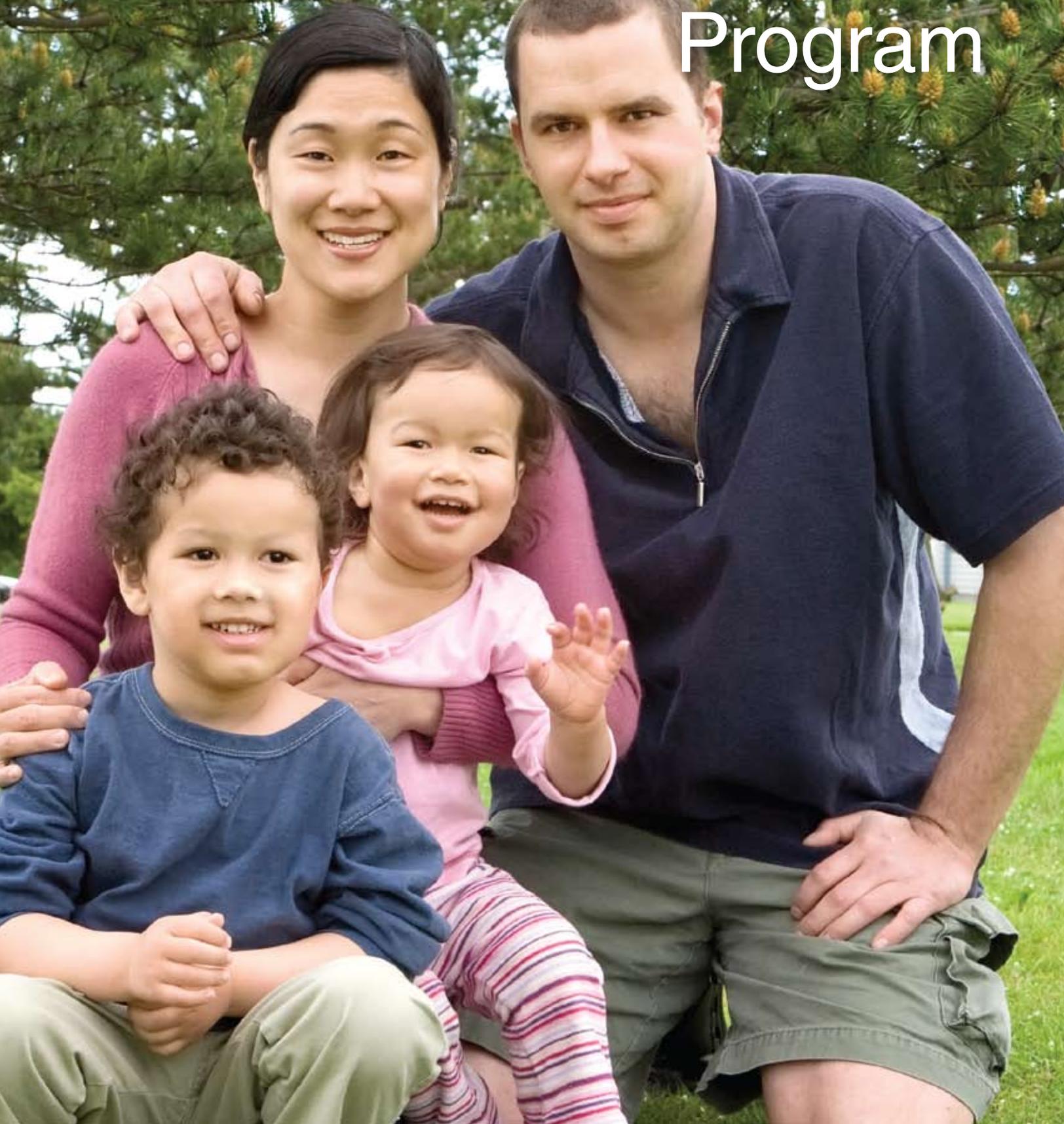


VI. Peer Reviewed Medical Research Program







Mission: Solutions



Vision

Find and fund the best medical research to protect and support the warfighter and their beneficiaries and to eradicate diseases that impact these populations.

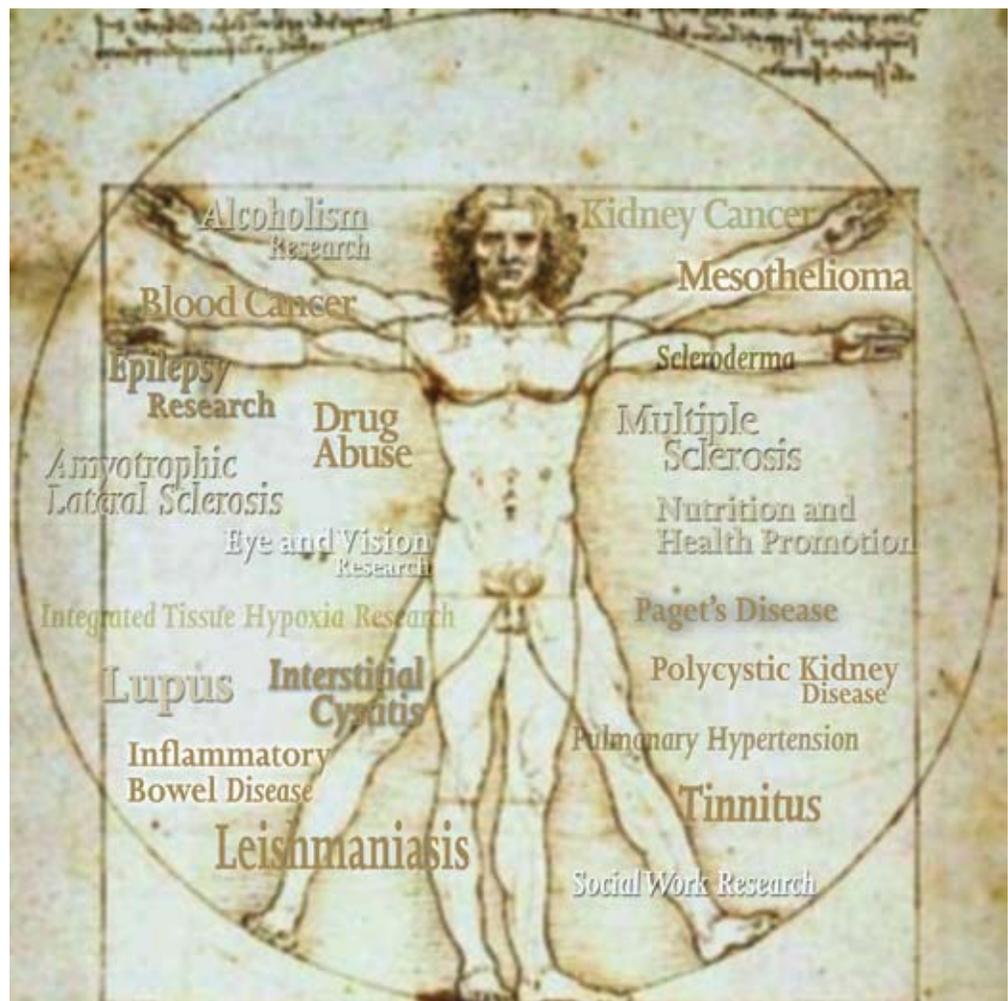
Mission

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

The Challenge

As we move through the 21st century, health and welfare issues facing the American people continue to evolve. While some important medical issues remain constant, many may differ from those faced by previous generations. In pursuit of its vision, the Peer Reviewed Medical Research Program (PRMRP) strives to continually address new challenges affecting the health of the Armed Forces, the U.S. veteran population, and their families with medical research that ultimately benefits the American public as a whole.

