



# 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 grown to encompass multiple targeted programs. The CDMRP has been responsible for more than \$7 billion in targeted appropriations from its inception in fiscal year 1992 (FY92) through FY12. Funds for the CDMRP are added annually by Congress to the Department of Defense (DoD) budget 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 applications and individual project performance, to award closeout.

## VISION

Improve the health and well-being of all military service members, veterans, and beneficiaries.

## MISSION

Identify and select military health-related research of exceptional scientific merit.

## Peer Reviewed Medical Research Program

Since 1999, the Peer Reviewed Medical Research Program (PRMRP) has supported research under topic areas directed by Congress, with an underlying goal of enhancing the health and well-being of military service personnel, the veteran population, and their families. Through FY11 (excluding FY07, in which no appropriation was made), Congress has appropriated \$544.5 million (M), which has supported 437 research awards. The FY12 PRMRP appropriation is \$50M. Through its inception, PRMRP has funded research projects in more than 90 congressionally directed topic areas that address a wide range of fields of study including cancer, infectious diseases, neurological injury and disorders, psychological disorders, health and wellness, restoration and regenerative medicine, advanced technology, health care delivery, and a variety of disease conditions.

The military provides medical services to millions of service members, their dependents, and veterans, and the PRMRP exists to support research for medical issues that affect this broad population, including children and the elderly. The PRMRP is committed to funding basic, translational, and clinical 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.

# Program Management

Program management is a collaborative effort involving Congress, consumer advocates, scientists, clinicians, and the DoD. Each annual cycle starts with a congressional appropriation, where funds are allocated for PRMRP and the topic areas for research application solicitation are determined. The award cycle includes a two-tier review process for application evaluation recommended by the Institute of Medicine of the National Academies. The first tier of evaluation is a scientific peer review of applications against specified criteria for determining scientific merit. The second tier is a programmatic review conducted by members of a Joint Programmatic Review Panel (JPRP) who compare submissions and make funding recommendations based on programmatic priorities, portfolio balance, and scientific and mechanism-specific criteria. The Commanding General of the USAMRMC issues the final approval for funding prior to award negotiations and execution of the proposed research project.

## Scientific Peer Review Panel Composition

The PRMRP scientific peer review panels are composed of respected scientists and clinicians, as well as dedicated consumer advocates, who are individuals affected by a disease or condition. Scientific reviewers 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. Both groups work together to provide an unbiased, expert review of the scientific and technical merit of the research proposals and their potential impact for patients and their families.

## JPRP Composition

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's vision and mission and develop an investment strategy annually to meet the needs of the military, VA, and civilian communities. In addition, programmatically relevant studies are recommended for funding by the JPRP members.

"As a member of the PRMRP Joint Programmatic Review Panel, I witness firsthand the incredible expertise, professionalism, commitment, and dedication that the entire CDMRP/PRMRP team utilizes to meet the stated mission and vision of this program. In fact, each year the JPRP re-examines that mission and vision to ensure that we have set the right course for the program. This process ensures that all of our efforts are clearly focused on achieving our stated goals within the constraints of the resources available. As such, I am truly honored to have the opportunity to serve this program and to be part of this team."



"I have been struck by

how well the PRMRP protects the interests of the scientific applicant while simultaneously providing a seat-at-the-table for disease advocates."

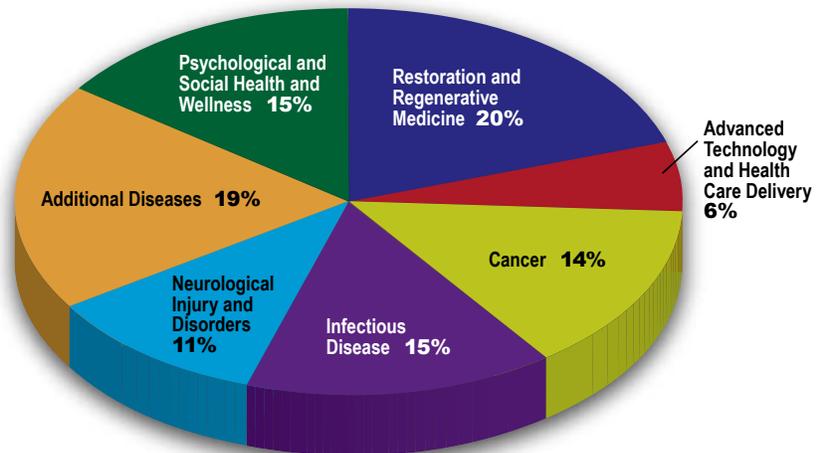
**Kent E. Vrana, Ph.D.,**  
**Scientific Reviewer**  
**PRMRP Peer Review**



**Lt Col David G. Watson**  
**Joint Programmatic Review Panel Member**

# Research Portfolio

As we move through the 21st century, health and welfare issues continue to evolve. In pursuit of its vision, the PRMRP supports medical research addressing a variety of challenges affecting the health and well-being of military service members, military retirees, veterans, and their beneficiaries. Each year, the PRMRP solicits research applications under topic areas directed by Congress, which address a wide range of fields of study. These topic areas can be classified into one of several broad categories (Figure 1).



*PRMRP Award Portfolio by Category and Percentage of Total Funding FY99-FY10*

## A History of Accomplishment

PRMRP awards have resulted in a variety of exciting outcomes and high-impact advancements. To date, PRMRP-funded investigators have reported more than:

- **1,240** Publications
- **30** Issued patents
- **180** Funding opportunities obtained



“Relevant is a hallmark of the research supported by the PRMRP. The PRMRP integrates scientific, consumer, and military expertise to identify timely and innovative research. Clinical, translational, and basic research is reviewed that has promise to advance diagnosis and treatment of a range of conditions and to enhance the lives of service members, their families, and civilians. It’s an honor—and intellectually engaging—to contribute to the PRMRP peer review process.”

