

Gulf War Illness Research Program

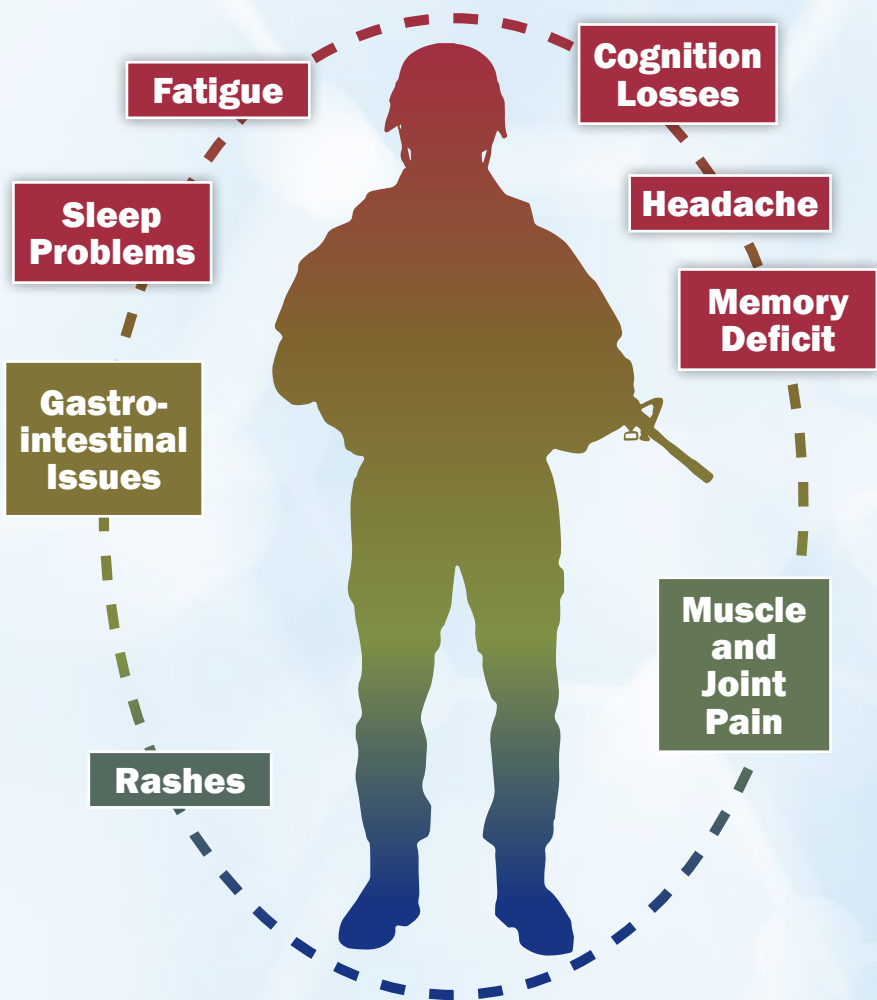


Congressionally Directed Medical Research Programs

HISTORY

The Congressionally Directed Medical Research Programs (CDMRP) was created 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. The CDMRP has grown to encompass multiple targeted programs and has received over \$11.9 billion in appropriations from its inception through fiscal year 2017 (FY17). In response to demonstrated need, targeted funds for the CDMRP are added to the Department of Defense (DoD) budget each year with specific guidance from Congress. These funds are in addition to what the President has laid out for the DoD and, because they are Congressionally mandated, cannot be further shaped. Through FY17, nearly 17,000 awards have been made across 47 individual programs. Under the auspices of the U.S. Army Medical Research and Materiel Command (USAMRMC), the CDMRP executes and manages these programs from receipt of funds to competitive selection of applications, through individual project performance to project closeout.

Gulf War Illness



What is Gulf War illness?

GWI is characterized by persistent symptoms such as widespread pain, cognitive and memory difficulties, debilitating fatigue, muscle and joint pain, gastrointestinal problems, respiratory symptoms, chronic headache, sleep problems, rashes, and other abnormalities that are not explained by traditional medical or psychiatric diagnoses. This complex set of chronic symptoms may affect as many as 250,000 Veterans of the 1990–1991 Gulf War, of the nearly 700,000 troops deployed to that region.

