The Congressionally Directed Medical Research Programs (CDMRP) office 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 many targeted programs and has received nearly $6.6 billion in appropriations from its inception in fiscal year 1993 (FY93) through FY11. Through FY10, more than 10,000 awards have been made across 25 individual 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, orthopedic injury, spinal cord 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 applications, through individual project performance, to closeout.

The CDMRP program management cycle includes a two-tier review process for application evaluation recommended by the National Academy of Sciences’ Institute of Medicine. The first tier of evaluation is an external scientific peer review of applications against established criteria for determining scientific merit. The second tier is a programmatic review conducted by an Integration Panel (IP) composed of program-specific researchers, clinicians, and consumers who evaluate applications 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 selected military health-related research topics each fiscal year. The MOMRP shared management responsibility for the GWVIRP with the CDMRP in FY06 with separate $5 million (M) appropriations. Although the GWVIRP did not receive funding in FY07, a $10M appropriation renewed the program in FY08, renamed the Gulf War Illness Research Program (GWIRP), to be managed fully by the CDMRP. Since that time, the GWIRP has been maintained with $8M appropriations in FY09, FY10, and FY11. The FY12 GWIRP appropriation is $10M. The program continues to support competitive peer-reviewed research of treatments to address the complex of symptoms that comprise GWI, identify objective markers (biomarkers) for the disease, and understand the pathobiology underlying GWI.

GWIRP-Funded Portfolio by Research Topic, FY06-FY11 (n=54 Projects*)

* 6 projects fit into 2 different research topics
The Integration Panel, or IP, is composed of 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 areas of research interest that can be addressed through certain award mechanisms in an annual vision setting meeting. This is also where an investment strategy for the program year is recommended. Later in the program year, the IP meets to recommend to the GWIRP (through individual confidentially administered voting) which applications best fulfill the program’s vision and mission while also demonstrating innovative science. The recommendations of 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 GWIRP has promoted high-quality, cutting-edge research to explore the pathophysiology underlying Gulf War Illness. Likewise, research funded by the program spearheaded evaluations of innovative treatment modalities. As we plan for the future, the program leaders and Integration Panel members collaborate, successfully developing new grant mechanisms that have the promise to address GWI from an integrated perspective. I am very proud to be part of such a proactive program that has as its first and foremost goal to make life better for the veterans to whom we owe so much.”

Dr. Gudrun Lange, FY12 IP Member

“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, FY12 IP Chair
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, FY12 GWIRP 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, FY09–FY11 GWIRP Consumer
Treatments…
To Improve Quality of Life

The GWIRP has offered Clinical Trial Awards (CTAs) and Innovative Treatment Evaluation Awards (ITEAs) and Investigator-Initiated Research Awards (IIRAs) to support pilot studies and 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.

**Q10 for Gulf War Illness**

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

Dr. Beatrice Golomb recently completed a 3½-year study involving 46 veterans with GWI and examining the benefits of daily coenzyme Q10 (Q10). Q10 is naturally produced in the human body where it is involved in cellular energy production as a key antioxidant. But levels of Q10 can be inadequate to meet needs when there is increased “oxidative stress” or impaired energy production. In the study, an FY06 IIRA, Dr. Golomb hypothesized that mitochondrial dysfunction, which is linked to cellular energy production, may contribute to symptoms of GWI and sought to assess whether Q10 conferred benefit to overall health and symptoms in GWI. Two dose levels (100 mg/day and 300 mg/day) were compared to each other and against placebo treatment, and subjects were treated for 3-month periods in a crossover design. Self-rated responses for overall health and symptom-based questionnaires were used as study measurements.

Initial reading of the study results found that the 100 mg dose led to better self-rated health scores than the 300 mg treatment, but neither dose demonstrated statistically significant improvement over the placebo treatment.

However, fatigue with exertion, which 54% (25) of subjects reported at baseline, demonstrated significant improvement with Q10 at 100 mg compared to placebo treatment in the study. The benefit to fatigue with exertion is important because increased exercise tolerance can enable a range of better outcomes. Increased exercise is a bridge to many health benefits (e.g., mood, function, cardiovascular outcomes, and cognitive performance) as well as quality of life benefits previously reported in ill Gulf War veterans.

These findings provide important preliminary information on effect size and variance relative to self-rated health, which could inform a larger trial of Q10 at 100 mg better powered to show benefit to global self-rated health.
# Innovative Treatment Evaluation Awards

## FY09

### Probiotic for Gulf War Illness  
**Dr. Ashok Tuteja, Western Institute for Biomedical Research**  
Irritable bowel syndrome (IBS) resulting from gastroenteritis is commonly found in ill Gulf War veterans. Dr. Tuteja is examining the potential of probiotic treatment (live bacteria that re-establish normal gut flora) to improve GWI-associated IBS, fatigue, joint pain, and headaches in a clinical trial of 80 Gulf War veterans.