Each year the PRMRP solicits proposals, under topic areas directed by Congress, which address research covering a wide range of topics, including combat casualty care, cancer, infectious disease, metabolic disease, and social issues. Whether addressing newly relevant challenges such as traumatic brain injury, or long-standing problems such as alcohol abuse, the supported research is advancing the field of medical research. Since 1999, the PRMRP has funded research in more than 60 topic areas. The following pages demonstrate how PRMRP awardees are addressing important medical issues in five broad areas, thus providing a snapshot of the PRMRP's response to the challenge of 21st century medicine.



*Fiscal Year 2008
Topic Areas*

Program Background

Since 1999, the 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. Through fiscal year 2008 (FY08), Congress has appropriated \$394.5 million (M), which has supported 247 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 war zone 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 is relevant to civilian needs.

Because the military also provides medical services to millions of nondeployed personnel and their dependents, military retirees, and veterans, there is also a need to support research for a wide range of medical issues that affect these populations, 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 Department of Defense (DOD) PRMRP was established in FY99 by Appropriations Conference Committee Report No. 105-746, providing \$19.5M to establish a medical research program “for research that focuses on issues pertinent to our military forces.”

Partners Meeting the Challenge

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; consumer advocates, scientists, and clinicians provide expertise to peer and programmatic review panels; researchers ask pertinent scientific questions and conduct potentially high-impact studies; and the DOD manages all phases of the pre- and post-award processes.

Consumer Advocates

As active members of many PRMRP peer review panels, consumer advocates participate with scientists and clinicians in determining the scientific merit and potential impact of proposals submitted to the PRMRP. Consumer advocates' firsthand experiences with a specific disease or condition provide a unique perspective that is complementary to the scientific expertise and at times enlightening to researchers and clinicians on the panels. This perspective helps scientists understand the human side of how research will impact the community and allows for funding decisions that reflect the concerns and needs of patients, the clinicians who treat them, and survivors and their families. An additional benefit is that consumer advocates take what they have learned back to their communities. As a result of this collaboration, there is an increased awareness of the importance of research and a stronger relationship between the scientific and consumer advocacy communities.

“During my TBI rehabilitation I never imagined sitting in a room with scientists, clinicians, caregivers, therapists, and academicians discussing the status and potential improvement of TBI recovery. Not only did it happen, but the peer review panel members listened carefully to my, and the other consumer reviewers', views and opinions about the value of research proposals with respect, interest, and consideration. We learned from each other.”

Ken Rich
TBI Consumer Advisory Board
Craig Hospital, Denver, CO
FY08 Peer Reviewer



Peer Review Panel Members

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 have had the pleasure of working on the program since 2001. I have always been impressed with the scientific rigor and programmatic relevance associated with the CDMRP. I have not found a staff or peer review group that works harder to serve the investigators and the government. It is truly a privilege to be associated with this program. The CDMRP is truly making a difference in the areas of medical science research.”

Nathan Schwade, Ph.D.
**Chemical and Biological Program Manager for
Threat Reduction at Los Alamos
National Laboratory
FY08 Peer Reviewer**

“I’ve been honored to serve as a reviewer and panel chair for the CDMRP topic areas concerning mental health, substance use, and family support. The review process allows me to contribute in a manner blending my academic career with my experiences as a former military active duty and reserve components member. As a citizen, taxpayer, and academic valuing evidence-based research to practice, I’ve been pleased with the professionalism I’ve consistently observed during 10 years of involvement with the CDMRP. The CDMRP has ensured that our troops and their families will benefit, now or in the future.”

Dale Alexander, Ph.D.
**The University of Houston
FY08 Peer Reviewer**





Joint Programmatic Review Panel

The PRMRP Joint Programmatic Review Panel (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. They develop investment strategies that meet the needs of the military, VA, and civilian communities. JPRP members review proposals and recommend the most programmatically relevant studies for funding.

"I am honored to work with the CDMRP to accomplish the mission of the PRMRP. The PRMRP has performed and will continue to perform a critical role in funding much-needed research to address the needs of warfighters."

Richard C. Vinci, D.D.S.
Navy Medicine Support Command
FY08 PRMRP Chair



"The aspect of the PRMRP that I find really exciting is its ability to have an immediate impact on the development and delivery of new diagnostics and therapeutics through funding scientifically meritorious basic and clinical research."

Stephen Ahlers, Ph.D.
Navy Medical Research Center
FY08 PRMRP Alternate Chair



“It has been an honor and privilege to serve on the Joint Programmatic Review Panel for the Peer Reviewed Medical Research Program. The panel members are among the most respected individuals in their areas. To serve with the best military officers representing the Service Surgeons General has been a fantastic yet humbling experience. Most of all, my greatest satisfaction has been knowing that we have selected the best research proposals, representing the best opportunity for medical breakthroughs for so many hopeful patients. My congratulations to all who have managed this superb program over all these years.

One of the highlights of my 40-plus years of federal service...has truly been serving on the PRMRP and other CDMRP panels.”

Salvatore Cirone, D.V.M.
Office of the Assistant Secretary of
Defense for Health Affairs
JPRP member since 1999



Richard C. Vinci, D.D.S. (Chair)
Rear Admiral, Dental Corps, U.S. Navy
Navy Medicine Support Command

Stephen Ahlers, Ph.D.
 (Alternate Chair)
Captain, U.S. Navy (Ret.)
Naval Medical Research Center

Carl Castro, Ph.D.
Colonel, U.S. Army
U.S. Army Medical Research and Materiel Command

Salvatore Cirone, D.V.M.
Office of the Assistant Secretary of Defense for Health Affairs

Brenda Cuccherini, Ph.D.
Department of Veterans Affairs

Jonathan Jaffin, M.D.
Colonel, U.S. Army
U.S. Army Medical Research and Materiel Command

John Lucas, Sc.D.
Office of the Assistant Secretary of Defense for Health Affairs

Mark Lyles, D.M.D., Ph.D.
Captain, U.S. Navy
U.S. Navy Bureau of Medicine and Surgery

Debra Malone, M.D.
Lieutenant Colonel, U.S. Air Force
U.S. Air Force Division of Science and Technology

Carl Manemeit, M.A.
Lieutenant Commander, U.S. Marine Corps
Marine Corps Warfighting Laboratory

Patrick McNeilly, Ph.D.
Commander, U.S. Public Health Service
Department of Health and Human Services

Donnamaria Jones, R.Ph., Pharm. D.
Lieutenant Colonel, U.S. Air Force
Office of the Surgeon General

Richard Schaefer, M.D.
Colonel, U.S. Army
Uniformed Services University of the Health Sciences

Eileen Villasante, Ph.D.
Captain, U.S. Navy
Bureau of Medicine and Surgery

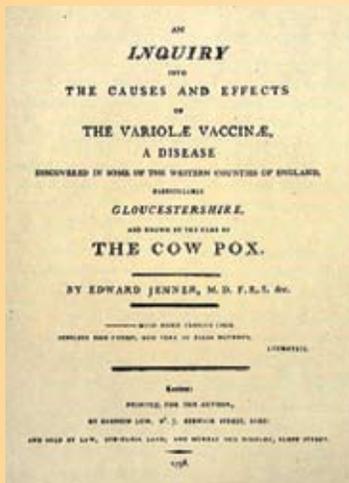
David Watson, Ph.D.
Major, U.S. Air Force
Air Force Research Laboratory

Finding Solutions

Infectious Disease

Infectious diseases are a major threat to the operational readiness of U.S. military forces. When U.S. Armed Forces are deployed to tropical regions, infectious diseases can cause significant casualties. Residents in areas where a disease is endemic typically develop natural immunity through lifelong exposure, but previously unexposed people who enter these areas as adults are readily susceptible to the disease. The development of preventive vaccines for complex tropical diseases is of high importance to the U.S. military. Such vaccines would also be of use to U.S. civilian travelers as well as local populations.