*Karen B. Schmaling, Ph.D., ABPP, Scientific Reviewer, PRMRP Peer Review*

- ❖ **Dr. Babs Soller** developed CareGuide™, a portable sensor system that noninvasively measures muscle pH, muscle oxygen, and hematocrit from light reflected on the forearm to assess tissue perfusion and guide treatment during resuscitation care.
- ❖ **Dr. James Childs** developed a handheld device with a 1,060 nm diode laser and demonstrated safety and efficacy in the treatment of pseudofolliculitis barbae in a 20-subject clinical trial.
- ❖ **Dr. Ronald Triolo** developed a hybrid neuroprosthesis that combines external bracing with electrical stimulation of paralyzed muscles to allow for mobility after paralysis from spinal cord injury.
- ❖ **Dr. Anthony Guiseppi-Elie** created and tested in small animals a biochip that can be temporarily implanted intramuscularly to telemetrically report local lactate and glucose levels to assess the potential for hemorrhagic shock during resuscitation and intensive care from traumatic injury.
- ❖ **Dr. Stephen Savarino** showed that bovine milk immunoglobulin collected from cows immunized with enterotoxigenic *Escherichia coli* (ETEC) antigens and administered orally provided protection against ETEC challenge (traveler's diarrhea) in humans.
- ❖ **Dr. Ai Lin** optimized imidazolidinedione derivatives and demonstrated in primates that they are orally active with potential curative and prophylactic activity against the parasite that causes malaria.
- ❖ **Dr. Patrick Kochanek** developed a polynitroxilated, pegylated bovine cell-free hemoglobin-based, small volume resuscitation fluid for traumatic brain injury combined with hemorrhagic shock that demonstrates potential as a neuroprotective agent.
- ❖ **Dr. Blake Hannaford** developed a prototype field-deployable surgical robot capable of telemanipulation that was successfully tested in a cross-Atlantic setting with simulated surgical tasks.
- ❖ **Dr. Mark Tommerdahl** developed a novel, noninvasive prototype system for quantitative assessment of cerebral cortical health and demonstrated the ability to detect differences in cerebral cortical function between subjects with and without autism.
- ❖ **Dr. Joseph Rizzo** developed a prototype, small animal model-scale retinal prosthesis with the potential 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.



"I have been participating as a consumer reviewer/advocate in the DoD/PRMRP for

several years, in the field of tinnitus (chronic and disabling ringing in the ears) that so many of our warfighters are bringing home with them. One major impact of this program has been to encourage investigators in the tinnitus field to continue to search for innovative breakthroughs that might save the Veterans Administration hundreds of millions of dollars in disability payments for this malady. The proposals that qualified for funding under the PRMRP have produced significant results in the direction of finding a cure."

**Mr. Scott Mitchell**  
**Consumer Reviewer**  
**PRMRP Peer Review**



Topic Areas Funded  
by the PRMRP  
in Advanced  
Technology and  
Health Care  
Delivery:

Advanced  
Proteomics

Advanced Soft  
Tissue Modeling

Anti-Radiation Drug  
Development

Biological Hazard  
Detection System

Chemical Weapons  
Treatment

Closed-Loop Frozen  
Blood Processing  
Systems

Medical Surgery,  
Military Relevant  
Diseases and Injury  
Management

Preclinical and  
Clinical Activities  
of Novonex/Ex-Rad  
Drugs

Radiation  
Protection

Real-Time Heart  
Rate Variability

Remote Emergency  
Medicine  
Ultrasound

Reserve  
Component Medical  
Training Program

## Advanced Technology and Health Care Delivery

Many advanced medical technologies are unable to be utilized in the front lines of a war or in remote locations without adaptations that work within varying constraints of available tools, trained personnel, and environmental conditions. Optimizing access to health care and protecting service members and the public from the exposures to chemical, biological, radiological, and nuclear hazards are challenges best addressed by advancing innovative technologies. The PRMRP funds research in several topic areas that seek to develop, transition, and/or deliver technologies for utilization wherever they are needed most. Examples of research in some of these areas are included here.



### Studying Nerve Agent Exposure

**Oksana Lockridge, Ph.D., University of Nebraska  
Medical Center**

Organophosphorous (OP) nerve agents are a class of chemical weapons with serious and potentially fatal effects. OPs exert their effects by blocking the enzyme acetylcholinesterase (AChE), leading to the buildup of acetylcholine, prolonged muscle contractions, progressive loss of bodily functions, and eventual death due to respiratory depression. There is evidence that some people suffer chronic illness from a dose of OP too low to inhibit AChE, which may indicate that OP-reactive proteins exist

that are more sensitive to OP exposure than AChE.

Dr. Oksana Lockridge received an FY06 Investigator-Initiated Award to identify new protein targets that are modified by exposure to OP and new bioscavengers for protection against nerve agent toxicity. Dr. Lockridge and her research team found that in addition to AChE, OP also permanently binds to the amino acid serine in plasma butyrylcholinesterase (BChE) and inhibits its enzymatic activity. Dr. Lockridge developed methods that have been used to detect OP agent adducts on BChE in plasma of exposed human subjects. While OP causes inhibition of BChE enzymatic activity, the binding also inactivates the OP and renders it harmless. The irreversible binding and inactivating function of BChE against OP poisons is an attractive feature for its use as a prophylactic agent to prevent incapacitation and death by chemical warfare using OP nerve agents. This potential has led to extensive research efforts devoted to producing large quantities of human BChE. In the course of her work, Dr. Lockridge optimized the production of the stable tetrameric BChE that has a half-life of 11–14 days, compared to the monomer half-life of 20 minutes, and therefore may be the best form of BChE preventive treatment against chemical exposure. Most recently, the investigators successfully utilized a mouse model to test the feasibility of using adenovirus to deliver clinically relevant amounts of BChE to prevent toxicity caused by exposure to nerve agents. These exciting results may one day lead to the development of a functional and practical prophylactic for the effects of exposure to OP.

