

**Gulf War Illness
Research Program**
**Peer Reviewed Medical
Research Program**
**Psychological Health and
Traumatic Brain Injury
Research Program**



Congressionally Directed Medical Research Programs



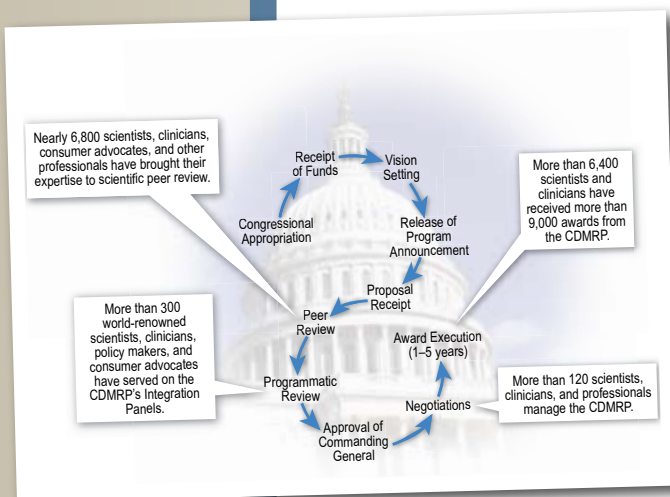
HISTORY

In 1992, the Office of the Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grass-roots effort led by the breast cancer advocacy community that implored Congress to appropriate funds for breast cancer research. This created a unique partnership among the public, Congress, and the military. Since that time, the CDMRP has grown to encompass multiple targeted programs and has received more than \$5.3 billion in appropriations from its inception through fiscal year 2009 (FY09). Each year, Congress adds funds for the CDMRP to the Department of Defense (DOD) budget in support of research programs including the Gulf War Illness Research Program (GWIRP), the Peer Reviewed Medical Research Program (PRMRP), and the Psychological Health/Traumatic Brain Injury (PH/TBI) Research Program.

PROPOSAL REVIEW PROCESS

The CDMRP uses a two-tier review process for proposal evaluation, with both steps involving dynamic interaction between scientists, clinicians, representatives from the military services, and consumer advocates. The first tier of evaluation is a scientific peer review of proposals weighed against established criteria for determining scientific merit. The second tier is a programmatic review of proposals that compares submissions to each other and recommends proposals for funding based on scientific merit, portfolio balance, and relevance to individual program goals.

A unique aspect of the CDMRP is the active participation of consumer advocates throughout the program's annual cycle. Consumers may be disease survivors, patients, family members, or persons affected by or at risk for a disease. Their firsthand experiences with a specific disease or condition provide a unique perspective that helps scientists understand the human side of how research will impact the community and allows for funding decisions that reflect the needs of patients, the clinicians who treat them, survivors, and their families.



GULF WAR ILLNESS RESEARCH PROGRAM

Nearly 700,000 men and women served in the 1990–1991 Gulf War. Studies consistently indicate that as many as 225,000 Gulf War veterans experience a variety of symptoms associated with their deployment. These symptoms often occur in clusters and include persistent headaches, somatic pain, fatigue, gastrointestinal difficulties, respiratory conditions, skin conditions, and cognitive problems. The GWIRP is committed to funding innovative projects that have the potential to improve the health and lives of affected service members and their families.

- Established in FY94 (managed by the U.S. Army Medical Research and Materiel Command's Military Operational Medicine Research Program)
- CDMRP-managed since FY06
- \$23 million in appropriations from FY06 through FY09
- 21 research projects funded by the CDMRP

PEER REVIEWED MEDICAL RESEARCH PROGRAM

The 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 diseases, metabolic diseases, and social issues.

