Gulf War Illness Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

U.S. Army Medical Research and Development Command

Congressionally Directed Medical Research Programs

The Congressionally Directed Medical Research Programs (CDMRP) were 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. Since then, the CDMRP has grown to encompass over 30 targeted programs and has been responsible for managing over $15 billion since its inception through fiscal year 2020 (FY20).

Application Review Process

The CDMRP uses a two-tier review process for evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first evaluation tier is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to award mechanism intent, relevance to program goals, and portfolio composition.

Gulf War Illness

VISION
Improved 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 of disease

What is Gulf War Illness?

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 Veterans of the 1990–1991 Gulf War.

About the Program

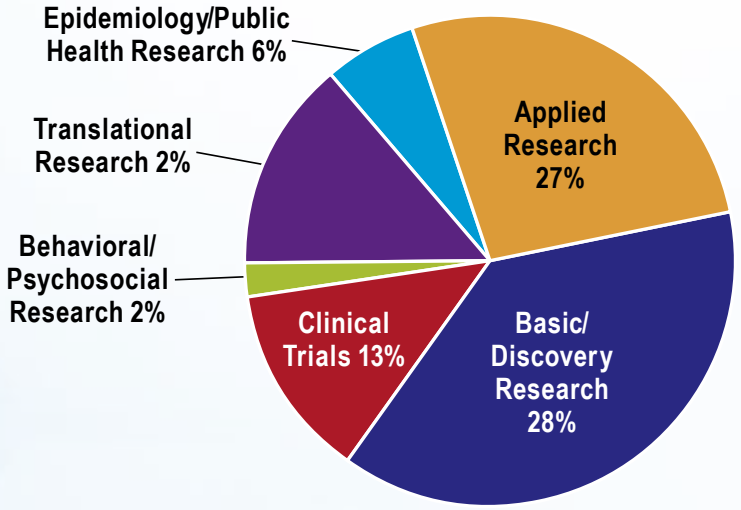
Department of Defense-funded GWI research began in 1994 with the establishment of the Gulf War Veterans' Illnesses Research Program (GWVIRP). From FY94 to FY05, the GWVIRP was managed by the U.S. Army Medical Research and Materiel Command's (now the U.S. Army Medical Research and Development Command [USAMRDC]) 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 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, which was renamed the Gulf War Illness Research Program (GWIRP), to be managed fully by the CDMRP. Since that time, the Peer-Reviewed GWIRP has been funded by an $8M appropriation each year from FY09 through FY11, $10M in FY12, $20M per year from FY13 through FY17, and $22M per year from FY18 through FY20. 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.

Research Program

GWIRP Funded Portfolio

The GWIRP portfolio includes over 200 research projects spanning investigations of basic pathobiology of GWI to trials of pharmaceuticals and other therapies. This pie chart shows the distribution of funding addressing different phases and areas of research.



The GWI Landscape

The GWIRP publishes a resource* describing what is currently known about GWI for the research, care provider, and Veteran communities.

Key Research Topics in the GWI Landscape

GWI Primary Features and Prevalence

- Symptoms of GWI
- Prevalence

Pathobiology of GWI

- Preclinical Investigations
- Clinical Investigations
- Case Definitions
- Imaging Studies
- Neurocognitive Findings
- Autonomic and Neuroendocrine Systems
- Neuroimmune Response
- Mitochondrial Dysfunction

Treatments

- Alternative or Mind-Body Interventions
- Anti-Inflammatory/ Immune Effector Therapies
- Central Nervous System (CNS) Stimulants or Depressants
- Physical Central Nervous System or Neural Stimulation
- Targeting the Gut-Brain Axis
- Targeting Mitochondria and Reactive Oxygen Species

GWIRP Overarching Challenges

Considering the current GWI Landscape, each application must address at least one of the following overarching challenges:

Treatments: Eliminate the health consequences associated with GWI and revolutionize treatment

Diagnosis: Better define and diagnose GWI

Subtyping: Distinguish symptom clusters to better target treatments, identify underlying causes, and elucidate differences in severity

Determinants: Validate exposures associated with GWI and impacts on organs and systems

Consequences: Determine whether GWI is associated with greater risk for developing other disease states including neurological diseases, cancers, or other life-threatening and severely debilitating conditions

Communication: Help Veterans, their caregivers, researchers and health care providers communicate effectively about GWI, its symptoms, and potential treatments

**The GWIRP landscape document is available at https://cdmrp.army.mil/gwirp/pdfs/GWIRP_Landscape_2020.pdf.*

Strategic Partnerships

Scientists and consumers working together to improve the health and lives of Veterans who have Gulf War Illness.