Research Program

VISION

Improved health and lives of Veterans who have Gulf War Illness

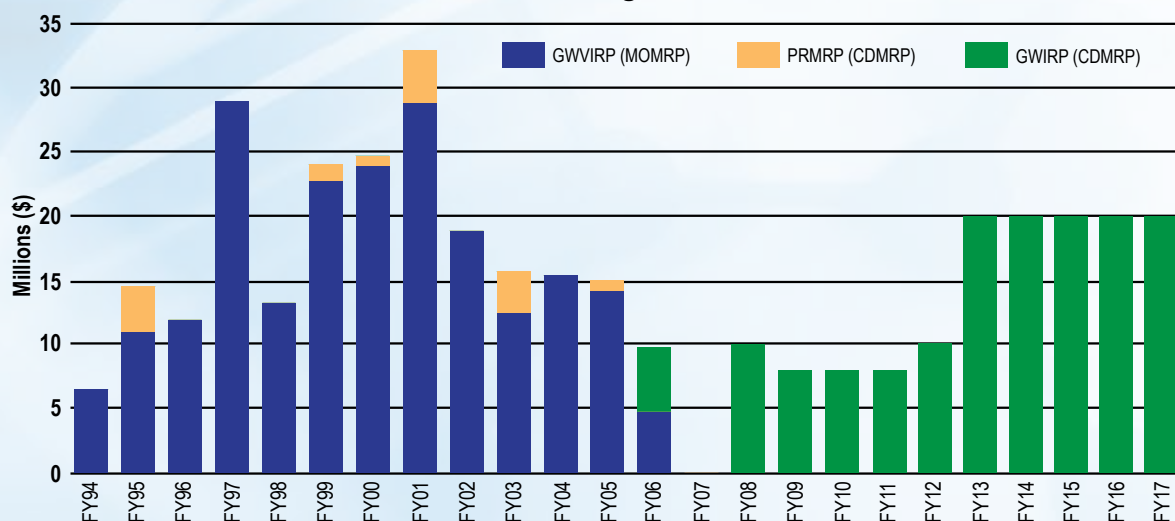
MISSION

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

ABOUT THE PROGRAM

DoD-funded GWI research began in 1994 with the establishment of the 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, which supports select 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 Gulf War Illness Research Program (GWIRP), to be managed fully by the CDMRP. Since that time, the GWIRP has been funded by an \$8M appropriation each year from FY09 through FY11, \$10M in FY12, and \$20M per year from FY13 through FY17. The program continues to support innovative, competitively peer-reviewed research to develop treatments addressing the complex symptoms that comprise GWI and its underlying causes, to identify objective markers (biomarkers) improving its diagnosis, and to better understand the pathobiology underlying GWI.

GWIRP Funding FY94–FY17



Award Application Review

The CDMRP uses a two-tier review process for application evaluation, which is critical to ensuring that each of the research program portfolios reflects not only the most meritorious science, but also the research that best meets the program vision and mission. The first tier of evaluation is a scientific peer review of applications measured against established criteria to determine scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, composed of leading scientists, clinicians, and GW Veterans with GWI. In this tier, the Programmatic Panel compares the applications to each other and makes recommendations for funding based on the scientific merit as determined in peer review, potential impact, relevance to program goals, and portfolio composition. The Commanding General of the USAMRMC issues the final approval for funding prior to award negotiations and execution.



Consumer Involvement

The two-tier review process established by the CDMRP brings together the expertise of scientists with the perspective and experience of “consumers,” the Gulf War Veterans themselves. This innovative approach, recommended by the National Academy of Sciences’ Institute of Medicine and adopted by other funding organizations, has proven to be an effective way to evaluate research applications for their potential to meet the program’s goals for those we seek to serve. As peer reviewers, consumers evaluate applications for scientific and technical merit as well as the potential successful impact of the research. As Programmatic Panel members, consumers make programmatic recommendations for the GWIRP’s vision, investment strategies, and funding selections intended to reflect the needs of the Veteran and research communities.



“I’ve been a consumer reviewer for five years. In that time, as technology has advanced exponentially, I’ve seen CDMRP-funded studies produce some very pertinent results. Each year I see new proposals build upon the results of previous studies as researchers work to find treatments to help our Veterans. Consumer reviewers bring the Veterans’ voice to the table and help focus the science on real human impact. Our opinions carry the same weight as the rest of the panel, allowing us to measure the impact in real life. This is a key part in why CDMRP is so important to our Veterans.”

Peter Greene, Consumer Peer Reviewer

Program Award Types

The award mechanisms offered by the GWIRP have evolved over the years as the field of GWI research has advanced. At the GWIRP's inception, funding for basic mechanistic research was offered to elucidate the molecular and genetic processes underlying GWI. As GWI research has progressed, awards supporting preclinical and clinical research were offered with the goal of identifying novel treatments for Veterans with GWI.

New funding opportunities developed to fill gaps and address program priorities

	FY06-FY11	FY12-FY14	FY15-FY16	FY17
Gap/Priority	Treatment Basic Research Disease Models Detection	Treatment Preclinical Research Detection Consortia	Treatment Clinical Translation Focused Topics Diagnosis New Investigators	Treatment Quality of Life Research Resources Focused Topics
Funding Opportunities Developed	<ul style="list-style-type: none"> Clinical Trial Innovative Treatment Evaluation Investigator-Initiated Research 	<ul style="list-style-type: none"> Clinical Trial Innovative Treatment Evaluation Investigator-Initiated Research Consortium 	<ul style="list-style-type: none"> Clinical Trial Treatment Evaluation Clinical Partnership Investigator-Initiated Focused Research Epidemiology New Investigator 	<ul style="list-style-type: none"> Clinical Consortium Qualitative Research Biorepository Investigator-Initiated Focused Research
	51 Awards	48 Awards	56 Awards	10 Awards

GWI Research Landscape

The GWIRP has developed a resource describing what is currently known about GWI for the research, care provider, and Veteran communities. This document, the "Gulf War Illness Landscape," covers topics most pertinent to the program's integrated, three-part, Congressionally directed mission: identifying GWI treatments and accelerating their clinical application; improving the definition and diagnosis of GWI; and, understanding GWI's pathobiology and symptoms.



