

CDMRP

IX. Gulf War Veterans' Illnesses
Research Program

Vision

Identification of beneficial treatments for 1991 Gulf War veterans that are affected by Gulf War illnesses.

Gulf War Illnesses

Nearly 700,000 men and women served in the 1990–1991 Persian Gulf War. Population-based studies consistently indicate that between 26 percent and 32 percent 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 also have symptoms that are difficult to explain using current diagnostic criteria for illnesses. It remains unknown whether they are experiencing these symptoms at a higher rate than comparable non-Persian Gulf War veterans. 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 the Persian Gulf veterans' experiences, others require scientific research.

Program Background

The Congressionally Directed Medical Research Programs (CDMRP) began managing the Department of Defense Gulf War Veterans' Illnesses Research Program (GWVIRP) in response to fiscal year 2006 (FY06) Appropriations Conference Committee Report No. 109-359, which provided \$5 million (M) for research on Gulf War Veterans' illnesses. A stakeholders meeting was held to develop a vision and investment strategy for the FY06 appropriation.

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.

Fiscal Year 2006 Summary

The intent of the GWVIRP is to fund research focused on chronic illnesses affecting veterans of the 1991 Gulf War. The goals of the program were twofold, to identify and evaluate currently available treatments for Gulf War illnesses and to identify objective indicators of pathology that distinguish ill from healthy veterans. Based upon these goals, proposals were sought using the Investigator-Initiated Research Award mechanism and the Exploration-Hypothesis Development Award mechanism. A total of 31 proposals was received across the two award mechanisms, and 9 awards were made, as depicted in Table IX-1.

Table IX-1. Funding Summary for the FY06 GWVIRP

Categories and 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



Supporting Our Gulf War Veterans... A Sampling of FY06 Funded Projects



Identification of Mechanisms Underlying Gulf War Illnesses

Carnosine dipeptidase 1 (CNDP1) polymorphisms have been detected more frequently in cerebrospinal fluid from individuals with Gulf War illnesses than healthy controls. Dr. James Baraniuk from Georgetown University will perform experiments designed to determine the effect of overexpression of this protein in the brains of individuals with Gulf War illnesses. Through this study, Dr. Baraniuk hopes to identify genetic and proteomic biomarkers for Gulf War illnesses. In addition, a double-blind, placebo-controlled study of oral carnosine supplements will be performed to determine if this dietary supplement is effective against Gulf War illnesses.

Neurological and Immunological Abnormalities in Ill Gulf War Veterans

U.S. Navy Seabees display the most symptoms of Gulf War illnesses of all 1991 Gulf War veterans. Seabees have reported using or being exposed to organophosphate-based pesticides and also reported taking pyridostigmine bromide tablets to protect against potential nerve agent attacks. Since pyridostigmine bromide has been shown to enhance the neurotoxicity of pesticides in animal studies, these two agents may contribute to the high rate of Gulf War illnesses reported in Seabees. Paraoxonase

is produced by the liver, is involved in the metabolism of organophosphates, and is a factor in determining the toxicity of some organophosphate-based pesticides. Dr. Christopher Phillips at the Naval Health Research Center will leverage data obtained from two previous U.S. Navy Seabee studies to determine if an individual's paraoxonase status affects his or her risk for Gulf War illnesses from potentially hazardous chemical exposures.



Identification of Promising Treatments

Evidence suggests that coenzyme Q10 improves symptoms common in Gulf War illnesses including fatigue, muscle pain, cognition, headaches, sleep disturbances, and breathing problems. Dr. Beatrice Golomb from the University of California, San Diego, will test the effects of coenzyme Q10 supplements on Gulf War veterans with chronic health problems consistent with Gulf War illnesses to determine its efficacy against specific symptoms and general quality of life.

Ongoing work performed by Dr. Julia Golier at the VA Medical Center in the Bronx, New York, has shown that distinct biological alterations are associated with Gulf War illnesses, including enhanced negative feedback inhibition of the hypothalamic pituitary-adrenal axis and reduced 24-hour plasma levels of adrenocorticotrophic hormone. These changes may be the result of glucocorticoid sensitivity. This study will examine the effects of mifpristone, a safe and tolerable glucocorticoid receptor antagonist, on individuals

with Gulf War illnesses in a randomized, double-blind, placebo-controlled, crossover trial.

