DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS (CDMRP) GULF WAR ILLNESS RESEARCH PROGRAM (GWIRP)

PROGRAM DESCRIPTION: Congress directed DoD involvement in Gulf War Illness research efforts beginning in 1994; the program was assigned to the CDMRP for execution management in Fiscal Year 2006 (FY06). Population-based studies indicate that approximately 25% to 30% of the men and women who served in the 1990-1991 Persian Gulf War continue to experience a variety of symptoms and illnesses including: chronic headache, widespread pain, cognitive difficulties, unexplained fatigue, gastrointestinal problems, respiratory symptoms, and other abnormalities that are not explained by traditional medical diagnoses or standard laboratory tests. Congressional directives for the GWIRP, which began in 2008 and that the program continues to follow today, include 1) studies of treatments for the complex of symptoms known as "Gulf War Illness (GWI)," 2) no studies based on psychiatric illness and psychological stress as the central cause, and 3) competitive selection and peer review to identify research with the highest technical merit and military value.

PROGRAM EXECUTION: The GWIRP's mission is to fund innovative GWI research to identify effective treatments, improve definition and diagnosis, and better understand its pathobiology and symptoms.

- The GWIRP has funded research at for-profit, nonprofit, public, and private organizations (e.g.) universities, colleges, hospitals, laboratories, and companies) and at government agencies, including the Department of Veterans Affairs (VA) and Centers for Disease Control and Prevention – National Institute for Occupational Safety and Health.
- The current GWIRP is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine. To ensure both scientific excellence and programmatic relevance, funding recommendations are based on portfolio composition, relative innovation and impact in addition to technical merit. Therefore, applications are not funded using an established "pay line." This model has received high praise from the scientific community, advocacy groups, and Congress. GWIRP awards are fully-funded from the program's Congressional appropriation for a given fiscal year. The GWIRP executes a new program cycle in each FY it is funded. There is no guarantee for continued funding of the program from one FY to the next, or that the level of funding will remain constant.
- Veterans with GWI participate as full members on all review and advisory panels.
- Programmatic recommendations for funding of GWIRP awards rests with the GWIRP Integration Panel (IP), which is composed of prominent members of the GWI research community and includes Gulf War veterans suffering from the disease. During annual vision setting, the IP advises the GWIRP on programmatic focus, current research landscape, and potential directions for the program year. Award mechanisms and Program Announcements are developed, and an investment strategy for the program year is determined. IP members make recommendations to the GWIRP on which applications best fulfill the program's vision and mission while also demonstrating innovative approaches and technical merit determined through the peer review process. The recommendations of IP members during vision setting, pre-application screening, and programmatic review enable the GWIRP to find and fund cutting-edge research, complement other federal GWI research programs, and to set important program priorities designed to benefit ill Gulf War veterans.

PROGRAM PORTFOLIO: The program has built a broad research portfolio of over 70 awards from FY06 to FY13. The GWIRP focuses on research into underlying pathobiology, therapeutic targets, marker identification, and symptomology of the disease. The GWIRP also supports clinical efforts to identify and test potential therapeutics and move interventions toward the clinic. To that end, the GWIRP has continued to offer basic research support under Investigator-Initiated Research Awards (IIRAs), early phase, pilot clinical trial support under Innovative Treatment Evaluation Awards (ITEAs), and support for larger, more definitive clinical trials under Clinical Trial Awards (CTAs). Through FY13, the GWIRP has funded 50 IIRAs ($37M), 10 ITEAs ($6.0M), and 4 CTAs ($4.6M), Of these, 16 awards are focused on developing treatments, 15 are pursuing biomarkers, 8 are examining symptoms, and 6 are investigating exposures, while others are conducting basic research related to Gulf War Illness. Examples of these funded awards include the following:

A. IIRAs:

(1) Drs. Steve Lasley at the University of Illinois College of Medicine at Peoria and James O'Callaghan of the Centers for Disease Control and Prevention - National Institute for Occupational Safety and Health found that combined exposures to the anti-inflammatory glucocorticoid, CORT, and the sarin surrogate diisopropyl fluorophosphate (DFP) may serve as an animal model of the pathobiology of GWI.