The Gulf War Illness Landscape is available from the CDMRP GWIRP website at:

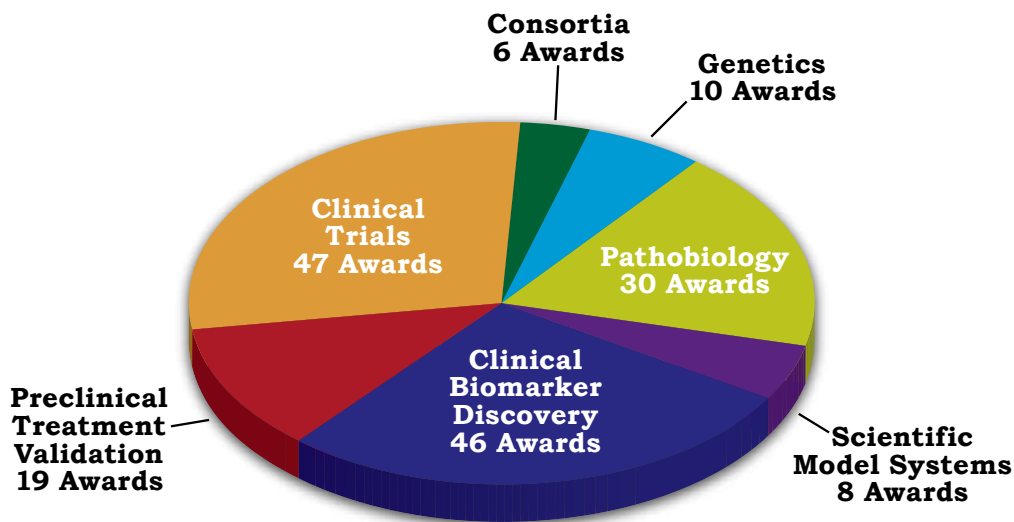
http://cdmrp.army.mil/gwirp/pdfs/GWIRP_Landscape.pdf



The GWIRP Portfolio

The GWIRP portfolio includes more than 160 research projects spanning investigations of the basic pathobiology of GWI to trials of pharmaceuticals and other therapies in Veterans. The pie chart below indicates the distribution of funding addressing different phases and areas of research.

GWIRP-Funded Portfolio by Research Topic, FY06–FY17



Topics for Understanding GWI

An understanding of GWI pathobiology is fundamental to identifying diagnostic markers of illness and targets for pharmacologic agents. Each year the GWIRP articulates Topics of Special Interest for pathobiological investigations. These topics address both understudied areas and areas where evidence indicates biological markers or targets hold significant promise for GWI diagnosis and treatment. Examples of Topics of Special Interest include: human body system dysregulation/abnormal crosstalk, molecular signatures underlying common clusters of symptoms, and genetic factors predisposing individuals to GWI. Special Topics of Interest for FY18 are listed in the Investigator-Initiated Focused Research Award Program Announcement/Funding Opportunity.

GWI Treatment Concepts

Coenzyme Q₁₀

- Oxidized CoQ₁₀ (ubiquinone)
- CoQ₁₀ in nanoparticles
- CoQ₁₀ with neuroprotective formulation

Nerve Stimulation

- Transcranial direct current stimulation
- Transcranial magnetic stimulation
- Vagus nerve stimulation
- Vestibular system stimulation

Targeted Immune System Modulation

- B-cell depletion
- Reduce NF-κB
- Inhibit glucocorticoid receptor (GCR)
- Reduce TNF-α + delayed GCR inhibition
- Block growth hormone-releasing hormone receptor
- Boost TH2 responses
- Block IL-1 receptor

Neuropharmacology

- NMDA receptor blockers
- Methylphenidate
- Intranasal insulin
- Naltrexone
- Detromethorphan
- Bacopa
- Low-glutamate diet
- Glutamate transporter (EAAT2) enhancers
- Memantine
- Flupirtine
- Riluzole

General/Multi-Acting Anti-Inflammatories

- Anatabine
- Prednisone
- Nasal irrigation (saline or xylitol)
- Anti-inflammatory probiotics
- Low fermentable saccharide diet
- Anti-inflammatory botanicals
- Fingolimod, gilenya, losmapimod, minocycline, palmitoylethanolamine, spiro lactone

General/Multi-Acting Antioxidants

- Resveratrol
- Flavenoid-rich polyphenols
- Carnosine
- Monosodium luminol
- Melatonin

Alternative medicine

- Yoga
- Acupressure
- Mind-body bridging
- Detoxification protocols
- Acupuncture

Other Preclinical Study Approaches

- Histone deacetylase inhibitors
- Inhibition of miRNA-124
- Cerebrovascular dilation
- Restoration of lipid homeostasis
- Restoration of CA⁺⁺ homeostasis

GWIRP Consortia: From

Nova Southeastern University FY12:

Understanding Gulf War Illness: An Integrative Modeling Approach

Under the leadership of Drs. Mariana Morris, Nancy Klimas, and Gordon Broderick, an FY12 GWIRP-funded consortium represents expertise in neurotoxicology, animal modeling, computational modeling, and clinical research. This multidisciplinary research team, based at the Institute for Neuro Immune Medicine at Nova Southeastern University, aims to develop a translational model of GWI that will identify molecular targets and predict effective therapeutic interventions while also uncovering underlying mechanisms of disease. Preliminary comparative analysis of cytokine expression profiles between GWI Veterans and GWI animal models, paired with computer simulations, led to animal trials of candidate treatment protocols conducted by Dr. Klimas. Following preclinical validation, the team moved forward with a combination treatment strategy using a tumor necrosis factor (TNF) receptor antagonist followed by a glucocorticoid receptor blockade in a Phase I study of Gulf War Veterans. The research team plans to repeat the dynamic modeling before and after treatment to further inform the computation model. Additional research outcomes include examination of the physiological effects of Gulf War-era chemical exposure and exercise stress in GWI animal models with a focus on cardiac, autonomic, and body compositions parameters. Results to date suggest there are cardiac changes associated with Gulf War-era exposures.