Deployed troops are at risk for another class of infectious diseases—those that spread rapidly in crowded living conditions such as barracks or troop ships and cause significant morbidity. Research to treat and prevent these diseases answers an important military need. The results are also of value for epidemics in child care centers, schools, restaurants, summer camps, hospitals, and nursing homes.



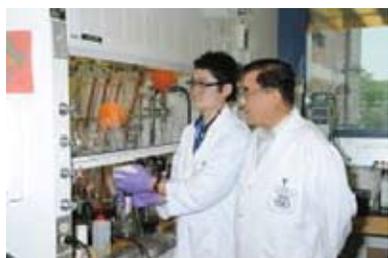
The First Vaccine

More than 200 years ago, English physician Edward Jenner demonstrated that deliberately exposing a person to small amounts of a disease-causing organism could stimulate the body's natural defenses to protect against a later challenge from the disease. Jenner used cowpox, a nonlethal virus related to smallpox, to protect subjects from smallpox infection. This first vaccine was delivered by smearing pus from a cowpox blister on an open cut. As scientists learned how to cultivate bacteria and viruses, they developed more sophisticated vaccines, first based on whole organisms, and then based on molecular fragments known as antigens.

Malaria

Historically, malaria has been a large cause of military casualties during deployments to tropical areas. The disease is caused by the intracellular parasite *Plasmodium*. After transmission by a mosquito bite, the sporozoite stage of the parasite establishes itself in the liver, and from there it enters a cycle of growth in red blood cells. The parasites eventually rupture the blood cells and release daughter parasites, called merozoites, which then continue the life cycle. Patients infected with malaria parasites experience a variety of symptoms including headache, high fever, muscle pain, and shaking chills. Worldwide, 350–500 million cases of malaria occur each year, and more than 1 million people die, most of them young children in sub-Saharan Africa. *Plasmodium* species are developing resistance to most of the antimalarial drugs currently available, lending urgency to the need for developing new drugs and effective vaccines.¹

Since 2001, the PRMRP has invested almost \$14M in malaria research, supporting the development of new classes of drugs, identification of new drug targets, and development of preventive vaccines.



Ai Lin, Ph.D.
Walter Reed Army Institute of Research

At the **Walter Reed Army Institute of Research**, **Dr. Ai Lin** is leading a team of scientists in exploring a new class of chemotherapeutics for malaria. With funds from an FY05 Advanced Technology Award, this group is synthesizing and testing imidazolidinedione derivatives with improved oral availability and a long half-life in the body. These drugs kill the parasite during the liver stage so they hold great promise for quickly curing an active infection, as well as preventing the establishment of infection and eliminating recurrences from dormant parasites in the liver.



Dr. Thomas Richie of the **Naval Medical Research Center** received an FY04 Investigator-Initiated Research Award to develop

a malaria vaccine that uses antigens from the sporozoite, liver, and blood stages of *Plasmodium* with an immunization strategy incorporating a DNA prime and adenovirus boost. A Phase I trial to establish the safety, tolerability, immunogenicity, and efficacy of an adenovirus-vectored vaccine encoding two malarial antigens is in progress.



Kami Kim, M.D.
Albert Einstein College of Medicine

Recipient of an FY04 Investigator-Initiated Research Award **Dr. Kami Kim** of the **Albert Einstein College of Medicine** is investigating a new drug target in *Plasmodium*. Dr. Kim constructed a “reporter” strain of the rodent parasite *P. yoelli* that can be viewed using luminescence in its mouse host. This luminescent parasite can provide real-time information on the site of action of malaria drugs by demonstrating where viable parasites remain in the mouse’s body after drug challenge. This promising research may lead to the development of safer and more effective drugs for malaria.

¹ Department of Health and Human Services, Centers for Disease Control and Prevention, *Malaria Facts*, 2007.

Zoonoses

A zoonosis is an infectious disease transmitted between vertebrate animals and humans. Frequently, the animal host is persistently infected and is therefore called the reservoir. Transmission may occur by direct contact or through an insect vector such as a tick. Zoonoses involve a variety of infectious agents such as bacteria, parasites, and viruses, which may be transmitted through food sources, close living conditions, or repeated handling.



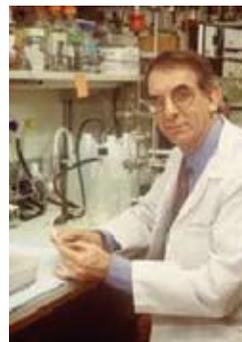
Hantaviruses carried by wild rodents cause hemorrhagic fever with renal syndrome (HFRS). This debilitating disease, with mortality rates of up to 15 percent, is a persistent problem for troops stationed in Korea.

Viral Hemorrhagic Fever Viruses:

- are RNA viruses
- may be sustained with an animal or insect as the natural reservoir
- are geographically restricted to the area of the host species
- have few cures or established drug treatments

An FY03 Program Project at the **Southern Research Institute** led by **Dr. Colleen Jonsson** is studying the molecular mechanism of inhibition of hantaviruses and other ribonucleic acid viruses by ribavirin, an effective drug with potentially dangerous side effects. The results are being used to design safe and effective treatments for HFRS as well as the closely related Rift Valley fever virus and Crimean-Congo hemorrhagic fever virus.

Tularemia is a highly infectious zoonotic bacterial disease. The causative bacterium, *Francisella tularensis*, can be transmitted by aerosols to cause severe pneumonia. A vaccine derived from whole bacterial cells has been used by the military but is



Marcus Horwitz, Ph.D.
University of California,
Los Angeles

not approved for general use. **Dr. Marcus Horwitz** of the **University of California, Los Angeles**, has achieved a breakthrough in the development of a safe and effective tularemia vaccine derived from bacterial antigens with support from an FY02 Investigator-Initiated Research Award. When immunized intradermally with this recombinant vaccine and exposed to aerosolized virulent *F. tularensis*, 100 percent of mice survived a lethal dose, and 75 percent survived a tenfold lethal dose.

Diseases in Close Quarters

When disease organisms can survive outside a host, they may be passed from person to person by direct touch or through aerosols from coughing and sneezing. When people are in close quarters, the speed and spread of disease are increased. Such robust disease organisms may also persist in the environment, lurking on countertops and cutting boards, in bedding, or in water supplies. Whether on cruise ships or troop ships, in nursing homes or resorts, pathogens find a welcome home when people are in close quarters.