(2) Drs. Nancy Klimas of the South Florida Veterans Affairs Foundation for Research and Education, Inc. and Gordon Broderick of Nova Southeastern University completed an integrative study of immune signaling molecules in GWI, Chronic Fatigue Syndrome (CFS), and normal subjects at rest and during exercise and created a model of immune system and hormonal interactions that correctly distinguish GWI and CFS sub populations.

(3) Dr. James Baraniuk of Georgetown University discovered unique alterations in brain structure and function in GWI-affected veterans. Dr. Baraniuk used fMRI to examine the effects of exercise on working memory in GWI patients. Following exercise, he found that the GWI patients have significant white matter dysfunction compared to controls. Additionally distinct cognitive responses, including central perceptual, and energy efficiency were identified in the GWI patient compared to controls. These responses could be further categorized into distinct GWI-related subtypes. These findings point to an inability to recruit cognitive resources during exercise-induced fatigue and are an indication that the heterogeneous GWI can be subdivided for more targeted treatments.

B. ITEAs:

(1) Dr. Ashok Tuteja of the Western Institute for Biomedical Research, is using a FY09 ITEA to study irritable bowel syndrome (IBS) resulting from gastroenteritis commonly found in ill Gulf War Veterans. Dr. Tuteja is examining the potential of pro-biotic 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. This study is ongoing.

(2) Dr. David Rabago of the University of Wisconsin, Madison, is using a FY10 ITEA to examine the effectiveness of routine nasal care plus saline or xylitol nasal irrigation compared to routine care alone as therapy for chronic rhino sinusitis and fatigue in 75 ill Gulf War

Veterans. Study outcomes will gauge responses to surveys and assess the cost-effectiveness of the treatment. Dr. Rabago will also examine pro-inflammatory cytokine markers and cell types in the mucosal profile to elucidate biomarkers of the condition. This study is ongoing.

C. Clinical Trials:

(1) Dr. Beatrice Golomb from the University of California, San Diego hypothesized that mitochondrial dysfunction, linked to cellular energy production, may contribute to symptoms of GWI and sought to assess whether coenzyme Q10 conferred benefit to overall health and symptoms in GWI. Initial analysis of the study results found that the 100 mg dose led to better self-rated health scores than the 300 mg treatment. More importantly, fatigue with exertion, which 54% (25) of subjects reported at baseline, demonstrated significant improvement with Q10 at 100 mg compared to placebo treatment. The benefit to fatigue with exertion is important because increased exercise tolerance is a bridge to many health benefits (e.g., mood, function, and cognitive performance) as well as quality of life benefits crucial to ill Gulf War Veterans. These findings provide important preliminary information that could inform a larger trial of Q10 better powered to show benefit to global health in ill Gulf War Veterans.

(1) Dr. Lisa Conboy from the New England School of Acupuncture, Inc. found that acupuncture provided improvement on the Physical Functioning Subscale (PFS) of the SF-36 in veterans with GWI. Effects were observed following 4-6 months of treatment.

In FY12, the GWIRP took a bold step by awarding two Consortium Awards (~$5M each). These awards were made to two Principal Investigators (PIs) who had received Consortium Development Awards in FY10. Dr. Kimberly Sullivan of Boston University was awarded for her collaborative project entitled "Brain-Immune Interaction as the Basis of Gulf War Illness Consortium (GWIC)." The objective of this study is to provide a cohesive understanding of the pathobiological mechanisms responsible for the symptoms of GWI in order to provide a targeted and efficient basis for identifying beneficial treatments and diagnostic markers. Dr. Mariana Morris of Nova Southeastern University was awarded for her collaborative project entitled "Understanding Gulf War Illness: An Integrative Modeling Approach." This project will integrate clinical understanding of the disease process with basic research efforts using a novel combination of animal and mathematical models. These awards are poised to propel the field of GWI research far beyond what could be accomplished by individual researchers' efforts alone.