"The Veterans with GWI who served our country deserve answers and treatments that only research can provide. I'm honored to be a part of the GWIRP and to help to identify research that will make a difference in their lives."

***Dr. Vicky Whittmore**, GWIRP Programmatic Panel Chair; National Institute of Neurological Disorders and Stroke*

"I'm grateful for the members of Congress that have stood by Gulf War Veterans, support which has never wavered. I'm grateful for the leadership within the Department of Defense that helps to make this program happen and helps to ensure that this program is indeed finding and funding the best research aimed at finding treatments and cures for Gulf War Illness."

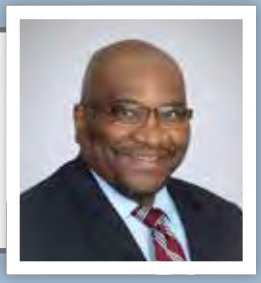
***Mr. Anthony Hardie**, GWIRP Programmatic Panel member, Programmatic Panel Chair Emeritus and Consumer; Veterans for Common Sense*

"As the world changes with the recent pandemic, it is more evident the importance of research. Being an advocate and consumer reviewer for Veterans who suffer from GWI as part of the CDMRP team has helped open many doors and answer questions for me and other Veterans. There is a real sense of satisfaction while sitting among some of the top research doctors in the U.S. during the review meeting and knowing they are listening to every word you have to say – where your opinion matters. The best part is that the Veteran voices are being heard and not just falling to the wayside."

***Mr. William "Bill" Watts**, Consumer Peer Reviewer*

"Although I have participated in GWIRP for only 2 years as a consumer reviewer, at the conclusion of each session I've always come away more optimistic about the research being done to help Veterans. I think it's great the insight and opinions of Veterans are a critical part of the process."

***Mr. Errol Manor**, Consumer Peer Reviewer*



"GWIRP has given me the opportunity to engage in research. I also have the privilege to serve as the Chair of the External Advisory Board of the Gulf War Illness Consortium (GWIC). This consortium is working on clinical trials to test potential therapeutics for Gulf War Illness. The GWIRP has not only worked towards improving the health and lives of Gulf War Veterans, but has also supported many researchers to explore their innovative ideas and advance their career, including myself. I salute the Gulf War Veterans and all the people who work for the GWIRP."

***Dr. Ashok Tuteja**, Scientific Peer Reviewer and External Advisory Board Member*

Research Award Mechanism Strategy

The GWIRP invests in different phases of research by offering different types of research awards:

Idea Award

- Innovative biomarker or treatment research
- Earliest stages of development
- High-risk/high-reward
- No preliminary data required

Research Advancement Award

- Preclinical expansion, replication, or comparative studies to validate preliminary or published data in GWI field
- Preliminary data required

Clinical Evaluation Award

- Proof-of concept clinical translation of validated GWI findings
- Large-scale biomarker research or early Phase I/IIa intervention clinical trials
- Strong preliminary data required

Therapeutic/Biomarker Trial Award

- Large-scale confirmatory and pivotal clinical trials to revolutionize GWI clinical care
- Sufficiently powered Phase IIb/III clinical trials
- Objective biomarkers of effectiveness required

Patient-Provider Health and Communications Award

- Development of tools/strategies to effectively communicate GWI research and clinical recommendations
- Goal: informing and raising awareness of current GWI research evidence base and evidence-based treatment strategies
- Requires Gulf War Veteran (with GWI) involvement

GWIRP New Investigator Award

- Supports investigators new to the field of GWI research at different stages of career development:
  - Transitioning Postdoctoral Fellow
  - Early-Career Investigator
  - New GWI Researcher
- Enables competing for funding separately from investigators with established programs of GWI research
- Must address at least one Overarching Challenge
- Strongly encouraged to collaborate with GWI-experienced investigator

The GWIRP has a special interest in the exploration of the following topics:

- Innovative treatments for GWI
- Causes and treatment strategies for:
  - Chronic widespread pain or fatigue
  - Cognitive/mentation difficulties
  - Sleep issues
  - Dermatological issues
  - Neurological dysfunction
  - Immune system dysfunction
  - Hormonal dysfunction
  - Gastrointestinal disorders
  - Sinus and respiratory problems
  - Headaches
  - Microbiome variants
  - Excretory liver/kidney abnormalities
- The impact of stresses on the severity and duration of the symptoms
- Disordered regulatory system crosstalk
- Identification of molecular signatures underlying symptoms
- Comorbidities, mortality, and sex or ethnic differences

GWIRP Treatment Accomplishments

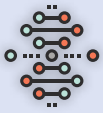
The primary focus of the GWIRP has always been to speed the development of effective treatments for Veterans with GWI. The program has built a broad research portfolio of awards featuring clinical trials as well as mechanistic research and studies addressing GWI symptomatology to inform treatment development. The GWIRP is currently funding numerous pilot clinical trials of investigative treatments. The results of several successful trials in Veterans are listed below. A full list of clinical trials can be viewed at **https://cdmrp.army.mil/gwirp/clinical_trials/GWIRPsct**.

Coenzyme Q10 Pilot Study	Found to reduce pain, fatigue, and cognitive symptoms in Veterans with GWI. The Department of Veterans Affairs (VA) is currently funding a Phase III study using ubiquinol, the reduced form of coenzyme CoQ10.
Carnosine Pilot Study	Found to reduce cognitive symptoms in Veterans with GWI, but not to impact their pain, fatigue, or other outcomes.
Acupuncture Pilot Study	Shown to improve GWI symptoms of pain, fatigue, sleep quality, and cognitive symptoms. In addition, Veterans were very comfortable with the treatment experience and acupuncturists.
Mind-Body Bridging Pilot Study	Shown to be an effective intervention in the management of disturbed sleep in Veterans with GWI.
Botanical Microglia-Modulating Agents Screening Study	Of nine botanical agents tested, four had a significant impact on GWI symptoms over baseline and placebo conditions. These agents were: resveratrol, stinging nettle, pycnogenol, and CurcumaSorb.
Methylphenidate Plus A GWI-Specific Nutrient Cocktail Pilot Study	This combination treatment had a significant reduction in overall symptom severity, as well as improved concentration disturbance symptoms, fatigue, sleep, and pain. There was also a significant reduction in serum lipid peroxide levels.
Neuronavigation-Guided repetitive Transcranial Magnetic Stimulation (rTMS) Pilot Trial	Treatment resulted in significant improvements in muscle pain as well as in concentration and fatigue. Improvements in headache and joint pain also trended toward significance. This pilot provided the foundation to design and conduct larger-scale, multi-center treatment trials of rTMS.

GWIRP-Supported Research Resources

Promoting the sharing of scientific research is critical for increasing the efficiency and effectiveness GWI research. The GWIRP established a listing of "Researcher Resources" where scientific tools, data collections and findings generated by GWIRP-funded researchers are available to the community. The GWIRP Research Resources include the following:

ANIMAL MODELS: Descriptions of experimental animals that mimic important aspects of GWI in humans and protocols for producing them in the laboratory.



MULTI-OMICS DATA SETS: Sets of data describing such features as gene sequences, protein expression, metabolic and hormonal activity, physiological and neuropsychological measurements, and other data in cohorts of ill Veterans.

COHORTS: Descriptions and contact information for past human studies involving substantial cohorts of ill and healthy Veterans. Depending on privacy restrictions, future researchers may be able to re-contact past participants to recruit them for future clinical research.

BIOMARKERS: Biochemical and physiological tests that have been used in studies to measure the extent of certain symptoms or other effects of GWI in ill Veterans.

COMMON DATA ELEMENTS: Common Data Elements (CDEs) for GWI that can be used to describe specimens or data related to GWI clinical research. A first draft of the CDEs were published in January 2019, and work to refine them and incorporate researcher suggestions is ongoing.

RECRUITMENT GUIDANCE: Information about Gulf War Veteran subject recruitment for GWI biomedical research to establish an effective and sustainable outreach and recruitment plan.

CLINICAL TRIALS: Summaries of all funded clinical interventions, both ongoing and closed, are available for the GWI community and have been classified into the following categories:

- Drug Interventions
- Nutraceuticals and Probiotic Interventions
- Complementary and Alternative Medicine
- Central Nervous System (CNS) Stimulation

**GWIRP researcher resources are available at https://cdmrp.army.mil/gwirp/resources/gwirpresources.*

Gulf War Illness Clinical Trial and In

Consortium Trials

Etanercept plus Mifepristone Phase Ib: Good safety, but only moderate efficacy, were achieved in a previous Phase I trial. This study will explore dosing at a higher level for an extended time.