Xi Jiang, Ph.D.
Cincinnati Children's Hospital

The Centers for Disease Control and Prevention reports that noroviruses are the most common cause of outbreaks of acute gastroenteritis in the United States. Noroviruses are so difficult to grow in cell culture that the development of effective vaccines and treatments has been severely hindered. **Dr. Xi Jiang** of **Cincinnati Children's Hospital** received an FY03 Investigator-Initiated Research Award to pursue an ingenious strategy to circumvent this problem. Having shown that human histo-blood group antigens serve as receptors for norovirus binding, Dr. Jiang developed a high-throughput screen for small-molecule compounds that block norovirus binding to these antigens, which are naturally secreted into saliva and the intestinal tract.

The Centers for Disease Control and Prevention reports that noroviruses are the most common cause of outbreaks of acute



Adrian Kajon, Ph.D.
Lovelace Respiratory
Research Institute

Since World War II, outbreaks of acute respiratory disease caused by adenovirus type 4 (Ad4) have affected military trainees at higher rates than the general public. With funds from an FY03 Investigator-Initiated Research Award, **Dr. Adrian Kajon** of the **Lovelace Respiratory Research Institute** performed a molecular epidemiology study of Ad4. Using genome typing of 724 Ad4 isolates obtained between 1997 and 2003 from cases of febrile respiratory illness in eight training centers, Dr. Kajon's study detected large amount of genetic variability was detected, including eight different genome types. In addition, the results suggest that Ad4 viruses persist in the environments of the training centers, serving as reservoirs of infection for entering trainees, as opposed to trainees carrying new Ad4 strains to the centers.

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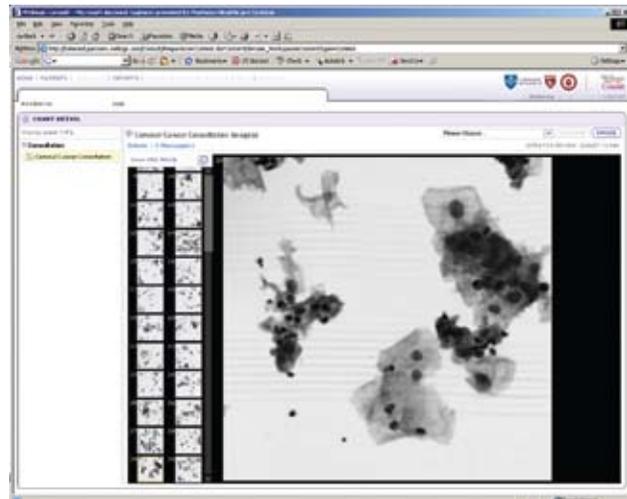
Cancer

Cancer is the second leading cause of death in the United States, accounting for approximately 23 percent of all deaths in 2005, the last year for which complete data are available. The American Cancer Society (ACS) estimates that more than 1.4 million Americans will be diagnosed with cancer in 2008.² Since President Richard Nixon declared war on cancer almost 40 years ago, a greater understanding of cancer biology has contributed to better diagnosis and treatment options for many cancers and a slow but steady decrease in the cancer mortality rate over the past decade. PRMRP-funded investigators continue to expand the knowledge of how genetic, lifestyle, and environmental factors cause cancer and to use this knowledge to develop new prevention strategies and treatments.

“I will also ask for an appropriation of an extra \$100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal. America has long been the wealthiest nation in the world. Now it is time we became the healthiest nation in the world.”

—President Richard M. Nixon, in his 1971 State of the Union address

Access to cervical cancer screening may be limited in areas where trained medical specialists are in short supply. **Dr. David Wilbur** of **Massachusetts General Hospital** proposed an innovative solution to this problem: low-resolution images of cervical cytology specimens acquired by an automated screening device are transmitted via the Internet to a secure website with image display software for review by cytology specialists. The software at the review station allows for an immediate report to be transmitted to the originating site. A Phase I trial of the system demonstrated its feasibility. A Phase II prospective study of 356 patients is under way with a larger Phase III trial in preparation. Thanks to an FY03 Advanced Technology Award to Dr. Wilbur, this system has the potential to provide an effective centralized method for triaging patient samples in countries or locations that lack trained cytotechnologists and pathologists.



The customized image reading station shows 30 fields for each case selected by the automated device displayed as thumbnails. The cytologist reviewer can enlarge each image for interpretation on the right-side screen.

² American Cancer Society, *Cancer Facts & Figures*, 2008.

Breathtaking

As the first and fourth leading causes of death in the United States, lung cancer and chronic obstructive pulmonary disease (COPD) take a high toll on the American population. COPD is the umbrella term for chronic progressive airflow restriction due to bronchitis or emphysema that leads to low blood oxygen and debilitating shortness of breath.

Chemicals in tobacco smoke and air pollution play a role in both diseases by stimulating the release of reactive oxygen species (ROS) that damage tissue and attracting inflammatory cells of the immune system. Individuals with COPD have an increased risk for lung cancer.

Tea is rich in polyphenols, natural compounds that scavenge ROS, making it a good candidate for a dietary intervention to counteract exposure to damaging oxidative stress. **Dr. Iman Hakim** of the **University of Arizona** received an FY02 Investigator-Initiated Research Award to conduct a clinical trial to test the ability of green or black tea to reduce biomarkers of oxidative stress in subjects with COPD and a history of smoking. The methodology of measuring these markers in blood, urine, and exhaled breath concentrate should prove useful for evaluating oxidative stress levels in individuals at risk for lung cancer.



Maria Czyzyk-Krzeska, M.D., Ph.D.
University of Cincinnati

Early-stage kidney cancer is almost asymptomatic. Patients with renal clear-cell carcinoma (RCC), the most common type of kidney cancer, frequently have advanced disease at the time of their diagnosis. Studies of the molecular basis of kidney cancer progression performed by **Dr. Maria Czyzyk-Krzeska** of the **University of Cincinnati**, recipient of an FY06 Investigator-Initiated Research Award, seek to improve the odds that patients with RCC will be diagnosed earlier, in time for successful surgical treatment. The von Hippel-Lindau tumor suppressor (pVHL) is known to play a role in RCC. While pVHL normally functions to target proteins for destruction, Dr. Czyzyk-Krzeska has identified a new role for pVHL: It activates a protein required for the expression of genes that protect against cancer.

Mending the Body

Changes in the way wars are fought as well as advances in military medicine are transforming the issues in combat casualty care. The use of body armor means more troops are surviving attacks that would previously have been fatal, but they are doing so with resulting traumatic brain injuries (TBIs), eye injuries, severe burns, or amputation. Other trauma-related injuries may be much less obvious and become manifest in health and wellness issues such as alcoholism or drug abuse. The approaches taken to solve these issues for the military will be useful for the civilian population as well, in areas such as TBI, wound healing after surgery, and improved treatment for fractures and spinal injury.



Injury to the anterior cruciate ligament of the knee can be a career-ender for a service member or even a weekend soccer player. **Dr. Christopher Wagner** of the **LifeCell Corporation** is supported by an FY05 Investigator-Initiated Research Award to develop a hybrid anterior cruciate ligament graft composed of acellular porcine tissue rolled up with polymer mesh. The graft's performance in pigs (whose hind-leg joint is a good model for human knees) was evaluated over a 12-month period, and its biomechanical performance exceeded that of currently available biological or synthetic grafts.