Starting in FY14, the GWIRP began encouraging investigators outside of the GWI community who might bring a unique approach under a New Investigator Award. The GWIRP also began investing in the expansion of successful past investigations to continue to move high impact research forward. These awards will add to the growing portfolio of GWIRP-funded, high-impact research designed to help our ill Gulf War Veterans.

The FY14 program cycle will be completed in May 2015. A list of the institutions and PIs recommended for funding thus far are available at http://cdmrp.army.mil/gwirp/awards/awards.shtml. Funding opportunities for the FY15 GWIRP are anticipated to be released in April 2015. Award data and accomplishments can be viewed on the GWIRP program page on the CDMRP website (http://cdmrp.army.mil/gwirp/default.shtml). Funded project data (FY08-FY13) are also available in FederalRePORTER at http://federalreporter.nih.gov/. A complete listing of clinical trials (early phase, pilot and later phase) supported by the GWIRP is attached.

CLINICAL TRIALS FUNDED BY THE DOD CDMRP GWIRP:

Log Number	PI	Contract	Organization	Title
GW060036 (closed)	Golomb, Beatrice	W81XWH-07-1-0667	University of California, San Diego	Q10 for Gulf War Illness
GW060048 (closed)	Golier, Julia	W81XWH-07-1-0602	VA Medical Center, Bronx, NY	A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multisymptom Illness
GW080059 (closed)	Conboy, Lisa	W81XWH-09-2-0064	New England School of Acupuncture, Inc.	Effectiveness of Acupuncture in the treatment of Gulf War Illness
GW080064	Meggs, William	W81XWH-09-2-0065	East Carolina University	Trial of Naltrexone and Dextromethorphan for Gulf War Veterans' Illness
GW093043	Tuteja, Ashok	W81XWH-10-1-0593	VA Medical Center, Salt Lake	Probiotic (VSL#3) for Gulf War Illness
GW093066	Carpenter, David	W81XWH-10-1-1004	New York, State University of, Albany	Gulf War Illness: Evaluation of an Innovative Detoxification Program
GW100054	Rabago, David	W81XWH-11-1-0390	Wisconsin, University of, Madison	Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Syndrome
GW100068	Nakamura, Yoshio	W81XWH-11-1-0517	Utah, University of	Investigating Clinical Benefits of a Novel Sleep-Focused, Mind-Body Program on Gulf War Illness Symptoms: An Exploratory Randomized Controlled Trial
GW110019	Lin, Vernon	W81XWH-12-1-0567	Cleveland Clinic Foundation	Effectiveness of Acupressure Treatment for Pain Management and Fatigue Relief in Gulf War Veterans
GW110054	Golier, Julia	W81XWH-12-1-0585	VA Medical Center, Bronx, NY	Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness
GW130015	Younger, Jarred	W81XWH-14-1-0623	Alabama, University of, at Birmingham	Treating Gulf War Illness with Novel Anti-Inflammatories: A Screening of Botanical Microglia Modulators
GW130022	Bayley, Peter	W81XWH-14-1-0615	VA Palo Alto Health Care System	A Multimodal Evaluation of the Comparative Efficacy of Yoga versus a Patient-Centered Support Group for Treating Chronic Pain in Gulf War Illness
GW130025	Bach, Ronald	W81XWH-14-1-0477	Minnesota Veterans Medical Research and Education Foundation	Gulf War Illness Inflammation Reduction Trial
GW130047	Kaiser, Jon	W81XWH-14-1-0607	K-PAX Pharmaceuticals, Inc.	A Prospective Open-Label Clinical Trial of Methylphenidate plus a GWI-Specific Nutrient Formula in Patients with Gulf War Illness and Concentration Disturbances
GW130070	Pasinetti, Giulio	W81XWH-14-1-0599	Mount Sinai School of Medicine, New York	Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness
GW130093	Serrador, Jorge	W81XWH-14-1-0598	Veterans Biomedical Research Institute, Inc.	Use of a Portable Stimulator to Treat GWI