### Gulf War Illness: Evaluation of an Innovative Detoxification Program  
**Dr. David Carpenter, State University of New York, Albany**  
Dr. Carpenter is applying the Hubbard detoxification therapy, including nutritional supplements, exercise, and sauna, in a clinical trial of 50 veterans with GWI. It is hypothesized that the therapy will improve general physical and mental health status and quality of life. Hubbard therapy has been used successfully in cases of environmental exposure in the past, including survivors of the 9/11 attacks.

## FY10

### Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Syndrome  
**Dr. David Rabago, University of Wisconsin, Madison**  
Dr. Rabago is examining the effectiveness of routine nasal care plus saline or xylitol nasal irrigation compared to routine care alone as therapy for chronic rhinosinusitis and fatigue in 75 ill Gulf War veterans. Study outcomes will measure responses to qualified questionnaires and assess the cost-effectiveness of the treatment. Dr. Rabago will also examine proinflammatory cytokine markers and cell types in the mucosal profile to elucidate biomarkers of the condition.

### Investigating Clinical Benefits of a Novel Sleep-Focused, Mind-Body Program on Gulf War Illness Symptoms: An Exploratory Randomized Controlled Trial  
**Dr. Yokio Nakamura, University of Utah**  
Sleep disturbance is commonly seen in veterans suffering from GWI. Dr. Nakamura is evaluating the clinical benefits of a novel mind-body intervention program called Mind-Body Bridging (MBB) for symptom management of ill Gulf War veterans with sleep disturbance and comorbidities, such as pain and fatigue, in a randomized, controlled clinical trial. MBB consists of cognitive and attentional (experiential) techniques for cultivating present-focused, nonjudgmental awareness of one’s body, emotions, and thoughts. Practice of MBB can lead to a greater sense of well-being, greater cognitive flexibility, and better acceptance of distressing sensations, emotions, and thoughts.
Biomarkers of Gulf War Veterans’ Illnesses: Tissue Factor, Chronic Coagulopathy, and Inflammation

Ronald Bach, Ph.D., Veterans Affairs Medical Center, Minneapolis, Minnesota

Many veterans of the 1990–1991 Persian Gulf War suffer from unexplained chronic and often debilitating health issues. It is estimated that 25% to 32% of the nearly 700,000 Gulf War veterans currently experience widespread pain, headaches, fatigue, cognitive deficits, and other symptoms. Preliminary evidence has indicated that a high percentage of ill Gulf War veterans may be in a hypercoagulable state, that is, an abnormally increased tendency toward blood clotting, the basis of which is unknown. Dr. Ronald Bach of the Veterans Affairs Medical Center in Minneapolis is using funds from an FY08 GWIRP Investigator-Initiated Research Award to further investigate this concept. Dr. Bach will examine the level of tissue factor (TF), the biological initiator of blood coagulation, in blood samples from ill Gulf War veterans and healthy controls. Overexpression of TF in the bloodstream can lead to disseminated intravascular coagulation (DIC) and impaired blood flow in the smallest of blood vessels. This restriction of microcirculation applied chronically can produce symptoms commonly associated with GWI, including fatigue, somatic pain, and cognitive difficulties.¹

Dr. Bach will initially try to find more evidence of clotting system abnormalities in ill veterans’ blood by measuring an expanded panel of coagulation markers, including D-dimer, which indicates fibrin clot formation, thrombin-antithrombin III complex, to indicate ongoing coagulation activity, prothrombin fragment 1.2, a measure of ongoing thrombin generation, and TF-procoagulant activity, which can initiate DIC. Serial samples taken over 24 months will be assayed to establish the chronic nature of the abnormalities. This analysis may also uncover new biomarkers for GWI. Dr. Bach will also assess immune function by measuring levels of inflammatory markers in the blood samples. This may indicate a possible state of chronic inflammation in ill veterans and may support a connection between chronic coagulation and immune function.

Structural MRI and Cognitive Correlates in Pest-Control Personnel from the Gulf War

Kimberly Sullivan, Ph.D., Boston University

Pesticides were widely used during the 1990–1991 Gulf War to protect troops from infectious disease-carrying insects. One class of these pesticides, organophosphates, is known to produce chronic neurological symptoms at sufficient exposure levels by inhibiting the enzyme acetylcholinesterase (AChE). Exposure to AChE-inhibiting organophosphate pesticides and antinerve gas pills (pyridostigmine bromide [PB]) has long been a suspected cause for the persistent health complaints of Gulf War veterans. Drs. Kimberly Sullivan and Maxine Krengel of Boston University used an FY06 GWIRP Investigator-Initiated Research Award to follow up on their earlier work (also supported by the CDMRP) with pesticide applicator personnel who also took PB tablets. The earlier study suggested that an objective biomarker for GWI may be attainable through magnetic resonance imaging of these veterans’ brains and subsequent morphometric analysis of appropriately defined cohorts of pesticide-exposed veterans. Based on this, the follow-on FY06 study compared high and low pesticide-exposed veterans in a pilot study to attempt to define this biomarker for brain pathology and associated neuroanatomical and cognitive effects.

