

VIII. Gulf War Illness Research Program

“A substantial proportion of Gulf War veterans are ill with multisymptom conditions not explained by wartime stress or psychiatric illness.”

Finding from the Congressional Research Advisory
Committee on Gulf War Veterans' Illness
September 2004

“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. Thank you to all involved in funding and implementing this program to help ensure that those who remain ill following their Gulf War service are not just lost in the shuffle.”

Anthony Hardie
Gulf War Veteran

Wisconsin Department of Veterans Affairs
FY06 and FY08 Integration Panel Member





Expanding Knowledge



Vision

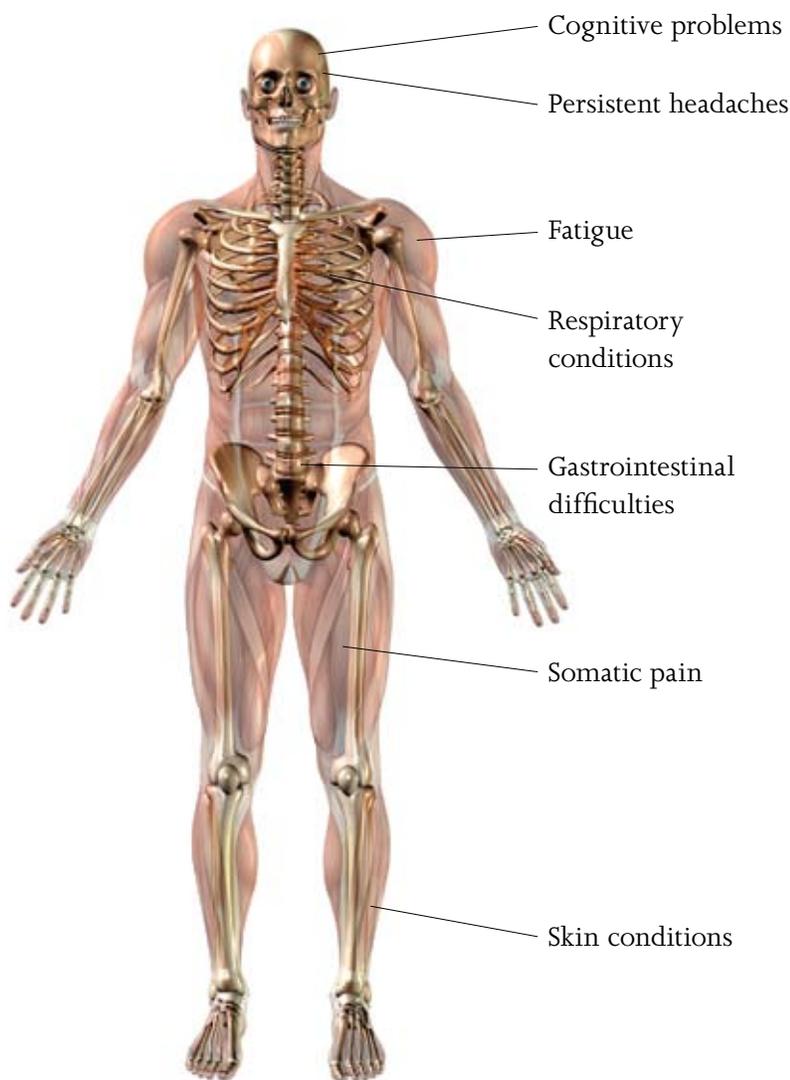
Improve the health and lives of veterans who have Gulf War Illness.

Mission

Fund innovative research to identify effective treatments for the complex of symptoms known as Gulf War Illness, improve its diagnosis, and better understand its pathobiology.

The Disease

Nearly 700,000 men and women served in the 1990–1991 Persian Gulf War. Population-based studies consistently indicate that as many as 225,000 of these Gulf War veterans experience a variety of symptoms and illnesses, such as persistent headaches, cognitive problems, somatic pain, fatigue, gastrointestinal difficulties, respiratory conditions, and skin abnormalities that may have been caused by their military service.¹ Some veterans experience symptoms that are difficult to explain using current diagnostic criteria for illnesses. It remains unknown whether these veterans are experiencing such symptoms at a higher rate than veterans of other wars. In addition, many veterans have questioned whether the illnesses that are common and diagnosable are etiologically linked to their service in the Persian Gulf conflict. While many medical questions have been answered with existing knowledge of Persian Gulf veterans' experiences, others require continued scientific research.



