

CDMRP 
Department of Defense

Gulf War Illness Research Program



U.S. Army Medical Research and Materiel Command

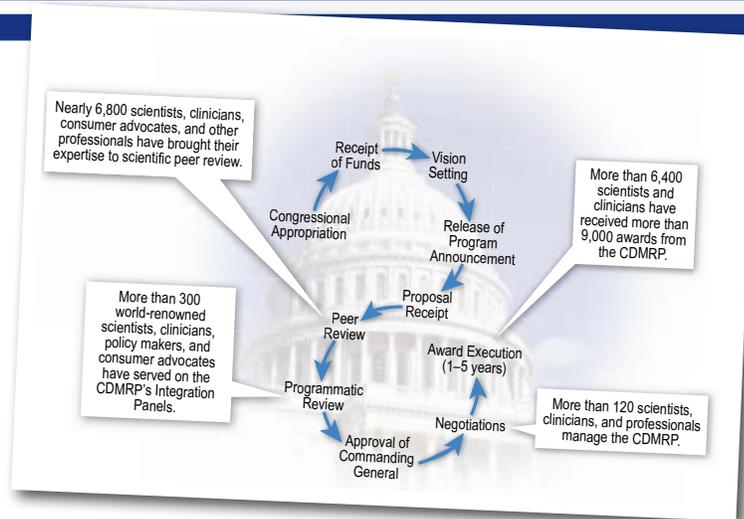


Congressionally Directed Medical Research Programs



HISTORY The Congressionally Directed Medical Research Programs (CDMRP) was born in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received almost \$5.9 billion in appropriations from its inception in fiscal year 1993 (FY93) through FY10. Through FY09, approximately 9,700 awards have been made across 19 different programs. Funds for the CDMRP are added by Congress to the Department of Defense (DOD) budget annually to provide support for targeted research programs in breast, prostate, and ovarian cancers; neurofibromatosis; autism; and other areas with military health interests including psychological health, traumatic brain injury, and Gulf War Illness (GWI). Under the auspices of the U.S. Army Medical Research and Materiel Command (USAMRMC), the CDMRP manages these programs from receipt of funds, competitive selection of proposals, through individual project performance, to closeout.

The CDMRP program management cycle includes a two-tier review process for proposal evaluation recommended by the National Academy of Science's Institute of Medicine. The first tier of evaluation is an external scientific peer review of proposals against established criteria for determining scientific merit. The second tier is a programmatic review conducted by a CDMRP-convened Integration Panel (IP) composed of program-specific researchers, clinicians, and consumers who evaluate proposals on innovation, potential impact, programmatic priorities, and mechanism-specific criteria. The Commanding General of USAMRMC issues the final approval for funding prior to award negotiations and execution.



Gulf War Illness Research Program

VISION

Improve the health and lives of veterans who have Gulf War Illness.

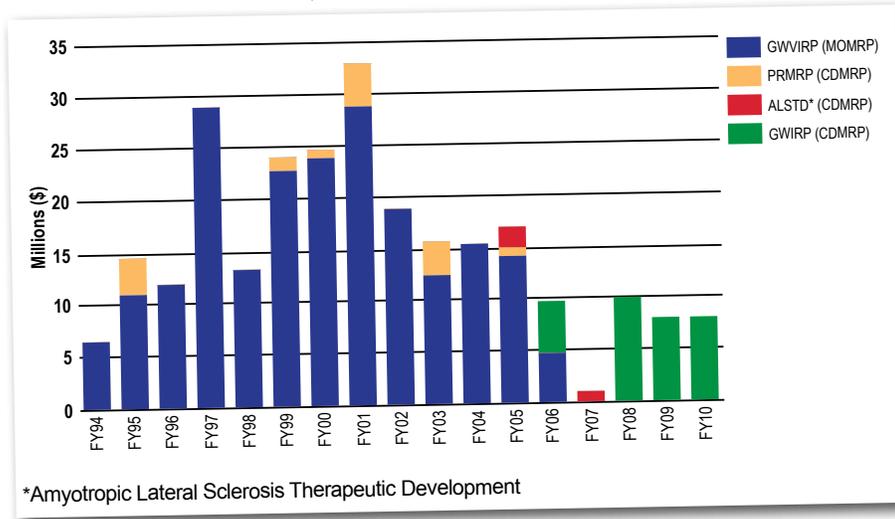
MISSION

Fund innovative Gulf War Illness research to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms.

