VIII PEER REVIEWED MEDICAL RESEARCH PROGRAM

In their efforts to protect our country, members of the military are subjected to a variety of diseases and injuries that are not commonly encountered by civilians. These include hearing loss due to the extremely loud noises generated by military equipment and explosives; musculoskeletal trauma experienced in times of war and during training exercises; exposure to deadly infectious diseases such as malaria, leptospirosis, leishmania, and hepatitis while deployed in third world countries; and acute lung injury and respiratory complications in members of the military who operate armored vehicles due to short, intermittent, high-level exposures to toxic gases (e.g., carbon monoxide, sulfur dioxide, ammonia, and nitrogen oxides) from engine exhaust and the firing of weapons. Research sponsored by the Peer Reviewed Medical Research Program (PRMRP) aims to preserve the health of our military forces by targeting these and other conditions of high military relevance.

Mission: To support biomedical research with direct relevance to military health.

Congressional Appropriations for Peer Reviewed Research:

- $194.5M in FY99–03
- $50M in FY04
- $50M in FY05

Funding Summary:

- 127 awards from the FY99–03 appropriations
- 29 awards from the FY04 appropriation
- ~39 awards anticipated from the FY05 appropriation

PROGRAM BACKGROUND

The Department of Defense (DOD) PRMRP was established in fiscal year 1999 (FY99) by Appropriations Conference Committee Report No. 105-746, which provided $19.5 million (M) to DOD to establish a medical research program that focused on issues pertinent to U.S. military forces. Congress directed the Deputy Secretary of Defense to work with the Surgeons General of the Services to establish a program to select medical research projects of clear scientific merit and direct relevance to military health. The U.S. Army Medical Research and Materiel Command (USAMRMC) became the Executive Agent for this new program through Joint Services coordination and the specific recommendation of the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. The USAMRMC instituted the plan recommended by the ASBREM Committee, one aspect of which required the formation of a Joint Programmatic Review Panel (JPRP), to determine programmatic priorities. The PRMRP JPRP is composed of representatives from the four military services, DOD (Health Affairs), and the Departments of Health and Human Services and Veterans Affairs. The JPRP provides programmatic and strategic direction for the PRMRP and serves as a recommending body to the USAMRMC Commanding General on final funding decisions.

From FY99 through FY05, Congress appropriated a total of $294.5M through the PRMRP to fund peer reviewed research focused on military health. A total of 156 awards have been made through FY04 reflecting the program's mission to support research with direct relevance to military health. Appendix B, Table B-5, summarizes the directions from Congress for the PRMRP appropriations and the investment strategy executed by the PRMRP for FY04 through FY05.

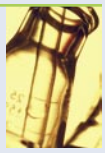
THE FISCAL YEAR 2004 PROGRAM

Congress again appropriated $50M to the PRMRP in FY04 to support peer reviewed research pertinent to the health of U.S. military forces. The PRMRP requested proposals in 25 topic areas: 22 recommended by Congress (Conference Committee Report No. 107-732, pp. 324–325) and three additional military relevant topic areas added by the Office of the Assistant Secretary of Defense for Health Affairs [OASD(HA)]. A total of 308 proposals were received across the 25 topic areas, and 29 were funded. Table VIII-1 provides a summary of the FY04 PRMRP topic areas in terms of proposals received, number of awards, and dollars invested.