¹ Research Advisory Committee on Gulf War Veterans' Illnesses. 2004. Scientific Progress in Understanding Gulf War Veterans' Illnesses: Report and Recommendations. United States Department of Veterans Affairs.

Program Background

The Gulf War Illness Research Program (GWIRP) was established in fiscal year 1994 (FY94) to study the health effects on warfighters deployed in the Persian Gulf War. From FY94 to FY06, the GWIRP was managed by the U.S. Army Medical Research and Materiel Command (USAMRMC) Military Operational Medicine Research Program (MOMRP).

Research pertaining to Gulf War Illness has also been funded through the Peer Reviewed Medical Research Program (PRMRP), which is managed by the USAMRMC's Office of Congressionally Directed Medical Research Programs (CDMRP). The PRMRP was established by Congress in FY99 to provide support for military health-related research of clear scientific merit. The FY00 and FY01 PRMRP congressional appropriation language included Gulf War Illness in the mandated research topic areas supported by this program. In addition, the PRMRP has funded studies addressing Gulf War Illness through the Military-Relevant Disease Management topic area. Furthermore, in FY05 through FY08, Congress appropriated funds for Amyotrophic Lateral Sclerosis (ALS) therapy development for Gulf War Illness under several programs. One program at the ALS Therapy Development Foundation (later ALS Therapy Development Institute) was administered by MOMRP in FY05 and then transferred to the CDMRP in FY07 with a \$1M appropriation. This program is being continued in FY08 with an additional appropriation of \$1.2M. A second research program at the Burnham Institute was initiated specifically for ALS therapy when \$2.6M was appropriated in FY06. A third was created when \$5M in funds were redirected to the CDMRP in FY07 creating the ALS Research Program (ALSRP). Research funded through this program is relevant to Gulf War Illness since veterans from the 1991 Gulf War are twice as likely as the general population to develop ALS.

In FY06, \$5M was appropriated to MOMRP to support ongoing research related to Gulf War Illness. In addition, the Defense Department Appropriations Conference report recommended that the Army provide \$5M to support a coherent research program for Gulf War Illness with four focus areas:

- ❖ Identification of mechanisms underlying Gulf War Illness;
- ❖ Chronic effects of neurotoxic substances to which veterans were exposed during deployment;
- ❖ Studies that expand on earlier research identifying neurological and immunological abnormalities in ill Gulf War veterans; and
- ❖ Identification of promising treatments.

The CDMRP began managing the GWIRP in FY06.² In FY08, a congressional appropriation of \$10M was made to continue the GWIRP. Figure VIII-1 shows the GWIRP funding history.

² Known as the Gulf War Veterans' Illnesses Research Program in FY06.