HISTORY

DOD-funded GWI research began in 1994 with the establishment of a Gulf War Veterans' Illnesses Research Program (GWVIRP) to study the health effects of service members deployed in the 1990–1991 Persian Gulf War. From FY94 to FY05, the GWVIRP was managed by the USAMRMC Military Operational Medicine Research Program (MOMRP). Research pertaining to GWI also was funded intermittently through the CDMRP's Peer Reviewed Medical Research Program (PRMRP), which supports military health-related research. The MOMRP shared management responsibility for the GWVIRP with the CDMRP in FY06 with separate \$5 million appropriations. Although the GWVIRP did not receive funding in FY07, a \$10 million appropriation renewed the program in FY08, renamed the Gulf War Illness Research Program (GWIRP), to be managed fully by the CDMRP. The GWIRP has continued in FY09 and FY10 with an \$8 million appropriation each year. The program is directed to support peer reviewed research of treatments for the complex of symptoms that comprise GWI, identification of objective markers (biomarkers) for the disease, and understanding the pathobiology underlying GWI.

DOD GWI Research Investment



GWIRP Funded Portfolio by Research Topic, FY06-FY09 (n=35 Projects*)



Integration Panel Members

Comprising the IP are prominent members of the GWI research community, including Gulf War veterans (i.e., consumers) suffering from the disease. The IP advises the GWIRP about programmatic focus and investment strategy annually and recommends proposals for funding that constitute a broad portfolio of research interests and address current research gaps. The recommendations of individual IP members enable the GWIRP to find and fund cutting-edge research and set important program priorities designed to benefit ill Gulf War veterans.



“The CDMRP program on Gulf War Illness is a highly innovative effort designed to develop new approaches to the understanding and treatment of Gulf War Illness. Like other CDMRP research programs, it utilizes specialized grant mechanisms to attract the kinds of research that can address this challenging health problem. CDMRP draws on the experience of Gulf War veterans and the expertise of scientists and clinicians who have worked extensively with this population to inform the development of award mechanisms and review of proposals.”

Dr. Roberta F. White, FY10 IP Chair



“As a member of the Integration Panel, it is both an honor and privilege to have an opportunity to shape the direction of today’s research into Gulf War Illness. While time has faded GWI from the national news headlines, it has not dimmed our hope that treatments and cures for GWI are waiting to be discovered and brought to bear against this insidious disease. We remain cognizant that our efforts and those of our researchers must be both diligent and unabated. It is only through continued research that we can provide the hope for, and one day, the end of suffering that our afflicted veterans require and deserve.”

Major David Watson, USAF

Consumers: 'Boots on the Ground' Advising the GWIRP

A unique aspect of the CDMRP is the active participation of consumer advocates throughout the program. Consumers are a vital part of all CDMRP programs as they represent the collective views of survivors, patients, family members, and those affected by and at risk for a disease. Consumers for the GWIRP are Gulf War veterans who are experiencing symptoms and illnesses that may be related to their military service in theater. They sit side by side with research professionals on both peer and programmatic review panels, and their voices play a pivotal role in maintaining an appropriate focus within the program.



"The 1991 Gulf War exposed hundreds of thousands of U.S. and coalition troops to a veritable toxic soup of chemical, environmental, and other hazards. For many of those who fell ill, their overarching Gulf War experience had only just begun. The clear treatment focus of this program—aimed at improving the lives of those ill with Gulf War Illness—is a welcome breath of fresh air."