Boston University School of Public Health FY12:

Brain Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC)

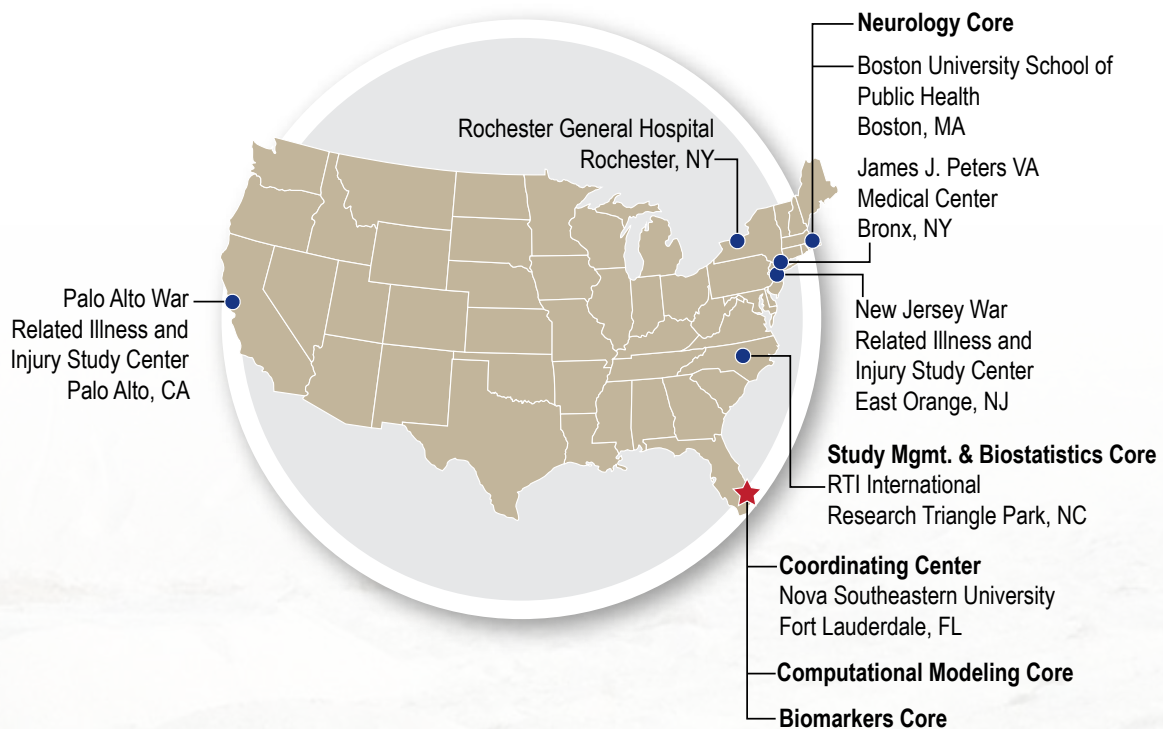
The GWI Consortium is led by Dr. Kimberly Sullivan of Boston University and brings together established GWI researchers from across the nation to investigate the pathobiological mechanisms responsible for GWI symptoms as they relate to brain-immune activation and chronic inflammation. This consortium has initiated a series of clinical and preclinical studies to identify pathways that can be targeted by glial-modulating interventions and other currently available treatments. Ongoing investigations include clinical case-control studies examining markers in the blood and brain fluid, brain imaging, and memory testing. Parallel preclinical studies are evaluating persistent effects of Gulf War neurotoxicants in vitro and in rodent models of GWI. Preliminary results from the preclinical studies provide strong evidence for a neuroinflammatory component to the illness, and studies of potential treatments are currently underway in animal models. On the clinical side, preliminary results comparing cytokine, chemokine, monocytes, and lymphocytes between ill Gulf War Veteran cases and controls indicate significant differences. Correlations between cognitive assessment data, neuroimaging data, and cytokine profiles have led to the identification of brain-behavior relationships in GWI. The consortium has also established neuronal cell lines differentiated from Gulf War Veteran-derived induced pluripotent stem cells. In the last year of this project, researchers will validate clinical results through increased Veteran recruitment.

Bench to Bedside

Nova Southeastern University FY17:

The Gulf War Illness Clinical Trials and Interventions Consortium

In FY17, Nova Southeastern University was awarded a Clinical Consortium Award to create a network of institutions focused on designing and executing Phase I and II clinical trials to test potential therapeutics for GWI. The consortium will build on current knowledge of mechanisms and mediators involved in GWI and will focus on existing drugs applied to GWI to expedite therapies to ill Gulf War Veterans. The consortium will initially conduct four Phase I-II clinical trials at the trial sites shown on the map below.