- Established in FY99
- \$444.5 million in appropriations through FY09
- 281 research projects in more than 79 unique topic areas
- Topic areas are diverse and have included cancer, childhood diseases, autoimmune diseases, infectious diseases, Gulf War Illness, bone-related diseases, alcoholism, drug abuse, and other health and wellness issues

PSYCHOLOGICAL HEALTH/TRAUMATIC BRAIN INJURY RESEARCH PROGRAM

The vision of the PH/TBI Research Program is to prevent, mitigate, and treat the effects of traumatic stress and TBI on function, wellness, and overall quality of life for warriors, veterans, families, caregivers, and communities impacted by PH issues and/or TBI with emphasis on complementing ongoing DOD efforts to ensure the health and readiness of our military forces. The CDMRP continues to support the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury in collaboration with other DOD agencies, the Department of Veterans Affairs, and the Department of Health and Human Services in their efforts to be responsive to these critical needs.

- Established in FY07
- \$341.6 million in appropriations through FY09
- 201 research projects funded by the CDMRP

Although each program is unique and emphasizes the specific needs of its research and advocacy community, programs within the CDMRP share many common features. Since its inception, the central philosophy and hallmark of the CDMRP remain innovation. Many of the award mechanisms offered by the CDMRP emphasize innovation through the support of revolutionary ideas, creative solutions, and breakthrough technologies. Specific award mechanisms for each program are developed each fiscal year that capture the current needs of the research and advocacy communities. Training and recruitment of the best and brightest is another fundamental component shared by many of the CDMRP programs. The CDMRP has supported new researchers in the field as well as established scientists interested in extending their expertise to the study of other diseases. Other award mechanisms offered by the CDMRP were designed to build and expand the nation's research resources by providing support to develop new products or establish centers or consortia that can provide a foundation for future research. Research funded under these various award mechanisms spans the broad spectrum of basic laboratory research through translational and clinical research. These mechanisms foster unique opportunities to promising investigators from academia, military research facilities, and industry.

The following selection of research highlights from the GWIRP, PRMRP, and PH/TBI Research Program demonstrates the efforts of investigators who are working to improve the quality of life of those affected by disease and accomplish the CDMRP's vision—to find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public.

Diagnosics



Biomarkers to Determine Prognosis Following TBI

*Ronald L. Hayes, Ph.D., Banyan Biomarkers, Inc.
FY06 PRMRP Program Project*

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. 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. Hayes leads a team applying state-of-the-art proteomic and metabolomic technology to identify and characterize biomarkers in cerebrospinal fluid, blood, and urine that are characteristic of specific post-injury pathological processes.

Better Testing for TBI in the Field

**Jamshid Ghajar, M.D., Ph.D., Brain Trauma Foundation
FY07 TBI Advanced Technology/Therapeutic Development Award**

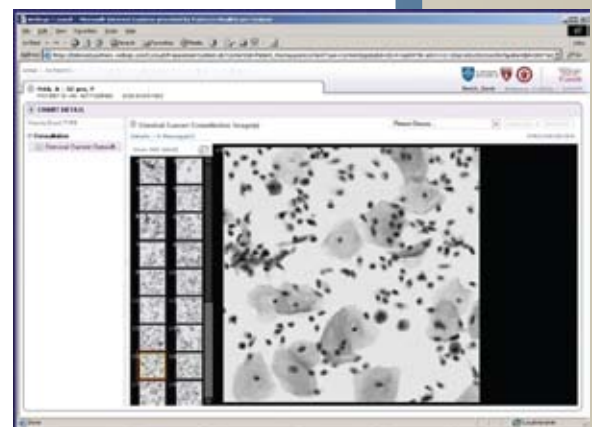
Dr. Ghajar and researchers at the Brain Trauma Foundation, along with researchers from the U.S. Army Research Institute of Environmental Medicine and Foster-Miller, Inc., received funding from a TBI Advanced Technology/Therapeutic Development Award to further test the validity, reliability, and sensitivity of a clinically tested eye-tracking device and related software for mild TBI (mTBI) called EYE-TRAC (Eye-Tracking Rapid Attention Computation). EYE-TRAC analyzes smooth pursuit eye movements to accurately detect subclinical attention and working memory deficits within seconds. The scientific rationale for the device's accuracy in detecting attention impairments following TBI is based on the disruption of the attention network in the brain due to shearing of anterior white matter brain connections. Normally this attention circuit produces a predictive brain state rather than a reactive state, allowing a person to interact fluidly. Predictive eye-target tracking can measure the timing disruptions resulting from mTBI-induced shearing of the attention circuit, which produces postconcussive "out-of-sync" symptoms. As such, EYE-TRAC can more accurately and in significantly less time (within seconds) diagnose mTBI as compared to current technologies. Thus far, Dr. Ghajar and colleagues are developing plans for the rugged outfitting of the device to be used as a portable, automated, goggle-like device. A prototype helmet-mounted device has been developed, and logistical issues relative to its use are being addressed. Thus, development of the eye-tracking device has progressed rapidly so far, and new subject testing has also been initiated. With this continued development, EYE-TRAC can eventually be used to assess fatigue in military personnel and distinguish PTSD from mTBI in the field or in forward medical facilities. The device will also be applicable for civilian use for diagnosing concussions from sports injuries and in emergency rooms where concussions from car crashes are a daily occurrence.