Catherine Uyehara, Ph.D., of Tripler Army Medical Center develops clinical strategies for the treatment of septic shock with surgical residents CPT Richard Delaney and CPT Danielle Holt

In a systemic bacterial blood infection, the immune response can combine with bacterial toxins to cause the life-threatening condition septic shock, in which blood pressure drops and blood flow carrying oxygen to vital organs is reduced, leading to organ failure and death. Recipient of an FY02 Investigator-Initiated Research Award, **Dr. Catherine Uyehara** of **Tripler Army Medical Center** used a pig model of septic shock to examine treatment of the low blood pressure with the hormone vasopressin. Results showed that treatment with vasopressin in the critical first hours of septic shock improves blood flow and oxygen delivery to the brain, heart, and kidneys.

Your Vital Information Highway

The spinal cord is the highway for nerve impulses needed for mobility and sensation. The National Spinal Cord Injury Statistical Center estimates that the U.S. incidence of spinal cord injury is 12,000 cases per year, with approximately 250,000 people currently living with such injuries. About 17 percent of these are veterans eligible for medical care and other benefits from the VA. The median age at injury was 28 in 2006. At this age, estimated lifetime costs for health care and living expenses (excluding costs of lost wages) range from \$600,000 for the least severe injury to more than \$3M for a tetraplegic with a high cervical (neck) injury. Scientists and clinicians continue to explore regenerative medicine approaches to restore full function to those with spinal cord injuries, but even partial improvements can reduce the financial cost as well as enhance quality of life.

Sources: National Spinal Cord Injury Statistical Center and the U.S. Department of Veterans Affairs



Richard Zeman, Ph.D., New York Medical College; Nengtai Ouyang, Ph.D.; and Xialing Wen

During the past decade, some researchers found evidence that tissue regeneration following spinal cord injury could be stimulated by x-irradiation. To achieve precise delivery of radiation to the spinal cord lesion without affecting surrounding tissue, **Dr. Richard Zeman** of **New York Medical College** is applying stereotactic irradiation in a rat model of spine injury with funding from an FY04 Investigator-Initiated Research Award. His studies have identified optimal dose sizes and target sites relative to lesions and suggested that novel physiologic processes contribute to the structural recovery of the spinal cord in response to x-irradiation.

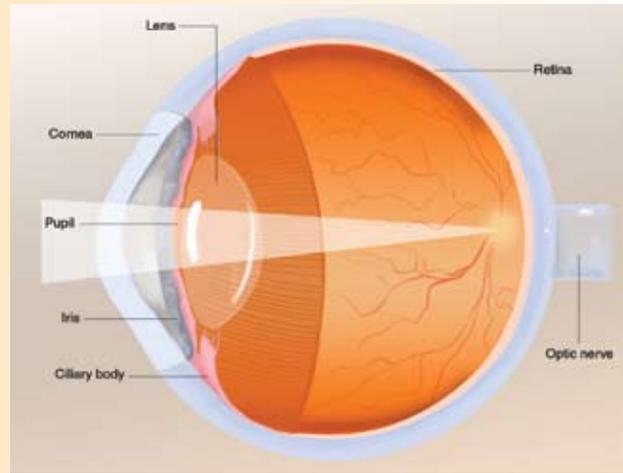


Combination computed tomography and x-ray image of mouse spine.

Invasive surgery to perform spinal fusion could be modified or eliminated if bone morphogenetic proteins (BMPs) could be delivered safely and effectively to the fusion site. **Dr. Elizabeth Davis** of the **Baylor College of Medicine** initiated an innovative research project funded by an FY06 Advanced Technology Award based on her finding that cells expressing recombinant BMPs stimulate endogenous BMP production that supports bone formation even though the recombinant cells are quickly cleared by the host immune system. Dr. Davis and colleagues have shown that this system is effective in stimulating bone formation when the recombinant cells are injected into the spines of immune-competent mice.

The Eyes Have It

The eye, a complex, fragile organ, is inherently difficult to repair. Because clarity must be preserved to maintain vision, the normal wound-healing processes of inflammation and scarring can be devastating to vision. To defend against scarring, eye tissues normally produce soluble factors that dampen the inflammatory response. The optic nerve and retina, which are extensions of the central nervous system, have many specialized cells that are critical for vision and do not regenerate once damaged.



Darlene Darrt, Ph.D., and Bruce Ksander, Ph.D., Schepens Eye Research Institute

In a severe trauma such as a penetrating eye wound, a strong inflammatory response is induced that overwhelms normal controls, and immune cells flood the eye to cause scarring. With funds from an FY02 Investigator-Initiated Research Award, **Dr. Darlene Darrt**, **Dr. Bruce Ksander**, and colleagues at the **Schepens Eye Institute** have shown that increasing the available amount of the eye's naturally occurring anti-inflammatory molecule, soluble Fas ligand, can block immune cell infiltration and scarring.



David Parke, M.D.; Michelle Callegan, Ph.D.; and Robert E. Anderson, M.D., Ph.D., Oklahoma Health Science Center

When a penetrating wound to the eye carries bacterial pathogens, the combination of the host immune response plus toxins secreted by the bacteria can combine for a vision-threatening infection inside the eye (endophthalmitis). At the **University of Oklahoma Health Sciences Center**, **Dr. Michelle Callegan's** research focuses on *Bacillus cereus*, a common pathogen in post-traumatic endophthalmitis that can migrate within the eye and release toxins to cause retinal damage. Dr. Callegan received an FY06 Investigator-Initiated Research Award to develop a multipronged attack on *B. cereus* that includes antibiotics, anti-inflammatory agents, and antitoxins.

Traumatic Brain Injury

TBI describes any injury to the head that disrupts brain function. It may be the result of a blow or jolt to the head or a penetrating head injury. While the flow of blood to brain cells is reduced, leakage of water into the brain causes dangerous swelling (edema) and pressure in the confined space of the skull. Restoring normal blood pressure and supply to the injured brain is critical for preventing continued brain cell death due to starvation for oxygen and nutrients.

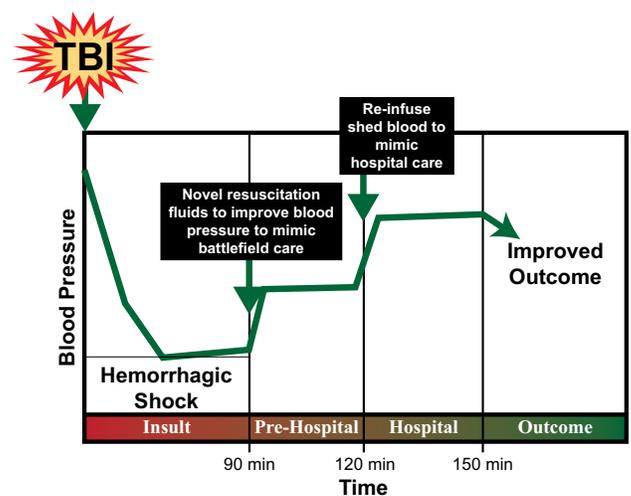


Ronald L. Hayes, Ph.D.
Banyan Biomarkers, Inc.