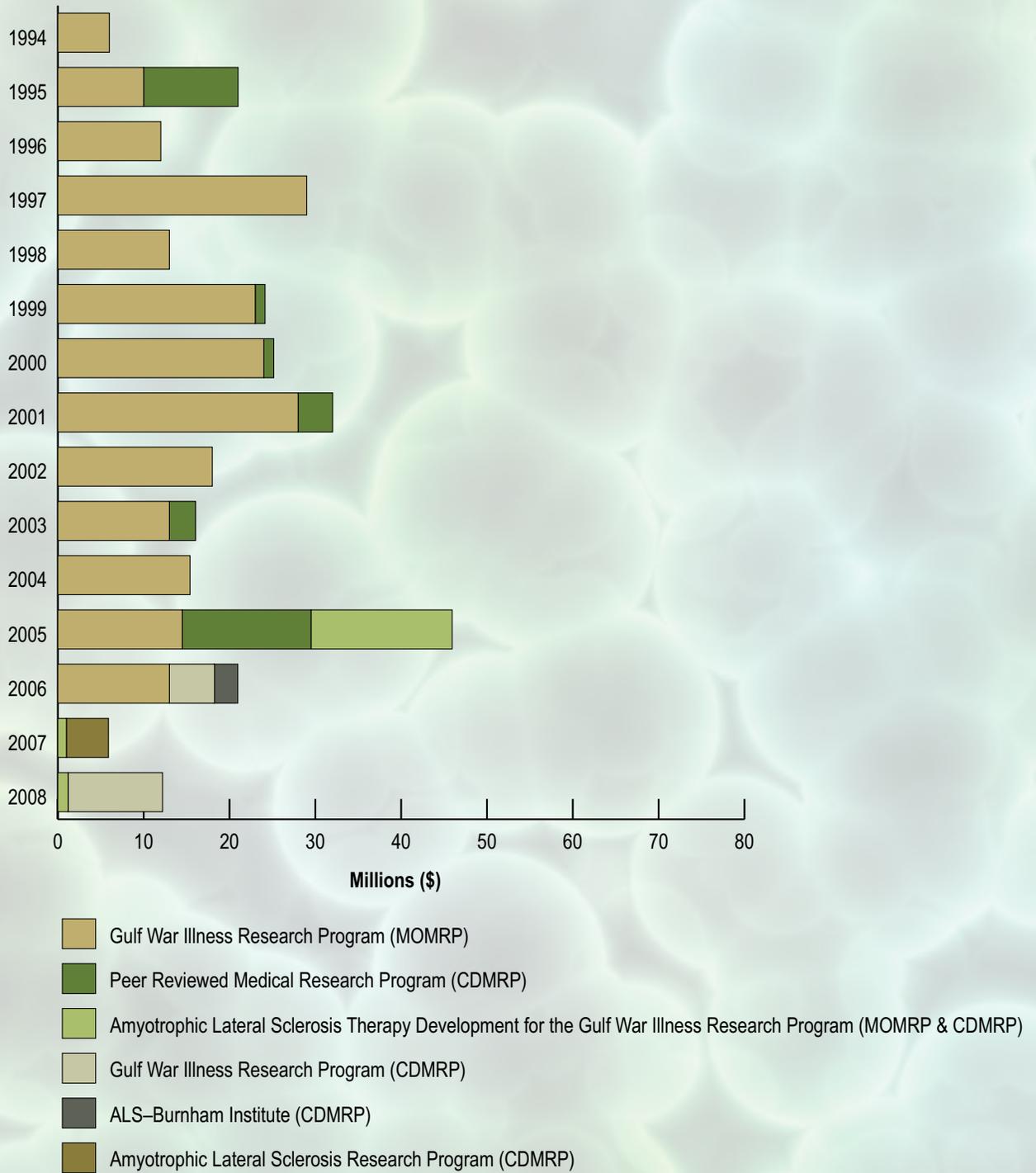


Figure VIII-1. GWIRP Funding History by Fiscal Year

Outstanding People

The individual contributions and dedication of outstanding people—consumer advocates, peer review panel members, Integration Panel (IP) members, and the scientific community—are impacting the health of our Gulf War veterans. The GWIRP values the dedication and efforts of all of these individuals who are expanding the existing knowledge of the pathobiology, diagnosis, and treatment of Gulf War Illness.

Consumer Advocates

A unique feature of the GWIRP is the active participation of consumer advocates in the program. Consumer advocates are veterans of the Gulf War who are experiencing symptoms and illnesses that may have been caused by their military service. Their voices play a pivotal role in the establishment and continuing growth of the program.

Peer Review Panel Members

Scientific peer review is a process in which panel members provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the program. Peer review panels are composed of leading investigators from scientific and clinical disciplines as well as consumer advocates. Scientific peer reviewers are selected for their subject matter expertise and experience with scientific peer review. 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. Additional details about peer review appear in Section I, Overview.

“CDMRP’s research program aimed at improved treatment, diagnostic testing, and understanding of Gulf War Illness has been greatly appreciated by scientists working in this arena and by veterans who continue to suffer from this difficult multisymptom condition 18 years after the Gulf War. I have been especially impressed with the program’s emphasis on innovative research focused on tangible results and with the program’s inclusion of ill veterans in all phases of the research funding process.”

Lea Steele, Ph.D.

**Kansas State University and U.S. Department of Veterans Affairs
FY08 Integration Panel Chair**

Integration Panel Members

The GWIRP IP is composed of representatives from the Department of Veterans Affairs; Army, Navy, and Air Force; industry; and consumer advocacy groups. Members of the IP provide programmatic and strategic direction to the GWIRP and make funding recommendations to the USAMRMC Commanding General.

“I am excited that there is additional funding for research on Gulf War Illness, through the GWIRP, as we need to be able to find the underlying cause(s) responsible for the symptoms. The GWIRP has several award types that should attract the best research proposals toward the goal of finding better means to diagnose and treat the disease. I am honored to be part of the program to help set its priorities and goals.”