Table VIII-1. Funding Summary for the FY04 PRMRP

Topic Areas	Number of Proposals Received	Number of Awards	Investment
Alcoholism Research	15	1	$1.3M
Amyotrophic Lateral Sclerosis	30	2	$2.8M
Anti-diarrhea Supplement	0	0	0
Blood-Related Cancer Research	25	2	$3.2M
Childhood Asthma	8	1	$1.0M
Chronic Pain Research	9	1	$1.8M
Epilepsy	11	1	$2.0M
Geneware Rapid Vaccine Development	1	1	$0.4M
Interstitial Cystitis Research	4	0	0
Interventional Cardiovascular Magnetic Resonance Imaging Technologies	1	0	0
Limb Loss and Paralysis Research	16	2	$3.2M
Lung Cancer Screening[a]	5	1	$0.7M
Malaria Vaccine Initiative [SBRI][b]	1	1	$2.0M
Military Medical Informatics Research	8	0	0
Military Relevant Disease Management[c]	80	8	$13.8M
Muscle Function Research	20	2	$3.4M
Muscular Dystrophy	5	0	0
Osteoporosis and Bone-Related Disease Research	35	3	$4.3M
Paget's Disease	0	0	0
Post-traumatic Stress Disorder	21	1	$1.0M
Providence Cancer Research Project	1	0	0
Pseudofolliculitis barbae[a]	0	0	0
Reserve Component Medical Training	3	1	$1.9M
Smoking Cessation[a]	6	1	$1.6M
Social Work Research	3	0	0
Total	308	29	$44.4M

[a] Topic area added by the OASD(HA).
[b] Seattle Biomedical Research Institute.
[c] With emphasis on research on malaria, leishmaniasis, and wound infections.



THE BUSINESS STRATEGY FOR THE FISCAL YEAR 2005 PROGRAM

Congress appropriated $50M to continue the PRMRP in FY05. The PRMRP requested proposals in 23 topic areas: 21 recommended by Congress (Conference Committee Report No. 108-622, pp. 365-366) and 2 additional topic areas with high military relevance added by the OASD(HA). Ten of the 21 topic areas recommended by Congress were new to the program in FY05. A total of 492 proposals were received across topic areas, as detailed in Table VIII-2, and approximately 39 awards are anticipated.

"The DOD CDMRP provides an extraordinary opportunity for top notch civilian researchers with novel and military relevant research ideas to perform research that will truly help our soldiers."

Sue Baum, M.D., FY05 Alternate JPRP Member

Table VIII-2. Topic Areas Offered and Proposals Received for the FY05 PRMRP

Topic Areas	Number of Proposals Received
Acellular Human Tissue Matrix Research[a]	6
Alcoholism Research	23
Amyotrophic Lateral Sclerosis	28
Anti-radiation Drug Development[a]	15
Autism[a]	35
Autoimmune Diseases such as Scleroderma and Sjögren's Syndrome[a]	29
Blood-Related Cancer Research	29
Childhood Asthma	5
Chronic Pain Research	19
Conjugate Vaccines to Prevent Shigellosis[a]	2
Diabetes Research[a]	34
Duchenne's Disease Research[a]	2
Epilepsy Research	8
Interstitial Cystitis	6
Lung Cancer Screening[b]	4
Lupus and Lupus-Biomarker Research[a]	29
Military Relevant Disease Management[b,c]	72
Orthopaedic Extremity Trauma Research[a]	45
Osteoporosis and Bone-Related Diseases Research	60
Paget's Disease	2
Post-Traumatic Stress Disorder	33
Social Work Research	4
Volume Angio CAT (VAC) Research[a]	2
Total	492

[a] Topics new to the program in FY05.
[b] Topic area added by the OASD(HA).
[c] With emphasis on research on Acinetobacter baumannii infections, obesity research, and smoking cessation.

SCIENTIFIC OUTCOMES AND ADVANCES

The PRMRP is supporting military health-related research ranging from basic science to the implementation of advanced products and technologies. The following research accomplishments, summarized by topic area, showcase the exciting progress that is being made by PRMRP-supported investigators to address health issues faced by active duty and retired Soldiers, Sailors, Airmen, Marines, and their families. Additional examples of scientific outcomes, products, and technologies resulting from PRMRP support can be found in the box stories on this page and page VIII-5 as well as in Section III of this annual report.

"The PRMRP should be viewed as a model for execution of congressionally directed research within the Department of Defense."