Boston University School of Public Health FY17:

Boston Biorepository, Recruitment, and Integrative Network for GWI

In FY17, the GWIRP awarded a Biorepository Resource Network Award to Boston University School of Public Health. The network will acquire, annotate, and store biological specimens and data collected during the course of clinical and preclinical investigations to serve as a resource for GWI researchers everywhere. The network leverages an existing collection of clinical specimens that were acquired from projects executed by the FY12 GWI research consortia.

Gulf War Illness



Gulf War Illness as a Brain Autoimmune Disorder

Apostolos Georgopoulos, M.D., Ph.D., University of Minnesota, Twin Cities

And

Human Leukocyte Antigen in Gulf War Veterans: Association with Symptoms and Inflammatory Markers

Lisa James, Ph.D., University of Minnesota, Twin Cities



Several lines of research implicate alterations in immune function as an underlying factor for the constellation of symptoms in GWI. Under a GWIRP Investigator-Initiated Research Award, Dr. Georgopoulos identified six human leukocyte antigen (HLA) class II alleles, or alternative gene forms, that appeared protective against GWI. Proteins from these alleles are known to attach to specific pathogen fragments to form a combined HLA-pathogen-epitope molecule, which, in turn, promotes the production of antibodies specific to that pathogen by plasma cells. These antibodies attach to and neutralize the circulating pathogen. The protective role of HLA alleles in

GWI was demonstrated by the fact that GWI symptom severity decreased with higher HLA allele counts. Dr. Georgopoulos went on to identify specific regional anomalies in brain communication that appeared to be associated with a number of HLA allele copies as well as symptom severity. A comparison of brain synchronicity in GWI to that of three immune-related diseases (multiple sclerosis, Sjögren's syndrome, rheumatoid arthritis) and four mental health disorders (schizophrenia, Alzheimer's disease, major depressive disorder, posttraumatic stress disorder) showed that GWI did not differ from the three immune-related disorders but did differ from the mental health disorders and that this distinction held for the HLA-related territory of brain communication. Lastly, preliminary data suggested that one of the six HLA protective alleles spares Gulf War-era Veterans from subcortical brain atrophy. This evidence underscores the interplay among specific immunity, brain function, and GWI, and strongly suggests that immune vulnerability, in addition to the hypothesis that GWI may be the consequence of toxic chemical exposures, is an important factor in developing GWI. This work is currently being expanded under a separate GWIRP-supported award to Dr. Lisa James. Under this award, Dr. James is conducting an epidemiological evaluation of the relationships between GWI, genotype, and immune system functioning in a large, randomly selected sample of Gulf War Veterans is being performed in order to rigorously evaluate immune system involvement in GWI.



Epigenetic Impacts of Stress Priming of the Neuroinflammatory Response to Sarin Surrogate in Mice: A Model of Gulf War Illness

Patrick McGowan, Ph.D., University of Toronto

Epigenetic modifications, including changes in DNA methylation and chromatin modifications that impact transcriptional regulation, have been suspected to play a role in mediating the symptoms of GWI. Dr. McGowan and his colleagues examined the brains of GWI rodent models to identify

Research Highlights

gene pathways potentially impacted by epigenetic modifications after an initial exposure to diisopropyl fluorophosphates (DFP), and the stress hormone corticosterone (CORT). Following RNA-seq analysis, mice exposed to DFP and CORT had a total of 206 and 667 differentially expressed genes in the frontal cortex and hippocampus, respectively, and 32 genes differentially expressed in both regions. Dr. McGowan noted that the genes with the largest fold change were all immune- and microglia-related, building upon previous reports in this mouse model. Of interest were changes in the NF-KappaB-related genes previously reported by GWI research groups as well as pathways under the broad theme of neuronal development and migration. Following DNA methylation analysis using Reduced Representation Bisulfite Sequencing, differentially methylated regions were identified; however, minimal overlap was found between the hippocampus and frontal cortex, and there appeared to be no significant enrichment for a particular annotated pathway. Interestingly, the region encoding the gene *Camk2b* was found to be differentially methylated in the hippocampus and to have differential histone (H3K27ac) binding in the cortex. This finding correlated with increased CaMKII protein expression reported in the blood of ill Gulf War Veterans. Overall, the lack of large coordinated changes in DNA methylation was unexpected and likely due to the short time point after treatment and to cellular heterozygosity. A pilot protocol enabling cell separation by fluorescence-assisted cell sorting (FACS) is underway with preliminary data pointing toward microglia as the primary cell type driving the neuroimmune changes. Results from this work, particularly alterations in the binding of H3K27ac, provide preliminary insights into epigenetic effects with the potential for long-lasting implications. Additional research is necessary to determine how transcriptional and epigenetic modifications mediated by toxicant exposures contribute to pathological outcomes in GWI.



High-Fidelity Design of Multimodal Restorative Interventions in Gulf War Illness

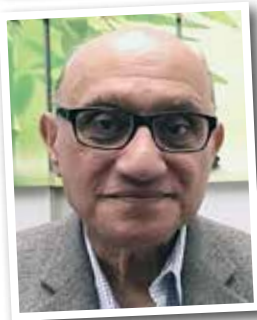
Dr. Travis Craddock, Ph.D., Nova Southeastern University

Because of the time and expense associated with developing new drugs, significant effort has been spent to repurpose existing drugs to treat GWI. Dr. Craddock and his team developed a bioinformatics-based approach to identify existing drugs that are used to treat other diseases or conditions that specifically target gene expression systems that are dysregulated in GWI. The researchers identified altered patterns of gene expression in Veterans with GWI and compared them to known disease gene expression profiles. They then identified those drugs that target the most commonly dysregulated genes using the PharmGKB database. GWI was found to have dysregulation in the TNF α and hormone receptor pathways. These findings suggest that GWI symptoms may be treatable using a range of drugs, including TNF α blockers, immunosuppressants, protein kinase inhibitors, hormone treatments, estrogen receptor antagonists, and monoclonal antibodies. Further studies will be needed to determine which drugs would be most beneficial for use in clinical trials.