The complex physiological events that follow TBI are difficult to predict from the tools currently available—brain imaging and neurological examinations. In pursuit of better diagnostic and prognostic tools for brain injury, **Dr. Ronald Hayes** of **Banyan Biomarkers, Inc.**

leads an FY06 Program Project team seeking to identify and characterize TBI biomarkers in cerebrospinal fluid, blood, and urine using a novel rat model of brain injury. In addition to using proteomics to identify protein biomarkers, the team is applying the relatively new science of metabonomics to identify other classes of biomarkers, such as low molecular-weight metabolites. Metabonomic profiling combines analytic techniques such as nuclear magnetic resonance with statistical modeling to study the metabolic response to genetic modifications or environmental stimuli, thus providing a dynamic view of the pathophysiological state.

When TBI occurs in combination with other penetrating injuries, blood loss leading to hemorrhagic shock exacerbates the effects on the brain. With funds from an FY05 Program Project Award, a research team led by **Dr. Patrick Kochanek** of the **University of Pittsburgh** is working with a novel mouse model of TBI plus hemorrhagic shock to test new formulations of intravenous fluids used to treat TBI. Such fluids are used to replace lost blood volume, mimic blood consistency, and carry nutrients to brain cells. The fluids designed by **Dr. Carleton Hsia** and his team at **SynZyme Technologies** also address another problem in TBI, chemicals called reactive oxygen species (ROS). Produced as part of the inflammatory response, ROS damage tissues and contribute to edema. The inclusion of ROS scavengers is an important feature of the team's next-generation resuscitation fluids, which have the potential to restore blood pressure and enhance survival using a small fluid volume while offering neuroprotection.



Health and Wellness

Obesity is frequently called an epidemic in the United States in the scientific and popular press. Most Americans are aware that type 2 diabetes and heart disease, which are associated with obesity, are on the rise. As increasing numbers of young Americans are classified as overweight or obese, fewer can pass fitness tests for enlistment in the Armed Forces. For recruits who make the grade, appropriate diet, exercise, and sleep habits are important for optimum performance while deployed.



Mental health is also an important component of wellness. Mental disorders such as anxiety, mood disorders, and substance abuse account for about 15 percent of the social and economic global burden of disease.³ Collateral effects of mental disorders on families, caregivers, and employers add to the burden. Post-traumatic stress disorder (PTSD) is currently of concern in the United States. While approximately 8 percent of the U.S. population will have symptoms of PTSD in their lifetime, up to 20 percent of veterans in the current conflicts may experience PTSD.⁴

The Metabolic Syndrome

A group of co-occurring symptoms, including abdominal obesity, insulin resistance, abnormal cholesterol (high triglycerides and low HDL [high-density lipoprotein]), and high blood pressure, is known to synergistically increase an individual's risk of heart disease, stroke, and type 2 diabetes. While genetics and increasing age play a factor in this "metabolic syndrome," it is also linked to a high-fat diet and inactivity. The molecular mechanisms underlying the syndrome are not understood, but the implications for health are disturbing. As rates of obesity and inactivity increase in the United States, occurrences of metabolic syndrome risk factors are increasing, even among young children.

Moller DE and Kaufman KD. 2005. *Annual Review of Medicine* 56: 45-62.



³ Global Burden of Disease and Risk Factors. Oxford University Press, 2006.

⁴ National Center for Post-Traumatic Stress Disorder.



Ira Tabas, M.D., Ph.D.
Columbia University College of
Physicians and Surgeons

Dr. Ira Tabas of the **Columbia University College of Physicians and**

Surgeons received an FY05 Investigator-Initiated Research Award to study the molecular mechanisms of arterial plaque rupture in coronary artery disease. Because the glucose-lowering drugs called thiazolidinediones (TZDs), used to treat type 2 diabetes, have shown benefits in preventing plaque formation, Dr. Tabas examined their effect on the stability of advanced plaque. His intriguing results show that an “off-target” pathway affected by TZDs has some molecular effects that are beneficial for plaque reduction but that, in addition, can actually stimulate the rupture of advanced-stage plaque, a cause of heart attacks. These results highlight the complex pathology of metabolic syndrome and also suggest that optimizing TZDs will improve their efficacy.

Coronary Disease: Taking the Long View

Arterial plaque is an accumulation of fat, cholesterol, cells, and cell debris in the inner lining of arteries. Plaque can reduce blood flow sufficiently to cause symptoms, but acute coronary events caused by plaque rupture can occur with no warning symptoms. Calcium also accumulates in plaque so the presence of coronary artery calcium (CAC) can be a predictor of subclinical coronary artery disease. This correlation had been well validated in older, high-risk patients, but its value in young, asymptomatic individuals was not clear in 1998 when the U.S. Army initiated the Prospective Army Coronary Calcium Project (PACC) with funding assistance from the PRMRP. Electron beam computed tomography (EBCT) was used to detect the presence of coronary calcium as well as the location, extent, and density of calcific deposits in active-duty personnel. The project included a prospective 5-year cohort study of 2,000 subjects. The results showed that CAC testing in 40- to 50-year-old Caucasian men had independent prognostic value for incident coronary heart disease.

As the project leader for the PACC, **Dr. Allen Taylor** of the **Walter Reed Army Medical Center** was well placed to conduct a follow-up study of PACC project participants. With funds from an FY04 Investigator-Initiated Research Award, Dr. Taylor is studying participants who had coronary calcium on their original EBCT scans for cardiovascular events in relation to CAC progression. This follow-up should result in extremely valuable 10-year actuarial data. In addition, the study examines the relationship between metabolic syndrome and CAC. The mean body-mass index of the active-duty population enrolled in the PACC project is 28, which is in the overweight range. Dr. Taylor has found that in the study cohort, metabolic syndrome components are significantly associated with CAC progression.

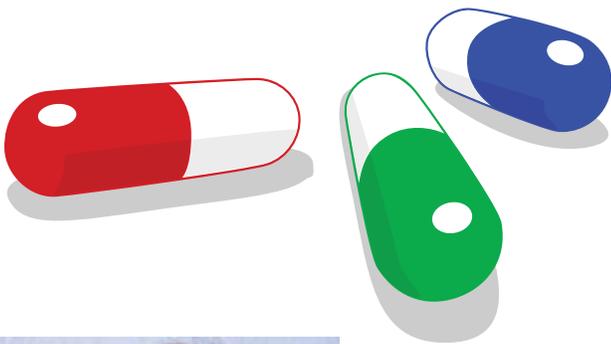


Allen Taylor, M.D.
Walter Reed Army
Medical Center

Fighting Bone Loss for Active Women

Individuals seeking to lose weight quickly, such as military troops preparing for their required semiannual physical, may combine extreme calorie restriction with excessive exercise. There is evidence that significant bone loss can occur with such weight loss tactics. In women, rapid weight loss may affect reproductive hormone profiles, resulting in menstrual cycle disturbances and decreased bone mass. Exercise-associated menstrual disturbance in female athletes is often associated with osteoporosis.

One factor in maintaining bone health is maintenance of sufficient vitamin D. There is a growing consensus that most people do not achieve sufficient levels of this critical vitamin, but there are insufficient data on the actual levels required. **Dr. John Gallagher** of **Creighton University** received an FY06 Investigator-Initiated Research Award to conduct a prospective clinical trial in women ages 25 to 45 with low serum vitamin D levels. The trial should help establish the appropriate dose of vitamin D to reach effective serum concentrations for bone health.



Mary Jane De Souza, Ph.D.
Pennsylvania State University



With funding from an FY05 Investigator-Initiated Research Award, **Dr. Susan Bloomfield** of **Texas A&M University** is studying how weight loss can be achieved without sacrificing bone health by subjecting female rats to different combinations of calorie restriction and exercise. This rat model allows Dr. Bloomfield to control diet and exercise and study bone architecture and formation in ways that would be difficult or impossible with human subjects.