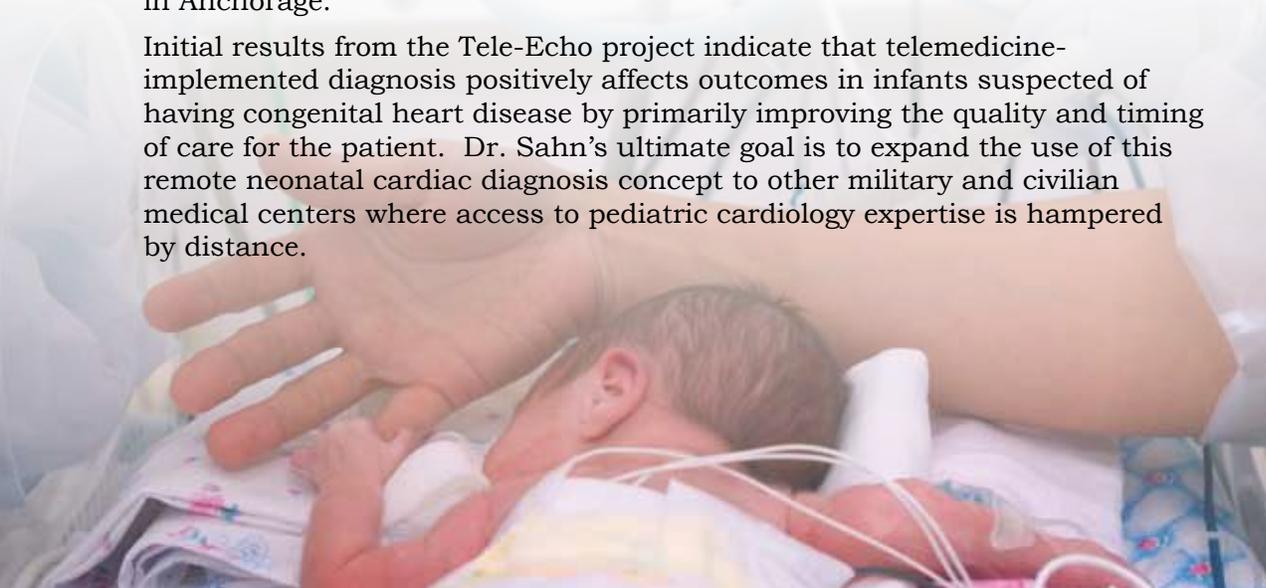
## Using Telemedicine to Get to the Heart of Neonatal Cardiac Disease

**David J. Sahn, M.D., University of Oregon, Portland, Oregon**

Echocardiography (ECHO) is an ultrasound of the heart that is used to diagnose, evaluate, and monitor a variety of heart conditions, such as congenital heart disease in infants. However, the expensive equipment and expertise required to perform and interpret neonatal ECHO results may not be available at remote health care facilities. Transporting an infant to another hospital for evaluation can cause distress for the infant and family, is time-consuming, and is costly. Dr. David Sahn, who received an FY02 Investigator-Initiated Research Award, hypothesized that “trained primary care practitioners or nurses can, with telemedicine supervision, successfully perform cardiac ultrasound exams on neonates at risk for heart disease and thereby impact time to diagnosis, improve outcomes, and decrease costs.”

To conduct the study, termed Tele-ECHO, primary care practitioners and nurses at several participating rural sites were trained to perform and evaluate ECHO on neonates at risk for heart disease using standard ECHO machines and handheld, portable ultrasound scanners from Sonosite, Inc. A secure telemedicine network was installed and tested at the participating sites and linked to pediatric cardiologist specialists at Madigan Army Medical Center (MAMC). To date, this award has helped to train numerous physicians and nurses from remote health care facilities in Alaska and the U.S. Pacific Northwest on the Tele-Echo system. The Tele-Echo system allows for realtime cardiac ultrasound to be performed by trained medical staff at remote sites while being supervised by experts in ECHO at Oregon Health & Science University (OHSU) or MAMC through voice and image transfer links on the Army medical network (MEDNET). The telemedicine MEDNET links also allow control of the scanning system settings by the experts at OHSU or MAMC. The project was conducted at three military installations in the U.S. Pacific Northwest and in Alaska, including a large Alaska Native Health Center in Anchorage.

Initial results from the Tele-Echo project indicate that telemedicine-implemented diagnosis positively affects outcomes in infants suspected of having congenital heart disease by primarily improving the quality and timing of care for the patient. Dr. Sahn’s ultimate goal is to expand the use of this remote neonatal cardiac diagnosis concept to other military and civilian medical centers where access to pediatric cardiology expertise is hampered by distance.



## Topic Areas Funded by the PRMRP in Cancer:

Blood Cancer

Cell Response to Anti-Cancer Agents

Chemo-Preventative Approaches to Smoking Related Illness

Childhood/Pediatric Cancer

Digital Mammography Imaging

Kidney Cancer

Lung Cancer Screening

Mesothelioma

Molecular Biology/Signatures for Tumors

Neuroblastoma

Pheochromocytoma

## Cancer

According to the American Cancer Society, more than 1.6M new cases and over 570,000 deaths from cancer are projected to occur in the United States in 2012. Although cancer death rates for men and women are declining, cancer remains a major health issue, causing one in four deaths in the United States (Cancer Statistics, 2012. R. Siegel et al., *CA Cancer J Clin* 2012; 62:10-29). The PRMRP has awarded several grants in cancer-related topic areas and seeks to expand the knowledge of how genetic, lifestyle, and environmental factors cause cancer and use this knowledge toward development of novel and effective therapies and prevention strategies. Examples of research in some of these areas are included here.



### Development of Augmented Leukemia/Lymphoma-Specific T-Cell Immunotherapy for Deployment with Haploidentical Hematopoietic Progenitor-Cell Transplant

**Laurence Cooper, Ph.D., University of Texas MD Anderson Cancer Center**

Although allogeneic hematopoietic progenitor-cell transplant (HPCT) may eradicate high-risk B-cell malignancies, including lymphoma and leukemia in pediatric patients, HLA (human leukocyte antigen)-matched siblings or unrelated donors are not readily available for every child. Due to the limited availability of HLA-identical donors, pediatric patients may benefit from transplantation of haploidentical (or half-matched) HPCs that are more widely accessible. While this procedure is potentially lifesaving, pediatric haploidentical recipients remain at significant risk for disease relapse and opportunistic infection. Recent clinical studies have demonstrated, however, that infusion with donor-derived T cells genetically modified to target antigens expressed by opportunistic pathogens can protect against infection after allogeneic HPCT. Based on these findings, Dr. Laurence Cooper hypothesized that treatment with donor-derived T cells genetically modified to target the CD19 antigen expressed by malignant B cells may improve the relapse-free survival rate of pediatric haploidentical HPCT recipients with leukemia or lymphoma. Therefore, with funding from an FY06 Advanced Technology: Product/Technology Down-Selection or Optimization Award, Dr. Cooper's research team developed novel methodology to generate CD4+ and CD8+ T cells that can eradicate malignant CD19-expressing B cells in a mouse model. Although infusion with HLA half-matched T cells can result in the development of a serious complication called graft-versus-host disease, Dr. Cooper demonstrated that blockage of CD28 prior to T-cell treatment limits the development of this life-threatening complication. Dr. Cooper has utilized these exciting preclinical results to obtain other funding with which he is currently evaluating this technology in a first-in-human clinical trial.