Novel Autoantibody Serum and Cerebrospinal Fluid Biomarkers in Veterans with Gulf War Illness

Kimberly Sullivan, Ph.D., Trustees of Boston University
Mohamed Abou Donia, Ph.D., Duke University Medical Center



Veterans suffering from GWI commonly report a wide range of symptoms including, but not limited to, fatigue, muscle pain, and cognitive problems. Study results have shown Gulf War Veterans with higher and/or specific combinations of toxicant exposures have significantly smaller brain white matter or hippocampal brain volumes that correlated with cognitive testing domains. Brain volumetrics has therefore been targeted as a measure of surrogate biomarkers of neurotoxicant exposure in this cohort due to a lack of identified blood biomarkers of past exposure that would be sensitive years after the initial exposure. Drs. Abou Donia and Sullivan are undertaking a study to identify objective biomarkers that could be used to identify nervous system injury in Veterans presenting with GWI symptoms. They hypothesize that following neural damage caused by Gulf War-relevant toxicant exposures, there is loss of cells and a breakdown of the blood brain barrier leading to leakage of specific neuronal and glial proteins into circulation,

with subsequent formation of their autoantibodies; such antibodies can be quantified and used as sensitive biomarkers for nervous system injury. To test this, blood samples from 20 Gulf War Veterans were collected and analyzed during a pilot study to assess the presence of nine autoantibodies against neural proteins. Elevated levels of serum autoantibodies against eight neuronal- and glial-specific proteins were observed, confirming the existence of neuronal injury/glia activation in Veterans with GWI. Drs. Abou Donia and Sullivan are hopeful that results from their ongoing, larger clinical study of blood, saliva, and cerebrospinal fluid will replicate the preliminary information obtained from the pilot study. Results may lead to creation of a diagnostic test that utilizes these blood-based autoantibodies as biomarkers for GWI. This type of diagnostic test also has the potential to distinguish subgroups within the GWI population, which could contribute to the development of individualized treatment strategies for GWI.



Microtubule Abnormalities Underlying Gulf War Illness in Neurons from Human-Induced Pluripotent Cells

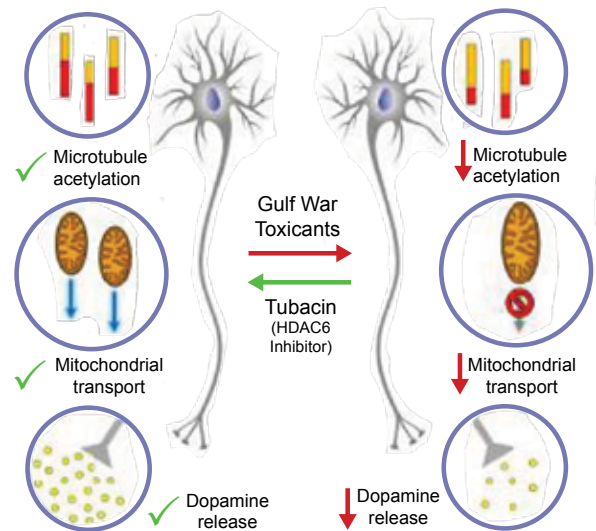
Peter W. Baas, Ph.D., Drexel University

GWI is a chronic multisymptom illness that affects around one-fourth of Gulf War Veterans. Many of these Veterans are believed to have been exposed to organophosphate (OP) nerve agents, which can cause a wide range of neurological disorders and other ailments. Microtubule abnormalities are commonly present in Veterans suffering from GWI, making microtubule-based therapies a viable option for treatment.

Development of effective treatments depends on animal models that neither share a similar genetic background or consider epigenetic factors relevant to human disease. With support from

Clinical Highlights

an FY14 New Investigator Award, Dr. Baas sought to develop and establish a repository of self-renewing human-induced pluripotent stem cells (hiPSC) from blood samples of Veterans who suffer from GWI. The repository will serve as a cell bank to test possible therapies and develop microtubule-based approaches to correct the cellular defects present in GWI. In a recent paper published in *Traffic*, Dr. Baas showed that tubacin, a drug that inhibits a tubulin deacetylating enzyme (HDAC6), is able to correct some of the cellular abnormalities present in GWI. Based on this work, Dr. Baas suggested that HDAC6 may be a novel therapeutic target for GW Veterans; he has been awarded a follow-up grant to continue his work by investigating the therapeutic potential of HDAC6 inhibitors on GWI.



