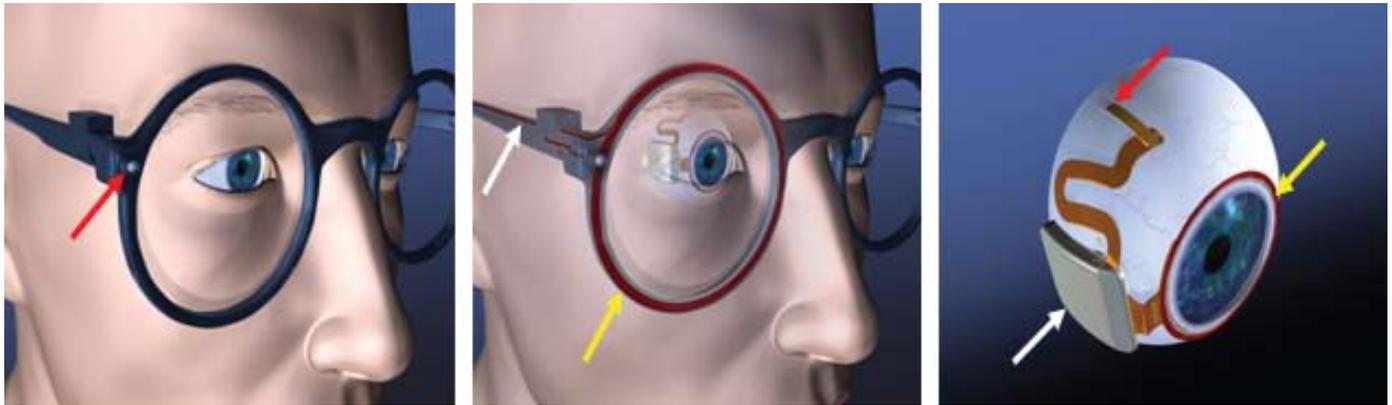
Joseph F. Rizzo III, M.D.

Massachusetts Eye and Ear Infirmary

Advanced Technology: Product/Technology Down-Selection or Optimization Award

In the industrialized world, the major cause of blindness is retinal disease, primarily, age-related macular degeneration (ARMD). While ARMD is a major cause of blindness among U.S. military service veterans, active military personnel suffer from substantially increased risks of blindness mostly from ocular blast injuries and laser-induced retinal injury. Dr. Rizzo is developing a retinal prosthesis that may be used to treat several forms of retinal blindness that are currently untreatable, including

blindness caused by battlefield laser injury to the retina and military-related, blast-induced blindness. The proposed implantable prosthetic will be a microelectronic device designed to interface directly with the retina. The device will capture visual images, communicate the images to electronic components that interface with the retina, and selectively deliver electrical pulses to the retina to create vision. Dr. Rizzo has made several important strides toward completion of the prosthesis, having developed the necessary electrode array, which transmits the visual information to the retina, and the titanium case, which houses the integrated circuit chip that interprets the visual information into electrical signals.



Graphic images of the designs of the Boston Retinal Implant Project. **Left:** Glasses support a small camera (red arrow) that collects visual images. **Middle:** A wire (white arrow) extends along the length of the sidebar to an external processing unit (not shown). Also embedded are two "primary" radiofrequency (RF) coils (yellow arrow). **Right:** The "secondary" RF coils (yellow arrow) are positioned just behind the circumference of the cornea. The titanium case (white arrow) provides a hermetic environment for the integrated circuit chip. The electrode array enters the eye through a small slit (red arrow) in the sclera.

Publications:

- Shire D, Kelly SK, Chen J, et al. 2009. Development and Implantation of a Minimally Invasive Wireless Subretinal Neurostimulator. *IEEE Transactions on Biomedical Engineering* 56(10):2502-2511.
- Winter JO, Cogan SF, and Rizzo JF. 2007. Retinal prostheses: Current challenges and future outlook. *J Biomater Sci Polym Ed* 18(8):1031-1055.

Patent:

- November 13, 2007. Patent 7,295,872. System for and method of power efficient electrical tissue stimulation.