## Improving Outcome in Malignant Pleural Mesothelioma (MPM) Using Pulsed-Protracted External Beam Radiation (PERT) and Intrapleural Delivery of Stem Cells

**Brian Marples, Ph.D., Beaumont Health System Research Institute, Royal Oak, Michigan**

MPM is a rare cancer affecting the lining of the lungs. Despite current treatment options including aggressive surgery, chemotherapy, and adjuvant radiotherapy (RT), the survival rate for MPM patients remains low. Additionally, clinicians are unable to administer tumoricidal RT doses to treatment sites due to the proximity of these sites to healthy tissue. Therefore, Dr. Brian Marples hypothesized that a novel PERT treatment schedule consisting of low-dose radiation pulses will preferentially target malignant cancer cells, while post-RT delivery of stem cells to the treatment site will facilitate the repair of the surrounding normal tissue. Dr. Marples' research team, with funding from an FY10 Concept Award, will investigate the efficacy of the PERT intervention and subsequent stem cell infusion in an animal model of MPM. This innovative approach has the potential to not only advance adjuvant RT but to also significantly improve MPM patient survival.



Topic Areas Funded  
by the PRMRP in  
Infectious Diseases:

Anti-Diarrhea  
Supplement

Arthropod  
Transmitted  
Infectious Diseases

Conjugate Vaccines  
to Prevent  
Shigellosis

Dengue Fever  
Vaccine

Disease  
Management  
Research

FungiFree

Geneware  
Rapid Vaccine  
Development

High Risk Infectious  
Disease

Infectious Disease  
Tracking System

Leishmaniasis

Listeria Vaccine for  
Infectious Disease

Malaria Vaccine  
Initiative

Military Relevant  
Disease and Injury  
Management

West Nile Virus  
Vaccine

## Infectious Diseases

Infectious diseases are a major threat to the operational readiness of U.S. military forces. Military deployment-related exposure to a combination of social, physical, psychological, and environmental factors can strain the immune defenses of soldiers. As such, research focusing on treatment and prevention of infectious diseases answers an important military need. This knowledge is also of a great value to civilians, especially during increasing global responses to humanitarian and natural disasters that are alike to military deployment (CK Murray et al. An approach to prevention of infectious diseases during military deployments. *Clin Infect Disease* 44; 424-430, 2007). Examples of research in some of the infectious disease-related topic areas funded by the PRMRP are included here.



### Listeria-Based Vaccine for Cutaneous Leishmaniasis

**Helene Marquis, D.V.M., Ph.D., Cornell University,  
Ithaca, New York**

Cutaneous leishmaniasis is a skin infection characterized by ulcers affecting approximately 12M people worldwide. It is caused by the parasitic protozoan called *Leishmania* that is transmitted through the bite of infected sandflies, endemic to countries in the Middle East that are major focal points of current U.S. military deployments. Existing drug treatments are extremely toxic, and attempts to develop

vaccines against parasitic antigens have met with mixed results in human clinical trials. Interestingly, people who live in countries affected by sandflies are more resistant to the disease because they develop an immune response to the sandfly saliva, which is released upon biting a host. Using support from an FY09 Investigator-Initiated Research Award, Dr. Helene Marquis proposed to develop a vaccine for cutaneous leishmaniasis using a nonvirulent strain of *Listeria monocytogenes* as a bacterial vector to deliver large amounts of sandfly salivary gland antigens into the cytosol of infected cells to provide long-lasting immunity against cutaneous leishmaniasis.

Dr. Marquis genetically engineered bacterial *Listeria* strains capable of secreting sandfly salivary gland proteins as antigens when multiplying in host cells. To investigate the immunogenicity of the vaccine strain, she vaccinated mice three times at 2- to 3-week intervals and challenged these mice 3 weeks later with an intradermal injection of *Leishmania* and sandfly salivary gland extract. The results showed that over a period of 65 days following infection, there was a significant decrease in lesion size and an overall 80% reduction in the burden of disease in the vaccinated mice compared to control (unvaccinated) mice. These promising results support the potential to develop an effective vaccine against cutaneous leishmaniasis, ultimately protecting our military and civilian aid personnel, U.S. and other travelers, and the individuals that live in countries where this disease is endemic. Overall, a prophylactic vaccine against cutaneous leishmaniasis could impact an estimated 350M people annually at risk of developing this disease.

## Development of Strategies to Treat and Prevent Norovirus Infections

***Xi Jiang, Ph.D., Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio***

Noroviruses (NoV) are the most common cause of acute viral gastroenteritis. Since the introduction of molecular diagnosis in the early 1990s, NoVs have been recognized as the most important cause of nonbacterial outbreaks of acute gastroenteritis in both civilian and military populations, yet there is no prevention or cure. NoVs are highly contagious, easily transmitted via contaminated water, food, or personal contact, and NoV infections are often debilitating. Importantly, military personnel are at an elevated risk for NoV outbreaks due to several factors, including crowded living conditions and limited access to sanitation supplies.