Salvatore M. Cirone, D.V.M., M.P.V.M., FY99–05 JPRP Member

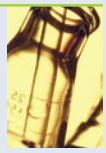
Acute Lung Injury/Acute Respiratory Distress Syndrome

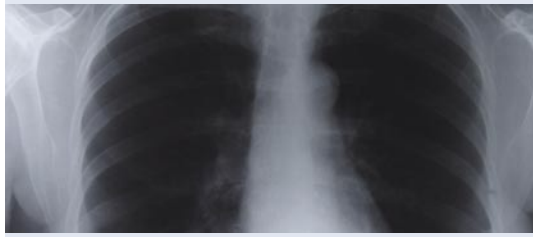
Leopoldo Careio, M.D., U.S. Army Institute of Surgical Research
Vladimir Muzykantov, M.D., Ph.D., University of Pennsylvania

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening conditions in which inflammation of the lungs and accumulation of fluid in the air sacs (alveoli) lead to low blood oxygen levels. ALI or ARDS can result from severe traumatic injury, hemorrhage, severe burns, and inhalation of smoke or chemicals, and resultant mortality rates are 20%–30%. The prevalence of ARDS appears to be increasing in modern combat, and it is also a likely major outcome of a chemical weapons attack on military or civilian personnel. Use of a lung-protective mechanical ventilator is the best available

SENSOR SYSTEM TO DETERMINE TISSUE PERFUSION AND GUIDE RESUSCITATION

There are many medical challenges to consider for far-forward medical care to reduce mortality and morbidity associated with major battlefield wounds and injuries. In particular, trauma and hemorrhage are leading causes of death in the United States and major concerns of the military. Significant loss of blood leads to shock, a condition of inadequate organ perfusion, and tissue oxygenation, and there is the need for intelligent medical systems to guide corpsmen and combat medics in triage and resuscitation of severely injured combatants. Dr. Babs Soller at the University of Massachusetts Medical School in collaboration with Luxtec Corporation has developed and tested a prototype, portable sensor system based on near-infrared spectroscopy to noninvasively measure tissue perfusion. This system quickly and accurately measures muscle pH, muscle oxygen tension, and hematocrit from light reflected from the palm of the hand and will guide combat medical personnel in resuscitation care and evacuation. The prototype device and additional units are currently in ongoing clinical trials and scheduled for product delivery to the USAMRMC's Core Combat Casualty Care Research Program later in 2005 for further field testing and evaluation.





treatment, but this requires sensitive equipment and close supervision and is not appropriate for battlefield or mass casualty situations. Dr. Leopoldo Cancio at the U.S. Army Institute of Surgical Research is exploring the use of an intravenous membrane oxygenator implanted directly in the vena cava to provide improved oxygen/carbon dioxide exchange in the blood without a large external pump, using sheep as a model. An alternative approach is being taken by Dr. Vladimir Muzykantov of University of Pennsylvania. Deposition of fibrin and blood clots in the lungs and oxidative stress in the lung vasculature contribute to ALI and ARDS. Delivering antioxidant and clot-dissolving enzymes directly to the lungs could help prevent the lung inflammation that leads to low blood oxygen levels. These enzymes can be directed to the lungs by linking them to antibodies targeting the surface of the endothelial cells such as those lining the lungs. Dr. Muzykantov is currently testing antibody delivery systems in mice, with plans to advance to larger animal models.