While decreases in estrogen are clearly linked to bone loss in women, FY05 Investigator-Initiated Research Award Recipient **Dr. Mary Jane De Souza** of **Pennsylvania State University** hypothesizes that there may be nonhormone-linked mechanisms of bone building. She is testing a regimen of increased calorie intake in women with exercise-associated menstrual disturbance for its effect in restoring normal menstrual function as well as decreasing bone loss.

Post-Traumatic Stress Disorder

PTSD, a psychiatric disorder that affects millions of people each year, can develop after a traumatic event such as combat exposure, abuse, or a natural disaster. Individuals with PTSD experience highly distressing memories or thoughts of the traumatic event. They may try hard not to think about the experience or go out of their way to avoid situations that remind them of the traumatic event. As a result, PTSD may be very disruptive, adversely affecting personal relationships and work performance through loss of productivity. Current military operations have highlighted the crucial need for a better understanding of PTSD to develop new preventive measures, diagnostic procedures, and treatment practices.



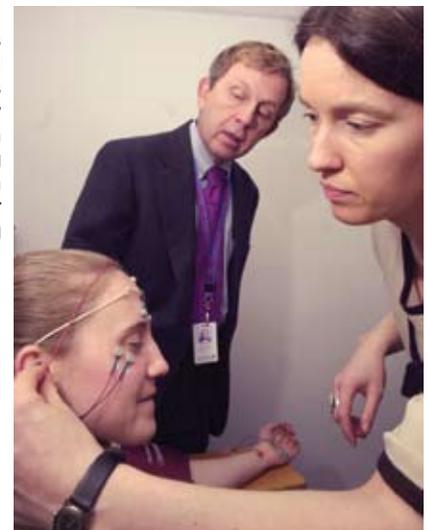
Melissa Polusny, Ph.D.
University of Minnesota
Minneapolis VA Medical Center

Modern military operations are relying on large numbers of Reserve Component troops in peacekeeping and combat missions. These troops are older, may experience less unit cohesion and less perceived support while deployed, and are more likely to

have family and civilian work responsibilities outside of the military. As a result, these troops may face significantly greater familial and occupational strain when deployed. **Dr. Melissa Polusny** and her colleagues at the **University of Minnesota** and **Minneapolis VA Medical Center** are conducting the Readiness and Resilience in National Guard Soldiers Project with funding from an FY06 Investigator-Initiated Research Award. This longitudinal cohort study of Minnesota National Guard troops that examines the effects of predeployment, deployment, and postdeployment risk and resiliency factors on Soldiers' subsequent utilization of mental health services and military retention/attrition.

According to **Dr. Roger Pitman's** model of PTSD, a psychologically traumatic event stimulates stress hormones so that the memory of the event is strongly fixed, or "consolidated." The result is a persistent memory that is too easily activated with consequent anxiety and dysfunction. Memory enhancement by stress hormones can be counteracted by the drug propranolol if it is administered soon after the traumatic event. At **Massachusetts General Hospital**, Dr. Pitman and colleagues have preliminary evidence that years after a traumatic event, patients who reactivate their traumatic memory become responsive again to propranolol treatment. Thanks to an FY06 Investigator-Initiated Research Award, they are now performing a controlled, randomized, double-blind study of this treatment in Iraq and Afghanistan veterans exhibiting combat-related PTSD.

Roger Pitman, M.D.,
of Massachusetts
General Hospital
observes as
research fellow
Ulrike Buhlmann
adjusts recording
electrodes on
volunteer
Michele Wedig





Chemical Exposure

During the past half-century, U.S. military engagements throughout the world have resulted in exposure to chemicals that may have contributed to the development of medical conditions and diseases. In many cases, there is insufficient evidence to draw a conclusion on the existence of an association or causal relationship between exposure and a medical condition or disease. The PRMRP supports research that will provide sufficient supporting data to draw valid conclusions about cause and effect in environmental exposures.

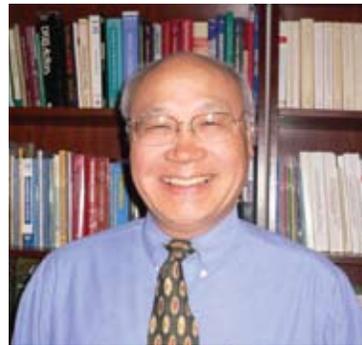
“The 670,000 service members deployed in 1990–1991 to Southwest Asia for Operations Desert Shield and Desert Storm (the Gulf War) were different from the troops deployed in previous similar operations: they were more ethnically diverse, there were more women and more parents, and more activated members of the Reserves and National Guard were uprooted from civilian jobs. The overwhelming victory that they achieved in the Gulf War has been shadowed by subsequent concerns about the long-term health status of those who served. Various constituencies, including a significant number of veterans, speculate that unidentified risk factors led to chronic, medically unexplained illnesses, and these constituencies challenge the depth of the military’s commitment to protect the health of deployed troops.”

Protecting Those Who Serve: Strategies to Protect the Health of Deployed U.S. Forces.
Institute of Medicine Report, 2000.



Gulf War troops took the nerve agent prophylactic pyridostigmine bromide and were also exposed to several pesticides used to control insects. It is possible that synergistic effects of these two classes of chemicals played a role in central nervous system symptoms reported by Gulf War veterans.

Dr. Maxine Kregel and colleagues of the **VA Boston Healthcare System** and **Boston University** were funded by an FY03 Investigator-Initiated Research Award to explore this hypothesis. They performed a neuropsychological analysis of Gulf War veterans divided into four categories depending on their pesticide and pyridostigmine bromide exposure. Preliminary results from this study show that the group with the highest exposure to both the pesticides and pyridostigmine bromide reported significantly more rapid and irregular heart rates, breathing trouble, sleep difficulties and fatigue, body tingling and twitching, anxiety, and mental confusion than the other three exposure groups.



Han Kang, Ph.D.
Veterans Affairs Medical Center

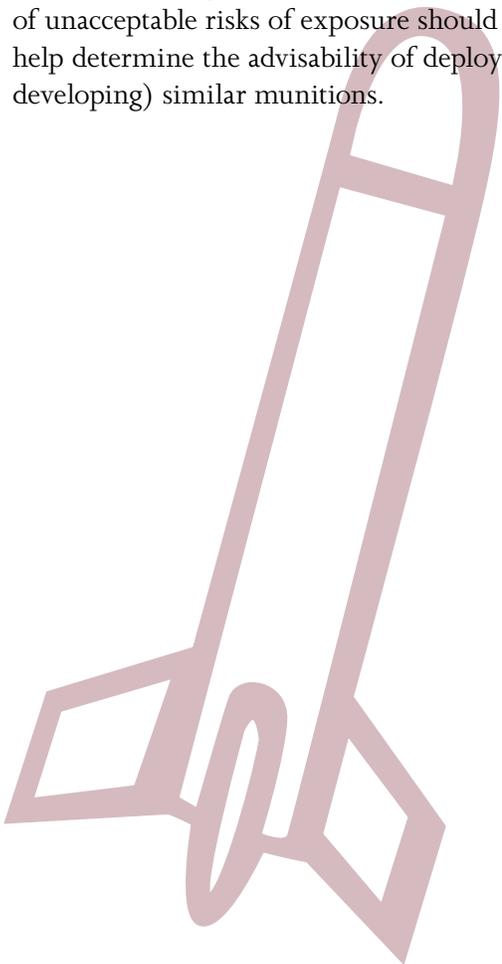
A permanent panel of 30,000 Gulf War-era veterans was surveyed for baseline health information in 1995. With funds from an FY01 Investigator-Initiated Research Award, between 2002 and 2006, **Dr. Han Kang** and colleagues at the **Veterans Affairs Medical Center** performed a longitudinal morbidity study on 9,970 of the 29,607 living members of the original panel. Data showed that 14 years after deployment, 1991 Gulf War veterans continue to report elevated associations for many adverse health outcomes when compared with veterans deployed elsewhere. Veterans of the 1991 Gulf War who participated in the study reported significantly higher rates of unexplained multisymptom illness, chronic fatigue syndrome-like illness, PTSD, and functional impairment; health care utilization; chronic medical conditions; indices of depression, anxiety, and alcohol abuse; and abnormal general health perception.