Previously, Dr. Jiang, recipient of an FY03 Investigator-Initiated Award, discovered that NoVs bind human histo-blood group antigens (HBGAs) as receptors. With this support, Dr. Jiang sought to further explore the NoV/host receptor interactions in support of developing novel strategies for preventing and treating NoV infections. First, the investigator characterized the genetic, antigenic, and receptor binding variations of NoVs in relation to the human HBGAs and demonstrated that NoVs have a highly conserved HBGA binding interfaces that segregate into two binding groups. In addition, he found that each binding interface contains at least two receptor binding sites and blocking one or both of these interactions significantly reduced virus binding to the receptor antigens. Based on these results, Dr. Jiang performed high-throughput screening for small molecule compounds that can block the interaction of NoVs to different types of HBGAs. Thus far, over a dozen lead antiviral compounds have been identified. Furthermore, Dr. Jiang found alternate strategies for inhibiting the NoV-HBGA interaction, including monoclonal antibodies and Chinese herbs. Finally, a 40-subject human volunteer challenge study was conducted where two cohorts of volunteers were exposed to a currently predominant GII-4 NoV. Results of the study revealed a strong association of subjects' HBGA types with susceptibility or resistance to NoV infection. Dr. Jiang's preclinical research and the new human challenge model provide extensive information and resources that can be utilized to develop vaccine and antiviral medications to combat norovirus outbreaks.



*Topic Areas Funded by the PRMRP in Neurological Injuries and Disorders:*

Amyotrophic Lateral Sclerosis

Autism

Chronic Fatigue Syndrome

Chronic Migraine and Post-Traumatic Headache

Defense and Veterans Head Injury Program

Dystonia

Epilepsy

Fibromyalgia

Fragile X Syndrome

Military Relevant Disease and Injury Management

Multiple Sclerosis

Neuroscience Research

Traumatic Brain Injury

## Neurological Injury and Disorders

The burden of neurological disorders and injury is extraordinary—with over 600 different types of known neurological disorders, about 1 billion people worldwide are affected, and that number is expected to rise (Report by the World Health Organization from March 1, 2007). U.S. deployed military troops experience high exposure to neurological injuries, with traumatic brain injury (TBI) becoming a signature of the modern war. PRMRP-funded research addressing neurological-related issues will greatly benefit both military and civilian populations. Examples of research in some of these neurological-related topic areas funded by the PRMRP are included here.



### Biomarkers for Fibromyalgia

**Richard Harris, Ph.D., University of Michigan, Ann Arbor, Michigan**

In contrast to pain resulting from stimulation of sensory receptors called nociceptors, the pain of fibromyalgia originates in the central nervous system. Such “non-nociceptive” pain responds poorly, if at all, to standard treatments such as opioids, nonsteroidal anti-inflammatories, or surgery, but fibromyalgia patients report pain reduction in response to acupuncture. With support from an FY06 Investigator-Initiated Award, Dr. Richard Harris

sought to identify neurobiologic correlates of fibromyalgia by performing functional neuroimaging using three imaging modalities on fibromyalgia patients treated with acupuncture. Positron emission tomography imaging revealed that at baseline, fibromyalgia patients had reduced mu opioid receptor (MOR) binding capacity in pain and sensory processing regions of the brain as compared to pain-free controls. During acupuncture, however, MOR binding increased, and long-term increases in MOR binding were maintained after several weeks of treatment. Using proton magnetic resonance spectroscopy, Dr. Harris and colleagues showed that fibromyalgia patients had elevated levels of the excitatory neurotransmitters glutamate and glutamine in the posterior insula, and following acupuncture and patient-reported reductions in pain, glutamate and glutamine levels in the posterior insula decreased. Finally, functional connectivity magnetic resonance imaging of fibromyalgia patients indicated increased connectivity between the insula and the default network, a network of brain regions that are active when the individual is not focused on the outside world and the brain is at wakeful rest. The degree of connectivity was directly associated with the intensity of ongoing spontaneous pain. Following acupuncture and a decrease in reported pain, a decrease in connectivity between the insula and the default network was detected.

Dr. Harris’ research has resulted in identifying three neurobiologic correlates of fibromyalgia that can serve as objective biomarkers for clinical studies of fibromyalgia treatment as well as suggesting possible underlying mechanisms for fibromyalgia, which is welcome news for the estimated 2% of Americans with this painful condition.

## Photoacoustic Imaging of Epilepsy

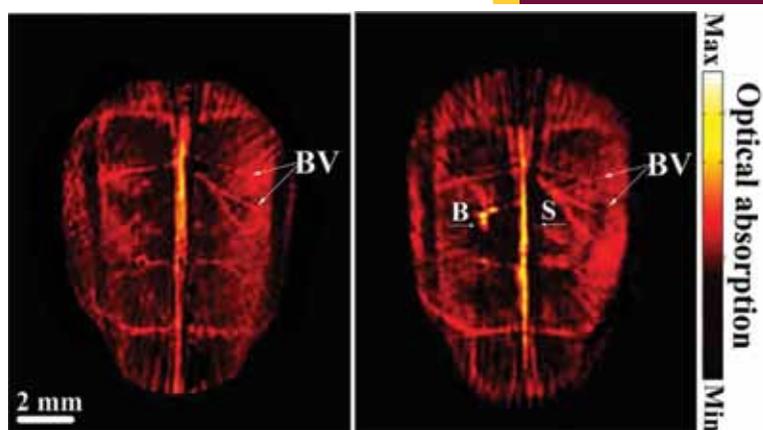
**Huabei Jiang, Ph.D., University of Florida, Gainesville, Florida**

Epilepsy is a brain disorder that involves repeated and spontaneous seizures caused by electrical disturbances, which in some cases originate from a defined brain region (seizure foci) and then are propagated to other parts of the brain. Many people with epilepsy can become seizure-free by using anti-epileptic drugs; however, approximately 25% of the drug-treated individuals do not respond to medication and surgically removing the abnormal area of the brain where the seizures are originating may be the only treatment for them. Since the success of surgical treatment depends on the precise localization of the seizure foci, a number of imaging technologies, such as magnetic resonance imaging and computed tomography, have been employed to guide the surgical procedure. However, these approaches have several limitations, including insufficient temporal resolution, inability to monitor the patient for duration of time, and in some cases a requirement for invasive techniques.

Dr. Jiang received an FY08 Advanced Technology/Therapeutic Development Award to advance the ability to localize seizure foci. Dr. Jiang will use photoacoustic tomography (PAT), a noninvasive imaging technique that combines the benefits of the high contrast of optical imaging and the high resolution of ultrasound imaging into a single modality to identify the seizure foci. Dr. Jiang hypothesizes that PAT offers the possibility to noninvasively track dynamic changes during seizure occurrence and plans to develop and evaluate the PAT system to monitor “real-time” changes that occur during seizure. “Real-time” visualization and analysis of the seizure events will increase the accuracy in identifying the seizure onset location, which will enhance the likelihood of successful surgical outcome.