DEVELOPMENT OF A DEVICE TO TREAT *PSEUDOFOLLICULITIS BARBAE*

Pseudofolliculitis barbae (PFB or shaving bumps) is an inflammatory condition of the beard area, usually observed in dark-skinned men with thick, coarse hair who shave regularly. Currently available depilatories, topical creams, and so-called PFB razors do not offer a permanent definitive answer for PFB and, at best, only temporarily ameliorate the condition. PFB can impact force readiness, compromise the ability to wear close-fitting protective facial gear, and affect the service members' quality of life. Therefore, this condition is considered a significant dermatologic disease in the U.S. Military; it affects more than 50% of African American servicemen. Laser- and lamp-based modalities that were initially developed for removal of unwanted body hair have the potential to provide a curative solution to the problem. Michael Smotrich from Palomar Medical Technologies, Inc. is developing a self-operated, portable, low irradiance PFB treatment device that can be used by individuals without physician supervision. Current protocols are in clinical trials at the Naval Medical Center in San Diego using a larger, physician-operated system. Further trials are planned with the Navy and Army for smaller units using self-treatment parameters. If successful, this device would not only be a great benefit to military service personnel, but to the general public as well.

Alcohol Abuse Research

Andrea Allan, Ph.D., University of New Mexico

Alcohol misuse in the military is costly and has been identified as an important factor in aggressive behavior in humans. Therefore, the military is attempting to de-glamorize alcohol use and reduce alcohol abuse among its military personnel. Dr. Andrea Allan and colleagues at the University of New Mexico are examining the impact of serotonin receptor 3 (5HT3) overexpression on alcohol preference, natural aggressive behavior, and alcohol-heightened behavior. Previous studies

Fiscal Year 2005 Joint Programmatic Review Panel Members

U.S. Air Force Representatives

Hendrick Ruck, Ph.D. (JPRP Chair)
Director, Human Effectiveness Directorate, Air Force Research Laboratory

Colonel James Riddle (JPRP Alternate Chair)
Chief, Biosciences and Protection, Human Effectiveness Directorate, Air Force Research Laboratory

Lieutenant Colonel Debra Malone, M.D.
Chief, Formulation Branch, Modernization Directorate, Headquarters, U.S. Air Force Division of Science and Technology

Major Donnamaria Robinson, R.Ph., Pharm.D.
Chief, Biomedical Research and Compliance, Office of the Surgeon General

Major David G. Watson, Ph.D.
Flight Commander, Laboratory Services

U.S. Navy Representatives

Captain Doug Forcino, Ph.D.
Program Director, Office of Naval Research

Captain Richard Haberberger, Ph.D.
Executive Officer, Naval Medical Research Center

Captain David Neri, Ph.D.
Deputy Director, Research and Development, Navy Bureau of Medicine and Surgery

U.S. Army Representatives

Colonel Bruno Petruccelli, M.D., M.P.H.
Director, Epidemiology and Disease Surveillance, U.S. Army Center for Health Promotion and Preventive Medicine

(Continued on next page.)

indicating that the 5HT3 receptor system mediates alcohol consumption and the subjective effects of alcohol are supported by Dr. Allan's work. Results of studies in mice indicate that overexpression of 5HT3 reduces alcohol preference, increases attention, and decreases the initial display of aggressive behavior. Recent work showed these mice have greater survival of newly formed neurons which may be associated with the improved learning and impulse control seen in these subjects.

Infectious Disease Research

Michael Biscoe, Ph.D., Portland Oregon Veterans Affairs Medical Center

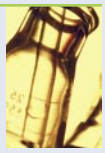
Treatment of malaria is becoming increasingly difficult because of the emergence of multidrug-resistant strains of *Plasmodium falciparum*, the causative agent of the most severe, often lethal, form of the disease. As a result, there is a pressing need to develop novel antimalarial agents. Dr. Michael Riscoe of the Portland, Oregon Veterans Affairs Medical Center has shown that xanthones disrupt the stage in which malaria parasites live in human blood cells by interfering with the parasites' ability to dispose of toxic waste products. Dr. Riscoe has synthesized xanthone analogues that are active against multidrug resistant *Plasmodium* parasites in laboratory tests and his group has performed preliminary studies in a mouse malaria model. The drugs were nontoxic to the mice and reduced the number of parasites in the blood by 90% in 4 days of once-daily treatment. Additional design, synthesis, and testing of xanthone analogs continues with the primary objective of impairing drug potency.