Sam Donta, M.D.
Donta Infectious Diseases
FY08 Integration Panel Member



FY08 GWIRP IP Members

Lea Steele, Ph.D. (Chair)
*Kansas State University
U.S. Department of Veterans
Affairs*

Sam Donta, M.D.
Donta Infectious Diseases

Anthony Hardie
*Wisconsin Department of
Veterans Affairs*

Cornelius Maher, M.D.
*Colonel, U.S. Army
U.S. Army Medical Command*

Mary Nettleman, M.D., M.S.
Michigan State University

Kerry Thompson, M.S., Ph.D.
*Captain, U.S. Navy
Naval Health Research Center*

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

Program Awards

FY06 in Review



These awards encompass a broad spectrum of research topics, from therapeutics, to research models, to the effects of chemical exposure, and will help expand knowledge, diagnosis, and treatment of Gulf War Illness. Each of the funded FY06 awards is profiled by research area.

Exposure-Related Investigations

Kimberly Sullivan, Ph.D.

Boston University School of Medicine

Dr. Kimberly Sullivan is elucidating objective biomarkers of ill veterans of the first Gulf War who were exposed to military pesticide (i.e., organophosphate) applicators. Dr. Sullivan will correlate their exposures to high or low amounts of organophosphates with changes in brain morphometrics measured by structural magnetic resonance imaging and alterations in measures of cognitive function. The results should contribute to better diagnosis and treatment of military personnel, including Gulf War veterans, exposed to organophosphates.



Stephen Lasley, Ph.D.

University of Illinois

The chemical properties and high density of depleted uranium render the metal well suited for military purposes. However, knowledge of depleted uranium neurotoxicity and its treatment is lacking despite the apparent neurological basis of several components of Gulf War Illness. A study led by Dr. Stephen Lasley is examining the therapeutic effectiveness of specific agents to reduce the neurotoxicity generated by implanted depleted uranium in a rodent model. Successful demonstration of the effectiveness of these drugs alone or in combination would have substantial benefits for the treatment of affected veterans.



Peter Baas, Ph.D.
Drexel University

Veterans of the first Gulf War are twice as likely to develop ALS compared with the general population. ALS is a debilitating neurodegenerative disease that typically afflicts both upper and lower motor neurons, and it causes widespread degeneration throughout the central nervous system. During the Gulf War, Soldiers were exposed to a number of different chemicals including pesticides, drugs to protect against nerve agents, and botulinum toxin vaccine. Any of these chemicals, potentially in combination with one another or with the stress of the military operation, could have triggered the degenerative nerve disease in these Soldiers. Dr. Peter Baas and colleagues are using a recently established animal model for ALS to determine if the nerve degeneration underlying the disease may have been caused by the various chemicals to which Soldiers were exposed during the Gulf War.

Christopher Phillips, M.D., Lt Col
Naval Health Research Center

U.S. Navy Seabees have been among the most symptomatic 1991 Gulf War veterans. Lt Col Christopher Phillips is determining whether self-reported exposures to pesticides and/or pyridostigmine bromide are tempered or enhanced by an individual's paraoxonase (PON1) status. PON1 is a high-density, lipoprotein-bound "A-esterase" active in metabolizing organophosphates and is an important factor in determining the toxicity for some organophosphate pesticides.

Clinical Studies and Quality of Life



Julia Golier, M.D.
Bronx VA Medical Center

Dr. Julia Golier and colleagues have previously described distinct biological alterations associated with deployment to the 1991 Gulf War and the development of chronic multisymptom illness (CMI) that could be reflective of disturbances in central processes that regulate neuroendocrine systems. It has been shown that disturbances in the hypothalamic-pituitary-adrenal axis can have deleterious effects on multiple systems including the immune system, the autonomic nervous system, and the central nervous system. Thus, the hypothalamic-pituitary-adrenal axis system may be a useful target of treatment in CMI. Dr. Golier and colleagues will determine whether mifepristone, a glucocorticoid receptor antagonist, can reduce the neuroendocrine alterations that have been described in Gulf War veterans. The effects of mifepristone on physical health, cognitive function, the hypothalamic-pituitary-adrenal axis, and symptoms associated with CMI will be determined in a randomized, double-blind placebo trial of mifepristone in Gulf War veterans.



Beatrice Golomb, M.D., Ph.D.
University of California, San Diego

Dr. Beatrice Golomb and colleagues are conducting a randomized, placebo-controlled, double-blind crossover study designed to determine whether the supplement coenzyme Q₁₀, a physiological cofactor critical to mitochondrial ATP synthesis, will alter subjective evaluation of health, fatigue, muscle pain, muscle strength, and other symptoms in a group of veterans showing criteria for Gulf War Illness.

William Meggs, M.D., Ph.D.