Anthony Hardie, Consumer



"Gulf War veterans and their families have struggled for years trying to get answers to their various medical problems since coming home. Funding for medical research on what these medical problems may be and how they might be treated to improve veterans' quality of life has always been scarce. The GWIRP process is very significant to us as veterans since we now have a seat at the table where we as consumers can provide influence in how these scarce research dollars are used to ensure maximum value is gained. Veterans' opinions are sought through this process, and our voices are being heard."

Chris Kornkven, Consumer



Treatments... To Improve Quality of Life

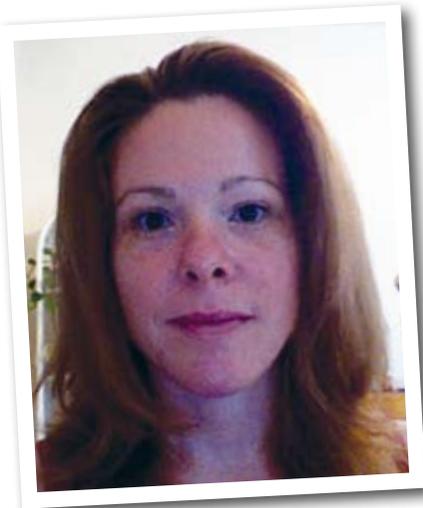


Clinical Trial Awards were offered by the program in FY08 to support pilot studies as well as larger more definitive clinical trials to investigate potential treatments for GWI. Several GWIRP-funded researchers are conducting clinical trials to test treatments for symptoms of chronic pain and cognitive dysfunction in ill Gulf War veterans.

Dr. Julia Golier from the Bronx Veterans Affairs Medical Center (VAMC) is currently conducting a randomized crossover 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.



Dr. Beatrice Golomb of the University of California, San Diego is addressing the needs of Gulf War veterans with chronic health problems like fatigue, weakness, and muscle pain. Dr. Golomb is conducting a clinical trial of the efficacy of coenzyme Q10 to improve these symptoms as well as overall quality of life for ill Gulf War veterans. Q10 already exists in cells and acts like a vitamin, helping cells produce energy, and is currently sold as a dietary supplement. Dr. Golomb's study, in addition to assessing efficacy for Q10, also will examine the dose effect and whether a higher dose of Q10 will be more effective. Q10 has provided benefit for symptoms reported by ill Gulf War veterans with similar conditions in the literature, signifying a strong rationale for efficacy. Subject enrollment has been completed and study appointments/treatments are under way.



Dr. Lisa Conboy of the New England School of Acupuncture 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 already has been used successfully to treat many of the main symptoms described in GWI—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.

Biomarkers... To Identify Unique Differences

To better understand the mechanisms of GWI, researchers are looking for biomarkers that indicate anomalies within the genome or protein expression profiles of ill Gulf War veterans compared to their healthy counterparts. Identifying these biomarkers can serve as an important step toward understanding how GWI progresses and what treatments may be effective to address its symptoms.



Dr. Nancy Klimas of the Miami VAMC and her team are looking for genes from the immune, endocrine, and nervous systems to elucidate differences between those with GWI and normal controls. Dr. Klimas hypothesizes that GWI is a subset of Chronic Fatigue Syndrome (CFS) and is using an FY08 GWIRP Investigator-Initiated Research Award to conduct a study comparing gene and protein expression in ill and healthy veterans during and after an exercise challenge. This study will build on an already completed smaller study showing problems with the regulation of immune function for both CFS and GWI. In the new project, more time points will be studied during and after the exercise activity to provide a richer data set for analysis. A team of biological systems experts will use powerful new analytical approaches compiled on a supercomputer to unlock connections within systems that contribute to disease symptoms. One of the goals is to create a model of how ill veterans have developed an altered state of homeostasis that maintains the diseased state. With such a theoretical model, interventions can be focused on the right mediators of this altered homeostasis and shift the balance back toward normal function and better health.