Kevin Porter, M.D., Naval Medical Research Center

Dengue fever is a mosquito-borne viral disease endemic in tropical regions around the world. Dengue vaccines in clinical trials use attenuated viruses. DNA vaccines have the potential to give a more robust immune response but have shown only partial protection to live virus challenge in mice and primates. Dr. Kevin Porter and colleagues at the Naval Medical Research Center are using mice as a model to explore the use of tetanus toxoid, aluminum phosphate, and monoclonal antibodies as adjuvants to improve the efficacy of the DEN-1 and DEN-2 DNA vaccines.

Stephen Savarino, M.D., Naval Medical Research Center

Diarrhea is a significant health threat for military and civilian travelers to developing countries. Incidence rates as high as 50% occur in areas with poor food and water sanitation. The military requirement for solutions in this area is becoming more acute. Since the inception of the war on terrorism, the global commitment of U.S. fighting forces has been increasingly concentrated in developing areas of the world.



Rehydration and antibiotic treatment are the cornerstones of disease management, but even with early institution of appropriate therapy, diarrheal diseases exact a cost in terms of lost duty and effectiveness. There is no licensed drug or biologic that provides a safe, effective mode of prevention for diarrhea, leaving an important deficiency in military and travel medicine. CAPT Stephen Savarino at the Naval Medical Research Center in collaboration with Johns Hopkins University is developing bovine milk immunoglobulins (BIgG) as a supplement with activity against enterotoxigenic *Escherichia coli*, the predominant cause of traveler's diarrhea. This investigational treatment has shown proof of principle as a safe, food-based anti-diarrheal supplement and is slated to begin clinical trials in 2005.

Toxin Assay Development

Jeffrey Mason, Ph.D., Armed Forces Institute of Pathology

The protection of military personnel deployed in hostile peacekeeping or combat situations depends on the early and rapid detection of biological toxins that can be lethal at extremely low concentrations. Dr. Jeffrey Mason of the Armed Forces Institute of Pathology is developing a simple and reliable field-deployable assay system for detecting biological toxins. The goal is to achieve high specificity at concentrations of less than 500 molecules for cholera and Botulinum toxins and 1,000 molecules for tetanus toxin. Dr. Mason and colleagues have developed an assay system in which tiny amounts of toxins are identified by an immunoassay linked to polymerase chain reaction amplification of DNA. They have achieved a sensitivity of detection of 2,500 molecules for botulinum toxoid and 3,000 molecules for tetanus toxoid.

BOTTOM LINE

Since 1999, the PRMRP has been responsible for managing $294.5M in congressional appropriations. The program has supported 156 exciting medical research projects in 54 military relevant topic areas through FY04 that have direct relevance to the health of members of the active duty military forces, retirees, and their beneficiaries.

Fiscal Year 2005 Joint Programmatic Review Panel Members

(Continued from previous page.)

Colonel Richard Scheafer, M.D., M.P.H.
Associate Professor and Chief, Department of Surgery, Orthopaedic Surgery Service

U.S. Marine Corps Representative

Lieutenant Commander Sharon Moser, M.B.A., M.H.A.
Project Officer and Head of the Expeditionary Medicine Branch, Marine Corps Warfighting Laboratory

Department of Health and Human Services Representative

Commander Patrick McNeilly, Ph.D.
Administrative Officer, Department of Health and Human Services; Public Health Advisor, Office of Human Research Protections, Office of the Secretary, U.S. Public Health Service

Department of Veterans Affairs Representative

Brenda Cuccherini, Ph.D.
Program Specialist, Office of Research and Development

Office of the Assistant Secretary of Defense (Health Affairs) Representatives

Salvatore Cirone, D.V.M., M.P.V.M.
Program Director, Health Science Policy

John Lucas, Sc.D.
Senior Program Management Officer