Alexander V. Prokhorov, M.D., Ph.D.
M. D. Anderson Cancer Center, University of Texas
Clinical Trial Award

According to a 2005 DOD survey, the highest burden of tobacco use within military branches is borne by the U.S. Army with 38% of respondents indicating that they smoke and 18% indicating that they use smokeless tobacco. Tobacco use is highest for younger members who are lower ranking and not college educated; over 50% of younger enlisted Army personnel with a lower level of educational attainment smoke. As nicotine addiction in younger adults is likely to result in a lifelong pattern of tobacco use, evidence-based prevention and cessation programs tailored and responsive to the needs of the U.S. Army are essential to producing successful large-scale prevention and cessation among Army personnel. As such, Dr. Prokhorov is developing and evaluating an innovative behavioral theory-based intervention to address the prevention and cessation of tobacco use among active junior enlisted Army personnel at Fort Hood, Texas. To accomplish this, Dr. Prokhorov is expanding upon previous methods utilizing multimedia educational videogames with animation and interactive activities to communicate facts about smoking and tobacco use in addition to offering insight into skills essential for adopting a tobacco-free lifestyle. Utilizing a group-randomized controlled trial, 2,000 enlisted Army personnel ages 18–35 will be recruited into intervention and control groups. The intervention group will receive an educational videogame with supplemental materials about tobacco use whereas the control group will receive standard care (tobacco use prevention and cessation booklet). Taken together, it is anticipated that following post-treatment assessment, participants in the intervention group will demonstrate lower rates of smoking initiation and smokeless tobacco use as well as increased rates of smoking cessation.





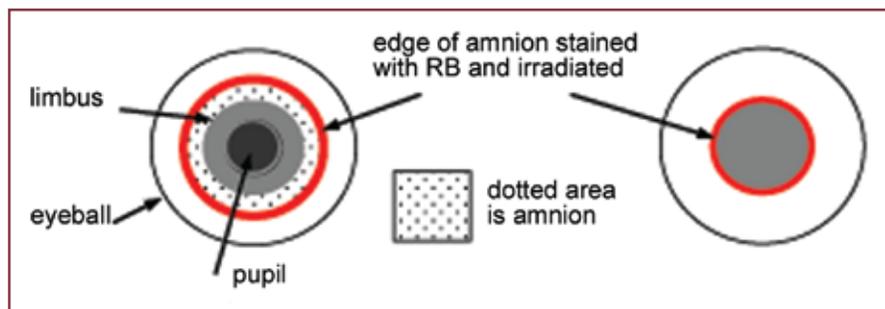
Irene Kochevar, Ph.D.
Massachusetts General Hospital
Anthony Johnson, M.D.
Brooke Army Medical Center
Translational Research Award

Many burn patients develop eye complications, such as infection or corneal ulceration and possible loss of sight, even when their eyes are not directly damaged by the burn. Facial scarring during burn injury recovery may cause the skin to contract away from the eyes, forcing a patient's eyes to remain open day

and night. This precludes blinking, which is needed to distribute tears over the cornea to keep them wet and healthy. When the cornea is dry for long periods, it becomes dehydrated, leading to loss of the epithelial layer, infection,

corneal ulceration, and, eventually, loss of vision. Dr. Kochevar and U.S. Army Colonel Johnson proposed to develop a new bandage to use with existing clinical materials to keep the corneas of burn patients healthy during the period when these patients cannot close their eyes. Current methods for maintaining a hydrated cornea involve frequent addition of moisturizing drops or covering the cornea with a layer of amniotic membrane held in a ring, which acts like an epithelial layer to protect and moisturize the eye. The former method is very inefficient, and the latter is very expensive because the amnion dissolves within 2 days and costs approximately \$900 per eye/membrane. The investigators plan to use protein crosslinking to decrease the degradation rate of the amnion and modify it to increase hydration of the cornea. Dr. Kochevar and COL Johnson believe that, if these studies are successful, corneal damage resulting from extended drying during recovery from severe facial burns will be minimized, resulting in retention of vision. In addition, care for these patients' eyes will be simplified during their recovery, and the costs of treating their corneas will be greatly reduced.

"We hope that our research will lead to development of a method for decreasing the cornea damage that occurs when patients cannot close their eyes."





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CDMRP.PublicAffairs@amedd.army.mil

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