Web-Based Diagnostics to Reach Those Far and Wide

**David Wilbur, M.D., Massachusetts General Hospital
FY03 PRMRP Advanced Technology Award**

Access to cervical cancer screening may be limited in areas where trained medical specialists are in short supply. Dr. Wilbur 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 of 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. 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.



Prosthesis Development

Envisioning the Six Million Dollar Man

*Ronald Triolo, Ph.D., Case Western Reserve University
FY04 PRMRP Investigator-Initiated Research Award*

According to the National Spinal Cord Injury Statistical Center, there are more than 12,000 new cases of spinal cord injury (SCI) occurring in the United States every year. SCI disrupts regular communication between the brain and appendages, affecting motor function and mobility, dramatically changing the affected individual's physical, psychological, and social quality of life. Dr. Triolo seeks to improve the quality of life for individuals with paraplegia following SCI through an innovative bracing system that will provide enhanced mobility. The ultimate goal is an articulated thoracic-hip-knee-ankle-foot orthosis that allows users to stand, walk, and climb stairs safely and efficiently with minimum effort.

Dr. Triolo received an award to support the development of the new "hybrid neuroprosthesis" for mobility after paralysis from SCI. The hybrid combines the best elements of external bracing (orthoses) with electrical stimulation of the paralyzed muscles to yield a new system to augment the function of the damaged nervous system. To date, Dr. Triolo's team has designed new trunk, hip, and knee mechanisms for the orthosis and integrated them into the neuroprosthesis. The bracing components provide mechanical support and stability when the lower extremity joints do not need to move very much, for instance during standing or when one foot is on the ground during walking or stair climbing, and are flexible when necessary so that the user can



take advantage of innate muscle power to propel his or her body forward or upward with electrical stimulation. This neuroprosthesis automatically synchronizes the action of the hip, knee, and ankle joints with electrical stimulation through algorithms that use real-time information from sensors located throughout the brace. Standard motion and metabolic analysis were adapted to evaluate the efficacy of the neuroprosthesis.

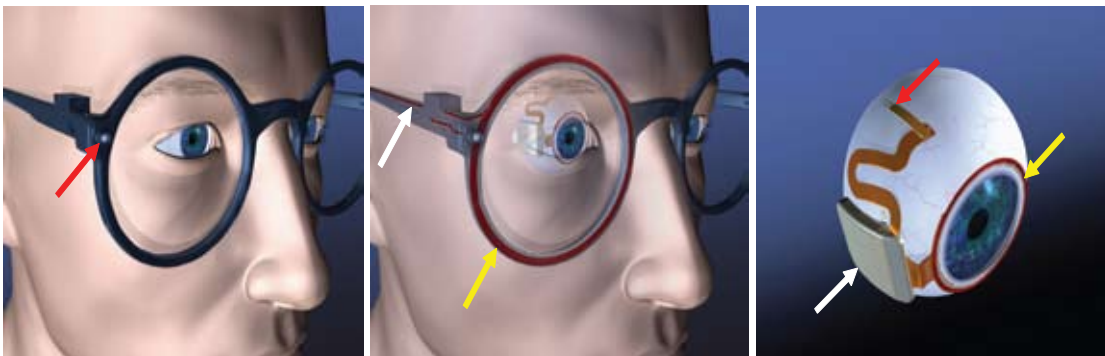
The hybrid neuroprosthesis is currently being tested by able-bodied volunteers for safety and design optimization as sequential modifications are made to the brace components. Two volunteers with SCI have participated in initial walking experiments to test the hip component and will participate in future tests of the other components as well as the completed system. Rate of progress on this project has surpassed Dr. Triolo's expectations, in large part because of active and highly productive collaborations with the Rehabilitation Research and Development Service of the U.S. Department of Veterans Affairs (VA), and the potential is high for the neuroprosthesis to improve the quality of life for military veterans and civilians with SCI-induced paralysis in the foreseeable future.