A Prospective Open-Label Clinical Trial of Methylphenidate Plus a GWI-Specific Nutrient Formula in Patients with Gulf War Illness and Concentration Disturbances

Jon Kaiser, M.D., K-PAX Pharmaceuticals

Many Gulf War Veterans experienced prolonged exposure to toxins while serving. In some, this toxicant exposure may have triggered a secondary mitochondrial disease, which may underlie or exacerbate GWI. Notably, GWI patients and those with known mitochondrial disease have overlapping symptoms, such as fatigue and cognitive dysfunction. Dr. Kaiser and Dr. Mark Holodniy, with the support of an FY13 GWIRP Innovative Treatment Award, tested a combination treatment that is designed to support the mitochondria of the nervous system in an open-label clinical trial in patients with GWI. The treatment, known as KPAX002, combines a low dosage of the central nervous system stimulant methylphenidate and a micronutrient formula intended to support mitochondrial metabolism. The combination of these two components supports the recovery of dysfunctional mitochondria in the nervous system leading to an improvement in clinical symptoms. Dr. Kaiser's team found that, after 12 weeks of KPAX002 treatment, patients had a 25% decrease in overall GWI symptoms. Additional clinical assessments revealed specific improvements in cognitive symptoms, pain, and sleep. Further, Dr. Kaiser's group found reduced levels of a biomarker for oxidative stress, suggesting improved mitochondrial function. These results suggest that remediation of mitochondrial dysfunction, combined with gentle stimulation of the nervous system function, can improve symptoms experienced by Veterans with Gulf War illness.

Making an Impact

Clinically Relevant Pathophysiology

Dr. Laila Abdulla – Lipid Metabolism

Peripheral lipid disturbances were found to be present both in Gulf War Veterans with GWI and in two preclinical rodent models of GWI. These data suggested dysfunction within ether and docosahexaenoic acid and arachidonic acid containing phospholipid (PL) species in relation to GWI. As these PL species play a role in inflammatory processes, these findings suggest a possible role for inflammatory imbalance in GWI.

Dr. Ronald Bach – Inflammation

A pilot study conducted on Veterans with GWI demonstrated that plasma levels of inflammatory proteins and blood cells were significantly higher in Veterans with GWI inferring chronic inflammation. Thus, chronic inflammation has been identified as a potential therapeutic target for GWI treatment. Dr. Bach is translating these findings under a GWIRP Clinical Trial Award to examine whether delayed-release prednisone, which has well-established anti-inflammatory properties, can alleviate symptoms of GWI.

Dr. Beatrice Golomb – Mitochondrial Dysfunction

A pilot study was conducted to examine the role of mitochondrial dysfunction (MD) in GWI using the phosphocreatine-recovery time constant (PCr-R), a robust measure of mitochondrial status. Compared to matched healthy controls, Veterans with GWI had significantly prolonged PCr-R, providing the first objective evidence for mitochondrial dysfunction in GWI. Recruitment has concluded for a larger follow-up study; a biopsy study that examines mitochondrial “respiratory chain function” (energy production) in muscle is underway.

Dr. Nancy Klimas, Dr. Gordon Broderick, Dr. Travis Craddock, Dr. Mary Ann Fletcher – Interactions Between Stress Response and Immune Response

Drs. Broderick and Craddock constructed a computer model of the immune hypothalamic-

pituitary-adrenal (HPA) axis and hypothalamic-pituitary-gonadal (HPG) axis simulating the influence of hormones and cytokines in GWI versus a healthy condition. Drs. Klimas and Fletcher collected and analyzed blood samples from Veterans with GWI under exercise challenge to determine if the patterns of hormone and immune proteins corresponded to dysregulation predicted by the model. The team found that levels of key hormones and cytokines in ill Gulf War Veterans aligned with simulated predictions of altered regulation, including a Th1/Th17 cytokine shift and specific involvement of the TNF and NFκB pathway.

Dr. Ashok Shetty – Oxidative Stress and Neuroinflammation

Dr. Shetty used a well-characterized GWI rat model to examine the efficacy of monosodium luminol-GVT (MSL-GVT), which suppresses oxidative stress and inflammation in GWI rats, on alleviating GWI mood and memory dysfunction symptoms. High-dose MSL-GVT was found to be effective in reducing inflammation and normalizing neurogenesis in the hippocampus. Dr. Shetty continues to partner with Bach Pharma for advanced development of MSL-GVT application and translation of this mechanistic research into a treatment trial to ameliorate symptoms of GWI in Veterans.

Treatments

Dr. Lisa Conboy – Acupuncture

A randomized controlled trial comparing biweekly to weekly acupuncture for 6 months showed that Veterans given biweekly acupuncture treatment had clinically and statistically significant improvement in self-rated pain (as measured by the McGill Pain Scale) and functioning, as measured by the Physical Functioning Subscale of

the SF-36. Dr. Conboy received additional funding in FY13 and FY14 from the GWIRP to further evaluate acupuncture as a treatment for Veterans with GWI and to design and implement a program for acupuncture practitioners to use in the clinic to treat the symptoms of GWI.

Dr. Beatrice Golomb – CoenzymeQ10 (CoQ10)

Veterans with GWI were given placebo, low, or high doses of CoQ10 for 3 months and were assessed with a general self-rated health (GSRH) score, self-rated symptom score, and summary performance score (an objective measure of physical function). Veterans dosed with the low dose (100 mg) of CoQ10 had improvement of GWI symptoms and physical function; GSRH improved in men. Benefit correlated to blood levels of coQ10. The VA is conducting a Phase III trial in Veterans with GWI to examine the efficacy of ubiquinol, the reduced form of CoQ10, on improving GWI symptoms.