Dense metals such as depleted uranium and tungsten can be used to make armor-piercing missiles. Such munitions are now in common use throughout the world. The health effects when these metals are internalized through embedded shrapnel are not well understood. Although tungsten may seem to be a benign substitute for uranium, research by the **Armed Forces Radiobiology Research Institute (AFRRI)** implicated tungsten alloys as carcinogens when implanted in rats. To expand these results and determine the human risk from the tungsten alloys, **Dr. John Kalinich** of AFRRI received an FY05 Investigator-Initiated Research Award to repeat 2-year exposure studies in mice to meet regulatory agencies' standards of evidence. Results of this work should help in formulating policies for military surgeons who must treat personnel wounded by fragments of the alloys. Indications of unacceptable risks of exposure should also help determine the advisability of deploying (or developing) similar munitions.

Acute toxicity from exposure to organophosphorus (OP) pesticides and nerve agents is due to irreversible binding to the neurotransmitter acetylcholinesterase. However, some people suffer chronic illness from a dose of OP too low to inhibit acetylcholinesterase, and **Dr. Oksana Lockridge** of the **University of Nebraska Medical Center** wants to know why. She received an FY06 Investigator-Initiated Research Award to test her hypothesis that individual differences in the level of expression of one or more additional targets of OP pesticides could explain these differences. By searching for these new OP targets, Dr. Lockridge also hopes to identify new biomarkers of OP exposure and new bioscavengers for protection against OP toxicity.



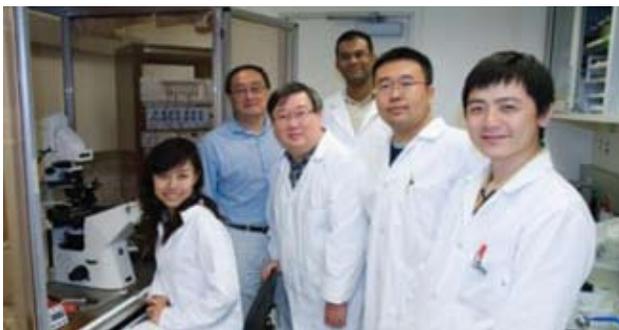
Oksana Lockridge, Ph.D., and
Research Associate Hasmik Grigoryan



Tackling Lou Gehrig's Disease

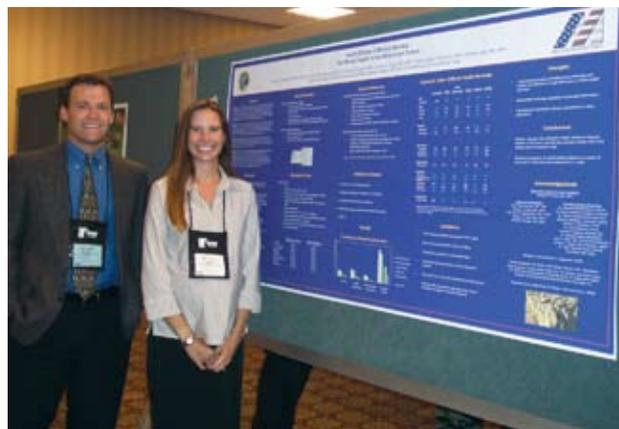
The fatal neurodegenerative disease Amyotrophic Lateral Sclerosis (ALS) is characterized by the selective death of motor neurons in the cortex, brain stem, and spinal cord. About 90 percent of cases are sporadic and of unknown, possibly environmental, etiology. A large epidemiological study* that followed Gulf War-era veterans concluded that those deployed to the Persian Gulf had a significantly increased risk of ALS compared with those deployed elsewhere. Based on this study, the VA decided to provide benefits to veterans who develop ALS.

*Source: Horner RD, Kaming KG, Feussner TR, et al. 2003. *Neurology* 61:742-749.



Yan Han; Li Niu, Ph.D.; Jae Seon Park, M.D., Ph.D.; Sabari Jayaseelan; Joe Wang; and Zhen Huang, Ph.D., State University of New York

Excitotoxicity, or overstimulation of neurons through glutamate receptor channels that in turn damages and kills them, plays a major role in ALS. With funds from an FY03 Investigator-Initiated Research Award, **Dr. Li Niu** of the **State University of New York at Albany** is developing small RNA molecules called aptamers that can block the neurotransmitter glutamate from binding with its receptor as a way to control the overstimulated receptors. Aptamers are single-stranded nucleic acids that are identified by probing a library of randomly generated sequences for interaction with the target of interest. Dr. Niu has identified promising water-soluble aptamers that have a very high affinity for the targeted glutamate receptor.



Tyler Smith, Ph.D., and Besa Smith Ph.D., at the Force Health Protection Conference

The deployed military population may encounter a variety of hazards that can adversely affect reproductive health. **Dr. Tyler Smith** of the **DOD Center for Deployment Health Research** at the **Naval Health Research Center** received an FY06 Investigator-Initiated Research Award to study whether parental deployment to Afghanistan or Iraq is associated with adverse health outcomes in offspring. This ambitious epidemiological study is facilitated by the availability of population demographic data from the Defense Enrollment Eligibility Reporting System, service member health care data from the Defense Health System, and data from the DOD Birth and Infant Health Registry, which monitors the birth and health outcomes of all DOD-sponsored babies through their first year of life.



The Program Today

FY07 Summary

Although Congress did not appropriate funds for FY07, the program continued to actively manage awards funded in previous years through monitoring research progress and capturing intellectual and tangible research results. The PRMRP continued to evaluate the program and update the PRMRP website with research highlights.

The Vision for FY08

The FY08 PRMRP received a congressional appropriation of \$50M to continue the peer-reviewed program, and research proposals were solicited across 21 congressionally directed topic areas. Four award mechanisms were offered: Investigator-Initiated Research, Translational Research, Advanced Technology/Therapeutic Development, and Clinical Trial Awards. These mechanisms were designed to solicit research proposals routed in basic research, translational research, and clinical research. All proposals were required to be responsive to the health care needs of the Armed Forces and family members, the U.S. veteran population, and the general public. In addition, alignment with current DOD research was encouraged. A total of 872 proposals were received across the 21 topic areas; approximately 26 awards are anticipated. The congressional appropriations and investment strategy executed by the PRMRP for FY08 are summarized in Appendix B, Table B-5.



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