Dr. Jiang has successfully constructed, calibrated, and tested the PAT system using a number of extensive phantom experiments that simulate detection of seizure focus. Additionally, Dr. Jiang built an animal interface and demonstrated feasibility of in vivo imaging of rat brain, providing three-dimensional and quantitative imaging of the rat brain for accurate epileptic seizure localization.

Dr. Jiang plans to continue his in vivo work by performing PAT and electroencephalography simultaneously to monitor seizure activity continuously and characterize changes during seizures.



Left: PAT of a normal rat brain. Right: Seizure focus detected by PAT (indicated by B). BV: blood vessels. B: Seizure focus chemically induced. S: injection of saline.

Topic Areas Funded by the PRMRP in Psychological and Social Health and Wellness:

Alcoholism/Alcohol Abuse

Drug Abuse

Health Care Information Protection Research

Nutrition and Health

Obesity-Related Disease Prevention

Military Nutrition Research

Post-Traumatic Stress Disorders

Sleep Management

Smoking Cessation

Social Work

## Psychological and Social Health and Wellness

Maintaining an effective military largely depends on ensuring the psychological and social health and wellness of its service members, veterans, and their families. An estimated 9.3% of mid-life veterans experienced at least one major depressive episode in the past year, with over half of those having severe impairment in home management, work, and close relationships with other and social life. One in four soldiers have a drinking problem, and soldiers frequently self-medicate with drugs and alcohol to avoid the effects of post-traumatic stress disorder (PTSD). Nearly two-thirds of American adults are either overweight or obese and subject to obesity-related disorders. The PRMRP supports research in a wide variety of topic areas that focus on improving the mental, social, and physical well-being of the service members, veterans, and their family members. Examples of research in some of these areas are included here.



### Melanocortin and Opioid Peptide Interactions in the Modulation of Binge Alcohol Drinking

**Todd Thiele, Ph.D., University of North Carolina, Chapel Hill, North Carolina**

Alcoholism is a major health problem in the United States. Frequent binge drinking is associated with numerous negative consequences including increased risk of accidental injury, violent behavior, depression, heart disease, and Type 2 diabetes. Binge drinking and heavy alcohol use occurs in 27% of the military

population, compared to about 15% in the civilian population, putting military personnel at an increased risk for all the associated health risks. Identification of the neurochemical pathways in the brain that modulate binge drinking may provide insight into pharmaceutical treatments to protect against this dangerous behavior.

Dr. Todd Thiele received an FY08 Investigator-Initiated Research Award to study the role of melanocortin, a brain peptide hormone, and its receptor (melanocortin receptor) in modulating binge drinking. Using an animal model of binge drinking called “drinking in the dark” that induces excessive alcohol drinking in mice, he found that a drug, MTII, that mimics the effect of melanocortin on its receptor reduces alcohol consumption in this mouse model and that this effect was mediated by a specific member of the melanocortin receptor family (MCR4). Since naltrexone, an opioid receptor antagonist, is currently approved by the U.S. Food and Drug Administration for treatment of alcohol abuse disorders, Dr. Thiele tested the effect of naltrexone with MTII to determine if modulating two different neurochemical pathways provides a synergistic treatment effect. He found that in binge drinking mice, the combination of MTII and naltrexone dramatically reduced alcohol consumption greater than the effect seen with either drug alone. These results have important implications for possible pharmacological medical treatment of binge drinking in the human population. Specifically, melanocortin receptor agonists aimed at the MC4R, as well as an opioid receptor antagonist, may prevent binge drinking in at-risk individuals and thus protect these people from the negative behavioral and biological consequences. Importantly, preventing frequent binge drinking will reduce the risk of developing future alcohol abuse disorders and alcohol dependence in both the military and civilian populations.

## Treatment of PTSD-Related Anger

**M. Tracie Shea, Ph.D., Brown University, Providence, Rhode Island**

PTSD is one of the most common debilitating and chronic psychological disorders diagnosed among military service members deployed to hazardous locations. In addition, there is an established association between experiencing trauma and exhibiting anger with negative consequences. This association, for combat veterans especially, is one possible factor interfering with recovery from psychological trauma. Dr. Tracie Shea received an FY04 Investigator-Initiated Research Award to adapt a cognitive-behavioral intervention (CBI) for the prevention of negative consequences of PTSD-associated anger in military personnel returning from hazardous deployment arenas.

Dr. Shea adapted a CBI technique originally developed by Dr. Raymond Novaco, adding several key elements: A cognitive restructuring component for the identification and modification of beliefs and interpretations; behavioral coping strategies; and inoculation training, which uses exposure through imagery to anger-inducing scenes. Adaptations specific for returning military personnel were made to the content. A randomized pilot study was conducted to evaluate whether treatment with the modified CBI would result in less anger and aggression, less severe PTSD symptoms, and better overall functioning and quality of life. Dr. Shea compared the outcome of the modified CBI to that of a supportive intervention (SI), which served as the control group. The SI employs problem-solving skills to address current stressors and concerns, along with education on common reactions to trauma and typical stressors. Study participants were military personnel, recently returned from a war zone deployment, who had been exposed to trauma. Each subject also exhibited at least two symptoms (one being anger/irritability) of hyperarousal associated with at least moderate impairment. Primary outcome measures assessed (1) expression and control of anger and (2) severity, type, and frequency of aggressive behavior. Secondary outcome measures included functional status and PTSD symptoms.

A comparison between pre- and post-treatment outcomes showed that Dr. Shea's modified CBI resulted in significant improvement on multiple anger outcome measures when compared to the SI control, though other symptoms of PTSD were not abated. The CBI group also demonstrated significant improvement in functioning, suggesting that the effects of this treatment extended beyond anger alone. Promisingly, these improvements were largely maintained over 3 months of follow-up, indicating a potential new anger management therapy that is deserving of further study.