The study found lower brain white matter volumes in highly symptomatic compared with less symptomatic Gulf War veterans with known exposures to pesticides as part of their military occupation as pesticide applicators and validated the previous findings. Specific pesticide exposures that showed significant differences with regard to brain volumetric correlations and with cognitive functioning were the organophosphate dichlorvos (used in pest strips) and the organochlorine lindane (a delouser). These particular exposures showed interactive effects when combined, resulting in significantly lower cerebral and cerebellar white matter and gray matter volumes.

Additional study results suggested a significant interaction effect and lower hippocampal volumes, as well as lower scores in visual memory assessments, for combined high N,N-diethyl-meta-toluamide (DEET) and PB exposure, suggesting both a structural and functional relationship. Although the findings were demonstrated in a small study sample (24 subjects across high- and low-exposure groups) and need to be further validated in larger samples, they correspond with published animal studies showing lower hippocampal volumes in similarly combined exposures and should be further clarified. The fact that these results implicate pest strips (dichlorvos), delousers (lindane), insect repellents (DEET), and antinerve gas pills (PB) suggests that these findings could be applicable to the larger cohort of Gulf War veterans because these pesticides were used by general military personnel in addition to the certified pesticide applicators examined in this study.
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 are creating mouse models of neurological dysfunction in attempts to better understand the underlying contributors of GWI symptoms, such as chronic pain, fatigue, and memory loss.

Treatment of Memory Impairment and Sensorimotor Deficits in an Animal Model for the Gulf War Veterans’ Illnesses

Mohamed B. Abou Donia, Ph.D., Duke University Medical Center

Research has shown that health issues described by ill Gulf War veterans may have been caused by exposures to pesticides and insect repellents, as well as antinerve gas medication, experienced during Gulf War deployment. Dr. Mohamed B. Abou Donia developed a rat model of Gulf War exposures that uses topical treatment of permethrin (insecticide) and DEET (insect repellent) to simulate chronic GWI symptoms. Dr. Abou Donia is using an FY08 GWIRP Idea Award to systematically study the potential benefits of the analgesic flupirtine to treat GWI using this rat model. Flupirtine has been used to treat pain and memory deficits associated with other disorders and has been shown to be safe and nonaddictive, although it is not FDA approved.

In the study, rats in the GWI model, either flupirtine-treated or untreated, are compared with flupirtine-treated and untreated normal controls for performance in a water maze test. Rats are timed as they try to find a hidden platform in a water tank from different starting points. Reduced swimming times indicate spatial learning and memory. The water maze test also gauges sensorimotor parameters, such as reflexes, motor strength, and coordination. In addition, researchers learn about cognition from observing the rats’ probing activity during testing. The study is currently under way, and data will be collected over the next 3 years. Dr. Abou Donia’s Gulf War exposures model has effectively reproduced GWI symptoms as the rats developed alterations in memory and neuropathology. The effects of flupirtine will be analyzed after all water maze and histopathological tests have been completed. If successful, this research would provide proof of concept that could ultimately lead to FDA approval of flupirtine for the treatment of GWI.
The GWIRP in FY12

- **Consortium Award (New for FY12)**
- Clinical Trial Award
- Investigator-Initiated Research Award
- Innovative Treatment Evaluation Award

For FY12, the GWIRP’s $10M congressional appropriation will center on the first-ever consortium for GWI research. The program plans to fund a consortium focused on understanding the pathobiology and characterizing disease symptoms in GWI, improving GWI biomarkers and diagnostics, and/or identifying novel treatments for GWI. The consortium will bring together a multi-institutional team of leading GWI and multi-symptom illness scientists and clinicians joining forces for a big impact on the GWI research community and Gulf War veterans fighting this disease. The three FY10 Consortium Development Award awardees will be eligible to apply for the award as they have spent the past year developing their consortium teams and action plans.

In addition to the Consortium Award, the GWIRP will again offer its mainstay Investigator-Initiated Research Award and Clinical Trial Award, along with the Innovative Treatment Evaluation Award, established in FY09. These awards will add to the growing portfolio of GWIRP-funded, high-impact research to help ill Gulf War veterans.
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