Dr. Yoshio Nakamura – Mind-Body Bridging

A sleep-focused strategy Mind-Body Bridging (MBB), was compared to a sleep hygiene education control (SED) in Gulf War Veterans suffering from disturbed sleep. Veterans treated with MBB had a significantly greater reduction in sleep problems and also reported greater improvements in PTSD, depression, and fatigue symptoms compared to Veterans treated with the SED. Additionally, the mean waking level of salivary alpha-amylase in the MBB declined to a greater extent than that in the SED at follow-up. Sleep-focused MBB can improve sleep and, possibly, co-occurring symptoms in GW Veterans.

Dr. James Baraniuk – Carnosine

Environmental and chemical exposures experienced by deployed Gulf War Veterans may have led to a prolonged production of reactive oxygen species (ROS), resulting in neuronal damage and neural dysfunction. L-Carnosine, a peptide closely related to a brain antioxidant dipeptide that protects the brain from damage caused by ROS, was given to Veterans with GWI during a 12-week randomized double-blind placebo controlled dose escalation study. Cognitive function and diarrhea associated with irritable bowel syndrome were improved by treatment with Carnosine, suggesting it may be a useful treatment for certain GWI symptoms.

Dr. Jon Kaiser – K-PAX Pharmaceuticals

GWI shares symptoms with known mitochondrial diseases including fatigue and cognitive dysfunction, suggesting that abnormal mitochondrial metabolism plays a role in GWI pathology. Dr. Kaiser tested the effectiveness of KPAX002, a combination treatment of methylphenidate plus a mitochondrial support nutrient formula that attempts to improve symptoms by “jump starting” dysfunctional mitochondria in the central nervous system of Veterans with GWI. Treatment with KPAX002 for 12 weeks led to improvement in cognitive symptoms, fatigue, pain, sleep, and a 25% overall decrease in GWI symptoms. These results suggest treatment of mitochondrial dysfunction can improve GWI symptoms.

Dr. David Rabago – Nasal Irrigation

Two common symptoms reported by Veterans with GWI are chronic nasal congestion and fatigue; nasal irrigation is safe and effective for both in the general population. In a 26-week, three-arm randomized controlled study of GWI patient experience, Dr. Rabago at the University of Wisconsin tested whether the addition of nasal irrigation with saline or xylitol to routine care improves these symptoms compared to routine treatment alone. Both irrigation groups safely improved substantially on the main measure, the Sino-nasal Outcome

Test questionnaire; participants were satisfied with care. There was minimal improvement in fatigue, and researchers were not able to detect changes in biological markers that might indicate a precise reason for the improvement.

Biomarkers

Dr. James Baraniuk – Exercise-Induced Phenotypes

GWIRP funds were used to examine the effect of exercise on cognition, fatigue, and systemic hyperalgesia in Veterans with GWI. Two subgroups of GWI Veterans were identified during the study. The Stress Test Associated Reversible Tachycardia (START) group experienced cognitive fatigue and disruption of cerebellar cognitive compensation after exercise. The Stress Test Originated Phantom Perception (STOPP) group experienced increased perception of pain and disruption of basal ganglia cognitive compensation after exercise. The cerebrospinal fluid of Veterans with GWI, subjects with chronic fatigue syndrome (CFS), and sedentary controls were analyzed for the presence of miRNAs related to central nervous injury before and after exercise. A differential miRNA expression pattern suggests there are distinct mechanisms mediating post-exercise malaise in START and STOPP GWI Veterans reflecting additional differences from individuals with CFS.

Dr. Jarred Younger – Immune Drivers of GWI

Blood was collected for 25 consecutive days from Veterans with GWI, healthy Veteran controls, and individuals with Fibromyalgia/Chronic Fatigue Syndrome to determine if GWI involves dysregulation of the immune system. It was found that the proinflammatory cytokines IL-1 β and IL-15 were elevated on days when GWI symptoms were most severe. The preliminary results suggest that GWI symptoms such as pain and fatigue may be driven by fluctuations in inflammatory cytokines.

Dr. Mohamed About Donia and Dr. Kimberly Sullivan – Autoantibody Serum and Cerebrospinal Fluid Biomarkers

Exposure to Gulf War-relevant toxicants may have contributed to a breakdown of the blood brain barrier leading to leakage of neuronal and glial proteins into the blood. Drs. About Donia and Sullivan hypothesized that autoantibodies are generated in response to these proteins and the antibodies can be used as a biomarker for nervous system injury. This team found that autoantibodies against eight neuronal- and glial-specific proteins could be detected in serum, suggesting the presence of neuronal injury and glial activation in Veterans with GWI. An ongoing clinical study is attempting to replicate these findings in a larger cohort compared with both healthy and symptomatic control groups (CFS, IBS).

Dr. Lisa Pierce – miRNA and Epigenetic Biomarkers

Dr. Pierce determined that exposure to Gulf War-relevant toxic chemicals (DEET, permethrin, pyridostigmine) and mild stress leads to chronic alterations in epigenetic mechanisms (miRNA expression and global DNA methylation/hydroxymethylation) in the hippocampus and other brain regions in rat models of GWI. Findings from this study identified a unique signature in the miR-124-BDNF-CREB pathway previously shown by other groups to be correlated with human cognitive agility. Inhibition of miR-124 is currently being investigated under a follow-on GWIRP award to Dr. Pierce.



For more information, visit
<http://cdmrp.army.mil>

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