*Topic Areas Funded by the PRMRP in Restoration and Regenerative Medicine:*

Acellular Human Tissue Matrix Research

Acute Lung Injury

Casualty Care Research Center

Cellular Matrix Research for Military Orthopaedic Trauma

Chronic Pain

Eye and Vision Research

Gulf War Illness

Integrated Tissue Hypoxia

Laser Eye Injury

Limb Loss and Paralysis

Lung Research

Military Relevant Disease and Injury Management

Muscle Function, Orthopaedic Extremity Trauma

Post-Traumatic Osteoarthritis

Respiratory Research

Tinnitus

## Restoration and Regenerative Medicine

Because of advances in protective gear and trauma care, high numbers of service members are able to survive significant traumatic injuries sustained in battle, particularly those to the extremities and head. In the civilian realm, traumatic injuries incurred in accidents, acts of violence, and disasters are a major cause of medical and disability costs. The PRMRP supports research in topic areas that focus on reconstruction and definitive care of a spectrum of combat and civilian injuries, with goals of enhancing recovery, reducing disability, and increasing quality of life for affected individuals and their families. Examples of research in some of these areas are included here.



### Self-Managing the Consequences of Major Limb Trauma

***Ellen MacKenzie, Ph.D., Johns Hopkins University, Baltimore, Maryland***

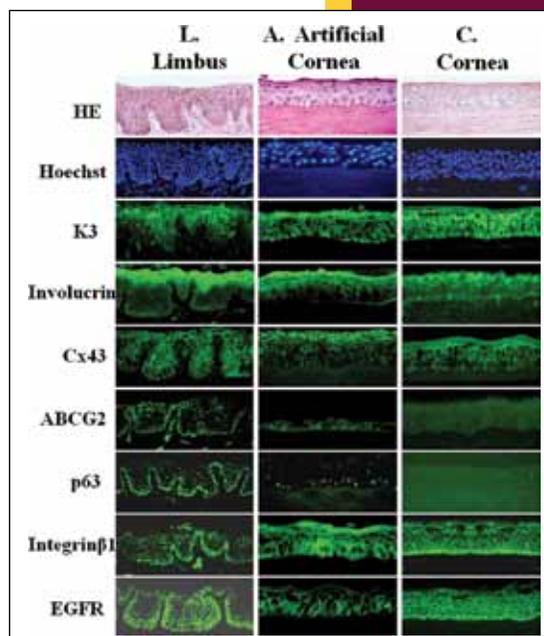
Injuries to the lower extremities are a leading cause of hospitalization among young adults and, despite improvements in orthopedic surgery, the rate of disability resulting from lower limb trauma remains high. Additionally, hundreds of young military personnel sustain traumatic limb injuries on the battlefield. Self-management interventions have been shown to improve overall function and quality of life following severe limb injury and to reduce secondary conditions such as anxiety, depression, and pain. Dr. Ellen MacKenzie, with funding from an FY05 Investigator-Initiated Research Award, has developed a web-based self-management intervention targeted toward acutely injured young adults called NextSteps. This intervention consists of 12 multimedia interactive lessons, telephone and web-based support services, and online resources. Individuals participate in two themed lessons per week over a 6-week period on subjects such as Taking Stock, Moving Forward, Managing Emotions, and Family & Friends. Facilitated online chats give NextSteps' participants an opportunity to interact with each other and share their personal experiences related to that week's lesson. Participants are also encouraged to access an online workbook and private journal throughout the 6-week course. Dr. MacKenzie and colleagues evaluated NextSteps in 30 civilian trauma patients recruited from outpatient centers at the Carolinas Medical Center and the University of Maryland. All subjects were interviewed at baseline prior to NextSteps, at completion of the intervention, and at 3 months following completion of the intervention. Feedback from participants in this pilot study was positive with 90% rating NextSteps as easy to use and 96% stating they would recommend NextSteps to a friend. Preliminary analyses revealed that both physical and mental health indices were improved 3 months following NextSteps, and anxiety was reduced at the conclusion of the intervention and after 3 months.

Dr. MacKenzie is adapting NextSteps to meet the unique needs of injured military personnel. This includes the addition of interventions for PTSD, information about the military and VA health care systems, tips for reconnecting with family and friends following deployment, and accessibility for those with mTBI. Once complete, NextSteps could be used to improve the self-management of severe lower limb injuries for both civilians and military personnel.

## Repair of Corneal Injury with Stem Cell-Based Bioengineered Tissue

**De-Quan Li, M.D., Ph.D., Baylor College of Medicine, Houston, Texas**

Among the many dangers to soldiers on the battlefield is the risk for eye injury or infection, as explosions and other threats can cause mechanical, thermal, chemical, microbial, and radiation damage to the cornea that can lead to impaired vision or blindness. The cornea serves as the primary defense for the eye and is maintained by limbal stem cells that may be cultivated for transplantation to heal the damaged eye. Approximately 110 military patients per year seek treatment for a damaged cornea, but there is a shortage in donor corneal tissue for this regenerating procedure. Dr. De-Quan Li of the Baylor College of Medicine received an FY06 Investigator-Initiated Research Award to engineer stem cell-based corneal constructs using human limbal epithelial progenitor cells (LEPC) to improve availability of this vision saving transplantation procedure. Dr. Li optimized the procedure for isolating human LEPC from limbal epithelial tissues or their primary cultures and selected cells for corneal tissue engineering based on a relatively undifferentiated state, high proliferative potential, and regenerative capacity. He then optimized a cell culture system for expanding the LEPC *ex vivo*, using a customized culture medium and a feeder cell layer composed of human fibroblast cell lines. To complete the construct, Dr. Li fabricated lamellar corneal stromal discs of optimal size (10–11 mm diameter) and thickness (100  $\mu\text{m}$ ) to cover the entire surface of the recipient cornea. These discs serve as the stromal substrate for the LEPC, facilitating the regeneration of a normal corneal epithelium. Biomarker analyses verified that this artificial epithelium has a very similar phenotype to naturally occurring corneal epithelium, suggesting that it may also function like the native cornea. Additional experiments demonstrated that the LEPC corneal constructs maintain regenerative capacity, completely healing alkaline burn wounds within 2–4 days in culture. Together, these results indicate that bioengineered corneal constructs may significantly impact the clinical treatment of eye injuries, with the potential to regenerate damaged corneas and ultimately restore vision.