Veterans of the 1991 Gulf War were exposed to a complex mixture of chemicals. Prolonged exposure to combinations of toxic chemicals has been shown to induce chronic illness in animals. Removal of these animals to an environment free from chemical exposure resolved the illness but left them with acute reactivity. These studies have been extended into humans in an approach referred to as "environmental medicine." In this study, Dr. William Meggs of East Carolina University will conduct a pilot study of a randomized, controlled, open-label trial of environmental medicine therapy for ill Gulf War veterans. It is believed that the environmental medicine approach will be successful in treating symptoms of Gulf War illnesses. In addition, this study will determine if markers of inflammation and autonomic dysfunction are elevated in these veterans and if these markers are affected by treatment.

Chronic Effects of Neurotoxic Substances

Clinical studies have shown that Gulf War illnesses are associated with decreased heart rate variance as well as neuronal damage in brain regions involved in the integration of central and autonomic nervous system control of cardiovascular function. Dr. Mariana Morris of Wright State University has developed an animal model of sarin-induced Gulf War illnesses. With this award, she will identify autonomic biomarkers for Gulf War illnesses and evaluate the efficacy of commercially available drugs against Gulf War illnesses in this animal model.

Veterans of the 1991 Gulf War are twice as likely to develop Amyotrophic Lateral Sclerosis (ALS) as the general population. ALS is a debilitating neurodegenerative disease that is thought to affect neuronal transport since neurons with the longest axons appear to be the most vulnerable to neurodegeneration in this disease. Dr. Peter Baas of Drexel University will use an animal model to determine whether various chemicals to which soldiers were exposed during the Gulf War diminish axonal transport thus contributing to the nerve degeneration underlying ALS.

Depleted uranium (DU) is well suited for military purposes because of its chemical properties and high density. As such, DU is currently used for tank armor and in munitions. However, the neurotoxicity of DU is not known. Dr. Stephen Lasley from the University of Illinois, Chicago, has demonstrated increased synaptic glutamate

concentrations and N-methyl-D-aspartate (NMDA) receptor upregulation resulting from chronic DU exposure. This study is designed to determine the pathophysiological mechanisms underlying DU neurotoxicity. In addition, the clinical potential of an NMDA receptor antagonist (memantine) and/or free-radical trapping agent (NXY-059) will be tested in a rat model of DU-induced neurotoxicity.

Pesticides were used widely during the 1991 Gulf War to protect troops from mosquitoes and fleas that carry infectious disease. Individuals involved in pesticide application were exposed to higher doses of pesticides than other Gulf War veterans. Pest control personnel also report more health concerns and perform lower in the psychomotor and visual memory domains of cognitive testing than their counterparts who were not involved in pest-control. Dr. Kimberly Sullivan from the Boston University School of Medicine will perform a study designed to determine whether pesticides could have caused lasting neurobehavioral deficits in 1991 Gulf War veterans who served as pest-control personnel. Structural MRI will be used to measure brain volumetrics and elucidate brain-behavior relationships in Gulf War veterans with known exposures to organophosphate pesticides as part of their military occupational specialty. It is hoped that this study will provide objective biomarkers to differentiate ill from healthy veterans.

A Team of Outstanding People

The individual contributions and dedication of the best people—including scientists, consumers, and research managers—are impacting the health of our Gulf War veterans.

Integration Panel

The GWVIRP Integration Panel (IP) is composed of representatives from the Department of Veterans Affairs; Army, Navy, and Air Force; industry; federal government; and consumer organizations. Representatives to the IP provide programmatic and strategic direction to the GWVIRP and make funding recommendations to the U.S. Army Medical Research and Materiel Command Commanding General.

FY06 GWVIRP IP Members

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

Carrolee Barlow, M.D., Ph.D., BrainCells, Inc.

James O'Callaghan, Ph.D., Centers for Disease
Control and Prevention

Anthony Hardie, Wisconsin Department of Veterans
Affairs

Captain David Neri, Ph.D., U.S. Navy Bureau of
Medicine and Surgery

Colonel Bruno Petrucci, M.D., M.P.H., U.S. Army
Center for Health Promotion and Preventive
Medicine

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

Lea Steele, Ph.D.
Kansas State University
U.S. Department of Veterans Affairs
Integration Panel Chair

"CDMRP's work in developing and funding the Gulf War Veterans' Illnesses Research Program has represented an important step forward in the government's efforts to address the difficult-to-diagnose conditions resulting from the 1991 Gulf War. I have been particularly impressed with the program's support of innovative research focused on tangible results that directly benefit ill veterans. Including scientists with direct experience with Gulf War illness in the review process, as well as veterans affected by Gulf War illness, has been important in ensuring that the funded research addresses highest priority issues. CDMRP's program management and staff have demonstrated a clear commitment to making a difference, and their professionalism has been the key element in making the program's initial year a success."