Dr. James Baraniuk of Georgetown University is looking at differentially expressed plasma proteins in symptomatic Gulf War veterans to find biomarkers for GWI. In an earlier study, 10 proteins were identified in the cerebrospinal fluid (CSF) of GWI and CFS subjects but not found in healthy subjects. One of the 10 proteins was carnosine dipeptidase 1 (CNDP1), which could become an effective biomarker if certain alleles (subtypes) prove to be associated with GWI. Dr. Baraniuk is now expanding on this earlier work through an FY06 GWIRP Investigator-Initiated Research Award by screening 100 Gulf War and non-Gulf War veterans to test their CNDP1 status as well as that of the other differentially expressed CSF proteins. These protein biomarkers could not only help to explain what may be causing the symptoms associated with GWI but also contribute to an effective diagnostic test for the disease.

Research Models... To Understand the Pathology of GWI

Animal models can play an important role in helping researchers understand the mechanisms of disease and aid in the development of new therapies. GWIRP-funded investigators in FY08 with Investigator-Initiated Research Awards are creating mouse models of neurological dysfunction in attempts to better understand the underlying contributors of GWI symptoms like chronic pain, fatigue, and memory loss.



Dr. Fiona Crawford of the Roskamp Institute is using mouse models to recreate the chemical exposures experienced by military personnel in the Gulf War. In particular, the animals will be exposed to pyridostigmine bromide, an antinerve agent drug, and the pesticides DEET and permethrin, thought to be significant contributors to GWI, in various combinations. The

mouse models will include mice genetically predisposed to cognitive decline following brain insult. Dr. Crawford will use the models to examine behavioral and cognitive performance in the mice and catalog the various deficits as well as neuropathological changes. Changes in brain pathology, particularly involving altered protein expression in the hippocampus, will be studied using state-of-the-art proteomic technology to identify potential targets for therapeutic intervention. The goal of the study is to identify underlying biological mechanisms relevant to GWI. Once identified, such mechanisms can enable the development and testing of novel therapeutics.





Dr. Stephen Lasley of the University of Illinois and **Dr. James O’Callaghan** (pictured) at the Centers for Disease Control and Prevention are researching the neuroinflammatory response as a contributor to GWI. Using a mouse model for GWI, they have found that exposure to a GWI-relevant nerve agent, DFP, (a surrogate chemical to sarin) leads to enhanced expression of proinflammatory mediators in the brain. They also are using high physiological levels of the rodent form of cortisol to mimic the stress of the war theater and have found this treatment to enhance neuroinflammatory responses after nerve agent exposure. They will develop this animal model further by combined exposure of DFP and stress hormone with chronic exposure to pyridostigmine bromide and DEET, two agents widely distributed to military personnel in the 1991 Gulf War. Animals will continue to be monitored well past the exposure regimen to simulate symptoms Gulf War veterans may be experiencing now. With this model the investigators hypothesize that neuroinflammation, which leads to typical “sickness behavior,” is central to the pathology of GWI and that treatment with an agent such as minocycline, already U.S. Food and Drug Administration-approved, could be effective in treating GWI symptoms. The model also could identify biomarkers of neuroinflammation, and by extension GWI, to help researchers better understand GWI pathobiology.



The GWIRP in FY10

- Investigator-Initiated Research Award
 - Clinical Trial Award
 - Innovative Treatment Evaluation Award
 - Consortium Development Award—
New for FY10

For FY10 the GWIRP was appropriated \$8 million to support research to better understand the pathobiology underlying GWI symptoms and to continue funding studies of treatments for GWI. The program's mainstay Investigator-Initiated Research Award and Clinical Trial Award will continue to be offered in FY10. FY09's Innovative Treatment Evaluation Award was received well by the research community, resulting in two awards made, and will also be back in FY10.

The GWIRP is making a bold step forward in FY10 by initiating development of a research consortium focused on GWI. The program is taking a measured approach by initially offering a Consortium Development Award in FY10, enabling organizations to make initial contacts and collaborations and sketch out a proposed consortium prior to submitting a full proposal. The full Consortium Award is expected to be offered in FY11.





For more information, visit
<http://cdmrp.army.mil>
or contact us at:
CDMRP.PublicAffairs@amedd.army.mil
(301) 619-7071