Phenotype of artificial corneal epithelium generated on donor stromal disc. Representative images of immunofluorescent staining for corneal epithelial markers (Cx43, K3, involucrin, ABCG2, p63, integrin  $\beta$ 1, and EGFR) with hematoxylin-eosin and Hoechst 33342 nuclear counterstaining on frozen sections of the artificial corneal construct (A), in comparison with those from donor tissues, limbus (L), and cornea (C).

## Topic Areas Funded by the PRMRP in Additional Diseases:

Autoimmune Diseases

Childhood/Pediatric Asthma

Diabetes

Duchenne's Disease

Epidermolysis Bullosa

Food Allergies

Inflammatory Bowel Diseases

Interstitial Cystitis

Lupus

Osteoporosis and Bone-Related Bone Diseases

Paget's Disease

Pancreatitis

Polycystic Kidney Disease

Pulmonary Hypertension

Scleroderma

## Additional Diseases

Over 9.6M Americans are eligible for medical care within the Military Health System, including active duty soldiers, military retirees (those who have at least 20 years of service), and their dependents. Additionally, millions of young and aging veterans receive care through the Department of Veterans Affairs. Childhood diseases, chronic conditions, diseases associated with aging, orphan diseases—all topic areas that have been funded within the PRMRP (see list in left sidebar)—greatly impact defense spending, readiness, and morale. The PRMRP funds basic, translational, and clinical research on a variety of globally relevant diseases and conditions to support the full complement of DoD beneficiaries. Examples of research in some of these areas are included here.



### **S-nitrosothiol (SNO) and Pulmonary Arterial Hypertension (PAH)**

***Lisa A. Palmer, Ph.D., University of Virginia, Charlottesville, Virginia***

PAH is characterized by increased pulmonary arterial pressure and structural changes in the lung vasculature, which, if not treated, can lead to the development of heart failure and death. Hypoxia (insufficient oxygen supply) is one of a variety of conditions and diseases associated with the development of PAH. A number of pathogenic pathways for hypoxia-induced PAH have been

described including impaired SNO signaling. In the pulmonary endothelium, SNO formation requires endothelial nitric oxide synthase (eNOS) whereas its breakdown involves S-nitrosoglutathione reductase (GSNO-R). Under healthy conditions, levels of SNO hemoglobin from the right ventricle of male and female mice are the same, suggesting that the activities of eNOS and GSNO-R are balanced. Notably, both proteins are regulated by sex steroids: eNOS activity is increased by estrogen and GSNO-R activity is decreased by testosterone. Dr. Lisa Palmer, recipient of an FY06 Investigator-Initiated Award, is determining the role of the SNO signal transduction pathway and the sex hormones in the development of PAH.

Dr. Palmer and her research team introduced a new animal model of PAH, which mimics the chronic hypoxia vascular pathology through chronic N-acetylcysteine (NAC) administration to normoxic mice (mice with a sufficient oxygen supply). NAC-treated mice exhibit increased right ventricular pressure and hypertrophy and pulmonary vascular remodeling. In blood, NAC was converted to S-nitroso-N-acetylcysteine (SNOAC), which resulted in decreased SNO levels. The researchers demonstrated that SNOAC was necessary for the development of PAH in this model. Examination of gender differences in this mouse model of PAH showed that the lungs of female mice have greater GSNO-R activity than the lungs of male mice. Also, castration, which results in testosterone depletion, resulted in increased GSNO-R activity in the males to the level seen in females; increased GSNO-R activity is associated with blocked development of PAH. These results suggest that the sex-related differences in GSNO-R activity levels may play an important role in male susceptibility to and female protection from the development of PAH.

## Targeted Therapy for Treating Polycystic Kidney Disease

**Thomas Weimbs, Ph.D., University of California, Santa Barbara, California**

Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in either the PKD1 or PKD2 gene, is the most common life-threatening hereditary disease, with an incidence of 1/400–1/1,000. ADPKD leads to renal epithelial cyst formation, fibrosis, and progressive destruction of kidney function. With no treatment available, most ADPKD patients eventually require lifelong dialysis or kidney transplantation. Dr. Thomas Weimbs' research team has previously shown that PC1, the product of the PKD1 gene, interacts with mammalian target of rapamycin (mTOR) and tuberlin, a negative regulator of mTOR. Also, they found that mTOR activity is highly upregulated in renal cysts in ADPKD compared to surrounding normal cells, and treating animal models with the mTOR inhibitor rapamycin was successful at specifically treating the cysts without affecting the adjacent normal tubule cells. Unfortunately, rapamycin was unsuccessful in human clinical trials when using the lower, more tolerable doses necessary to avoid immunosuppression. Frustrated by the inability to treat ADPKD with tolerable doses of rapamycin, Dr. Weimbs designed a conjugated form of rapamycin that could be targeted to the folate receptor on the kidney cells and avoid systemic effects.

With funding from an FY06 Investigator-Initiated Research Award, Dr. Weimbs synthesized and tested this conjugated form of rapamycin (EC0371/FC-rapa), which is taken up via folate receptor-mediated endocytosis and then cleaved intracellularly to reconstitute the active drug. His research showed that folate receptor is highly expressed in renal cyst-lining cells in human ADPKD tissue and two mouse PKD models, and in vitro testing showed that FC-rapa inhibits mTOR activity in a dose- and folate receptor-dependent manner. Additionally, treatment of PKD mouse models with FC-rapa resulted in inhibition of mTOR activity, inhibition of renal cyst growth, and preservation of renal function. Renal cyst growth was even inhibited in a ten times lower dose of FC-rapa in mouse models, providing kidney-specific inhibition of the mTOR pathway without causing detrimental systemic effects. Dr. Weimbs' findings suggest that FC-rapa has the potential to alleviate renal cystic disease in humans without the complications of systemic immunosuppression, providing hope that the first treatment for ADPKD is on the horizon. Moreover, this study suggests that, in addition to ADPKD, the targeting of folate-conjugated compounds to kidneys may be a promising approach for treating other renal epithelial disorders.





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<http://cdmrp.army.mil>  
or contact us at:  
[CDMRP.PublicAffairs@amedd.army.mil](mailto:CDMRP.PublicAffairs@amedd.army.mil)  
(301) 619-7071