Optimization of Microelectronic Methods to Produce an Implantable Retinal Prosthesis to Treat Blindness

Joseph Rizzo, M.D., Massachusetts Eye and Ear Infirmary
FY06 PRMRP Advanced Technology: Product/Technology Down-Selection or Optimization Award



Dr. Rizzo and his colleagues are developing a retinal prosthesis that may be used to treat several forms of retinal blindness that are currently untreatable, including blindness caused by battlefield laser injury to the retina and military-related, blast-induced blindness. The implantable prosthetic will be a microelectronic device designed to interface directly with the retina. This device will (1) capture visual images, (2) communicate the images to electronic components that interface with the retina, and (3) selectively deliver electrical pulses to the retina to create vision. It intends to permit "customizable" adjustments to accommodate the unique visual needs of each patient and improve their quality of life.



Quality of Life



Pilot Trial of Inpatient Cognitive Therapy for the Prevention of Suicide in Military Personnel with Acute Stress Disorder or PTSD

*Marjan Holloway, Ph.D., Uniformed Services University of the Health Sciences
FY07 PTSD New Investigator Award*

PTSD is a significant public health problem and a prevalent mental disorder diagnosed in military service members exposed to combat service. Research has shown there is a strong association between PTSD and suicide and, in fact, PTSD shows the strongest association with suicide behavior of any anxiety disorder.

Dr. Holloway, a New Investigator Awardee, is working to develop, implement, and evaluate an evidence-based, inpatient, cognitive-behavioral care plan for service members and their beneficiaries with symptoms of either acute stress disorder or PTSD who are hospitalized following a suicide attempt. Dr. Holloway proposes to deliver a brief, targeted intervention to individuals who are admitted to Walter Reed Army Medical Center following a recent suicide attempt. The intervention will include six 1-hour therapy sessions in the first 3 days after study enrollment. Study subjects also will be assessed via face-to-face, phone, and web-based interviews at 1-, 2-, and 3-month intervals post-treatment. Dr. Holloway hypothesizes that targeting at-risk individuals immediately following a suicide crisis will reduce the likelihood of future complications.

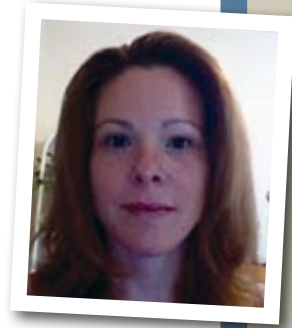
As a result of this study, Dr. Holloway hopes to produce a new manual of Post-Admission Cognitive Therapy and significantly reduce the number of subsequent suicide attempts by suicidal individuals. In addition, she proposes

that such an intervention may mitigate psychological risk factors associated with suicide such as depression, hopelessness, suicide ideation, and PTSD symptoms. If successful, the development and dissemination of an innovative, inpatient-focused intervention for traumatized individuals with suicidal behavior will significantly contribute to national and military suicide prevention objectives.