East Carolina University

The underlying hypothesis of the research of Dr. William Meggs is that chemical exposures during the Gulf War led to an intolerance of chemicals at levels found in daily life and that avoidance of these chemicals improves health. The objective of this study is to conduct a randomized, controlled, open-label study of environmental medicine therapy for ill Gulf War veterans. The environmental medicine therapy will consist of a controlled environment (i.e., living in an environmentally controlled room with relatively clean air, eating organically grown foods free of chemical contaminants, and drinking filtered spring water, along with adjunct therapy such as provocative-neutralization testing, vitamin and nutrient supplementation, and sauna-detoxification) to relieve symptoms in Gulf War veterans.

Genetics and Research Models

James Baraniuk, M.D.

Georgetown University

In previous studies, Dr. James Baraniuk and colleagues showed that the protein carnosine dipeptidase 1 (CNDP1) was detected significantly more frequently in subjects with co-existing Gulf War Illness and chronic fatigue syndrome than in healthy controls. CNDP1 cleaves two important brain antioxidants in half, homocarnosine and carnosine. Dr. Baraniuk will perform a cross-sectional study to identify genetic (CNDP1 alleles) and proteomic biomarkers in Gulf War Illness. The antioxidant and neuromodulatory effects of homocarnosine, carnosine, and their amino acids provide the rationale for a double-blind, placebo-controlled study of oral carnosine, an over-the-counter dietary supplement that is one substrate of CNDP1, as a treatment for Gulf War Illness. Safety and efficacy issues will both be addressed prospectively.

Mariana Morris, Ph.D.

Wright State University

Autonomic neural dysfunction has been observed in veterans with Gulf War Illness. Dr. Mariana Morris of Wright State University is developing a mouse model for Gulf War Illness using low-dose sarin exposure. The mice show prolonged deficits in autonomic function similar to the human condition. This model will help researchers understand the mechanisms of and treatments for the central neural pathologies that have been associated with this illness.



The Program Today

FY06 Summary

The goals of the FY06 program were to identify and evaluate current treatments for Gulf War Illness and to identify objective indicators of pathology that distinguish persons affected with Gulf War Illness from unaffected veterans. This led to the solicitation of two award mechanisms, the Exploration–Hypothesis Development Award and the Investigator-Initiated Research Award. A total of 31 proposals were received across the 2 award mechanisms and 9 awards were made, as depicted in Table VIII-1.

Table VIII-1. Funding Summary for the FY06 GWIRP

Award Mechanisms	Proposals Received	Awards	Investment
Exploration–Hypothesis Development	11	2	\$0.2M
Investigator-Initiated Research	20	7	\$4.3M
TOTAL	31	9	\$4.5M



The GWIRP Team

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Colonel (Retired), Program Manager

James Phillips, Ph.D.
Grants Manager

Andrew Durrschmidt, M.S.
Program Specialist, Azimuth

Brett Chaney, M.B.A.
Program Coordinator, SAIC

Dettrick Stith, Ph.D.
Peer Review Coordinator
SRA International

The Vision for FY08

Although the GWIRP did not receive appropriations in FY07, Congress appropriated \$10M in FY08 to continue the program. The program has offered 3 award mechanisms—Idea Awards, Investigator-Initiated Awards, and Clinical Trial Awards—to investigate the causes of Gulf War Illness and improve the lives of veterans living with it. The program specifically emphasized areas of research in the pathobiology, detection, and treatment of Gulf War Illness. Highlights of the FY08 award mechanisms follow:

- ❖ **Idea Awards** support highly innovative, high-risk/high-reward research that could ultimately lead to critical discoveries or major advancements for treating the complex symptoms of Gulf War Illness, improving its diagnosis, and better understanding its pathobiology.
- ❖ **Investigator-Initiated Awards** are funded at a higher dollar amount and are intended to encourage potentially high-impact research that will lead to the identification of effective treatments for Gulf War Illness.
- ❖ **Clinical Trial Awards** support pilot studies and larger more definitive clinical trials to investigate potential treatments for Gulf War Illness.

Table VIII-2. Award Mechanisms Offered and Pre-Proposals Received for the FY08 GWIRP

Award Mechanisms	Preproposals Received
Idea	34
Investigator-Initiated Research	58
Clinical Trial	21
TOTAL	113

A pre-proposal screening phase was required in FY08. A total of 113 pre-proposals were received across award mechanisms, as shown in Table VIII-2, and approximately 11 awards are anticipated. Appendix B, Table B-7, summarizes the congressional appropriations and the investment strategy executed by the GWIRP for FY08.