Acupuncture: A Non-Traditional Method to Improve the Quality of Life for Those with Gulf War Illness

*Lisa Conboy, Sc.D., New England School of Acupuncture, Inc.
FY08 GWIRP Clinical Trial Award*



Dr. Conboy will conduct a clinical trial investigating the effectiveness of acupuncture in treating ill Gulf War veterans. Dr. Conboy is optimistic about the potential benefits of acupuncture because it has already been used successfully to treat many of the main symptoms described in Gulf War Illness—fatigue, moodiness, insomnia, and pain. Acupuncture treatment in the study will be individually designed to address each participant's symptoms, making this a unique approach.

Participants will receive twice-weekly treatments for 2 months, and the results of these treatments will be compared to untreated controls. After this initial phase, all participants will receive weekly treatments for an additional 4 months. Outcomes will be assessed with commonly used health survey instruments including the widely used SF-36 health survey, which measures overall personal health.



Hormonal Regulation of Extinction: Implications for Gender Differences in the Mechanisms of PTSD

*Laura Schrader, Ph.D., Tulane University
FY07 PTSD Concept Award*

The most common diagnoses in male and female soldiers seeking medical attention from VA medical facilities following service in Operation Iraqi Freedom/Operation Enduring Freedom are PTSD and depression. Studies focusing on PTSD and similar mental disorders indicate that women suffer from these disorders at approximately twice the rate of men. Although there is an increased incidence of PTSD and depressive disorders in women, the neurobiological mechanisms underlying gender differences of PTSD are poorly understood. Previous investigations indicate that changes in chromatin structure or epigenetic mechanisms involved in regulating gene transcription occur during learning and stress, an effect that may contribute to the development of specific pathologies. Given the ability of hormones to regulate gene expression, Dr. Schrader proposes that female hormones may play a role in the predisposition of females to PTSD via epigenetic mechanisms.

Pilot data generated in collaboration with Dr. Jill Daniel at Tulane University reveal that females exhibit increases in conditioned fear but decreases in extinction as compared with males. This suggests that a traumatic event has increased significance and is more difficult to suppress in females. Thus, using Pavlovian fear-conditioning and extinction paradigms as an animal

model for the development of pathological fear in humans suffering from PTSD, Dr. Schrader is currently investigating whether estrogen predisposes females to increased fear learning and/or an inability to extinguish fear. Further, Dr. Schrader is assessing whether blockade of histone deacetylase (HDAC) and modulation of chromatin structure via HDAC inhibitors such as sodium butyrate influences the extinction of fear memories. In addition, the hippocampus (a brain region involved in emotional, learning, and memory processes) is being investigated in animals exposed to fear conditioning to determine whether hormones mediate changes in chromatin structure and alter epigenetic effects that occur during the acquisition of fear memories. This research will provide a better understanding of hormonal regulation of fear acquisition and inhibition and may elucidate a mechanism contributing to the predisposition of females to an increased incidence of PTSD and other anxiety-related disorders.

Finding the Path to Healthy Weight Loss

Susan Bloomfield, Ph.D., Texas A&M University
FY05 PRMRP Investigator-Initiated Research Award

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 weight loss. In women, rapid weight loss may affect reproductive hormone profiles, resulting in decreased bone mass. Dr. Bloomfield 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.





Mifepristone for the Treatment of Gulf War Illness

*Julia Golier, M.D., Veterans Medical Center, Bronx, New York
FY06 GWIRP Investigator-Initiated Research Award*

Dr. Golier is currently conducting a randomized cross-over clinical trial of mifepristone, a glucocorticoid receptor antagonist, to establish its efficacy in improving physical

health and cognitive function in Gulf War veterans with chronic multisymptom illness (CMI). Dr. Golier had previously described distinct biological alterations in the hypothalamic-pituitary-adrenal axis associated with deployment to the Gulf War and the development of CMI and hypothesizes that mifepristone can improve musculoskeletal symptoms and cognitive functioning in these veterans. Improvement in a recognized 36-point health survey and cognitive tests will be the primary outcome measures for the study. Participants are currently being screened and enrolled in the study.



**More information about the Military Health Research Forum host programs
and other programs managed by the CDMRP may be found at:**

<http://cdmrp.army.mil>