Etanercept plus Mifepristone Phase II Expansion: This trial will employ a more robust, placebo-controlled design using the best dosing protocol inferred from previous studies. The number of endpoints measured will be increased in an expanded subject pool.

Bacopa monnieri Phase II: A "tele-trial" of this well-known Ayurvedic dietary supplement will use web and telecommunication technology for a nationwide, virtual, placebo-controlled trial of Bacopa with subjects participating in their homes to improve cognitive function. Researchers will assess cognition, physical function, sleep, pain, other symptoms, and overall quality of life.

Physical Health Function and Oxidative Stress After Antioxidant Treatment in GWI: This phase II study will test whether NAC promotes central nervous system recovery from chronic oxidative stress and depletion of antioxidants in GWI participants.

Entercept followed by Mifepristone: The concept of a "one-two punch" using Entercept and Mifepristone was developed by the GWICTIC team using detailed computer models of the human immune and hormonal systems. In GWI, these systems are "over-primed," resulting in an exacerbated neuro-inflammatory response to everyday physical and immune challenges. The computer modeling suggested that blockade of the glucocorticoid receptor using Mifepristone could reset system readiness to a normal state, but only if the immune system is "quieted" by prior treatment targeting immune mechanisms governed by Tumor Necrosis Factor-alpha using Entercept. This one-two combination will only work if the treatments are given sequentially.

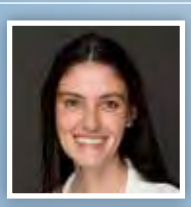
*For more details see, https://www.nova.edu/nim/GWICTIC/index.html.

GWICTIC Team



Center Directors:

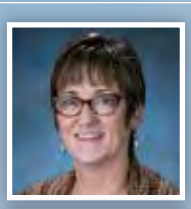
- Nancy Klimas, M.D., Principal Investigator (PI), Director of the Operations Center
- Rebecca McNeil, Ph.D., Co-PI, Director for Study Management and Biostatics Core
- Amanpreet Cheema, Ph.D., Director of Research Operations, Administrative Director



Facility Directors:

- Kimberly Sullivan, Ph.D., Neuroscience Core
- Kristina Aenlle, Ph.D., Biomarker Core
- Maria Abreu, Ph.D., Biomarker Core
- Travis Craddock, Ph.D., Computational Modeling Core
- Gordon Broderick, Ph.D., Computational Modeling Core
- Rebecca McNeil, Ph.D., Study Management and Biostatics Core

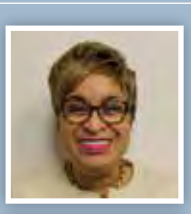





Research Site Directors:

- Drew Helmer, M.D., Michael E. DeBakey VA Medical Center, Houston
- Alison Bested, M.D., South FL
- Kimberly Sullivan, Ph.D., Boston University
- Wes Ashford, M.D., Ph.D., Palo Alto War-Related Illness and Injury Study Center
- Dikoma Shungu, Ph.D., Weill Cornell Medical College
- Helena Chandler, Ph.D., WRIISC, East Orange NJ






Patient Advocate Representatives:

- Mr. Jimmy Arocho, USA, SFC, Retired
- Ms. Denise Nichols, RN, USAF, MAJ, Retired
- Ms. Marylyn Harris, Advanced Registered Nurse Practitioner, USA, Veteran
- Mr. Todd Anthony Langeland, USMC and USA, Veteran
- Mr. Harvey L. Marshall, Jr., USA, Veteran

Administrative Staff:

- Ms. Zena Kirby, Program Manager

Boston Biorepository, Recruitment, a

BBRAIN
Boston Biorepository, Recruitment and Integrated Network for GWI

Resource Site 1
Boston University School of Public Health*

Resource Site 4
San Francisco VA

NETWORK COORDINATING CENTER

Resource Site 2
Miami VA/NOVA Southeastern University*

Resource Site 3
Bronx VA

** Resource Site and Biorepositry Storage Site*

BBRAIN ORGANIZATIONAL STRUCTURE

Steering Committee

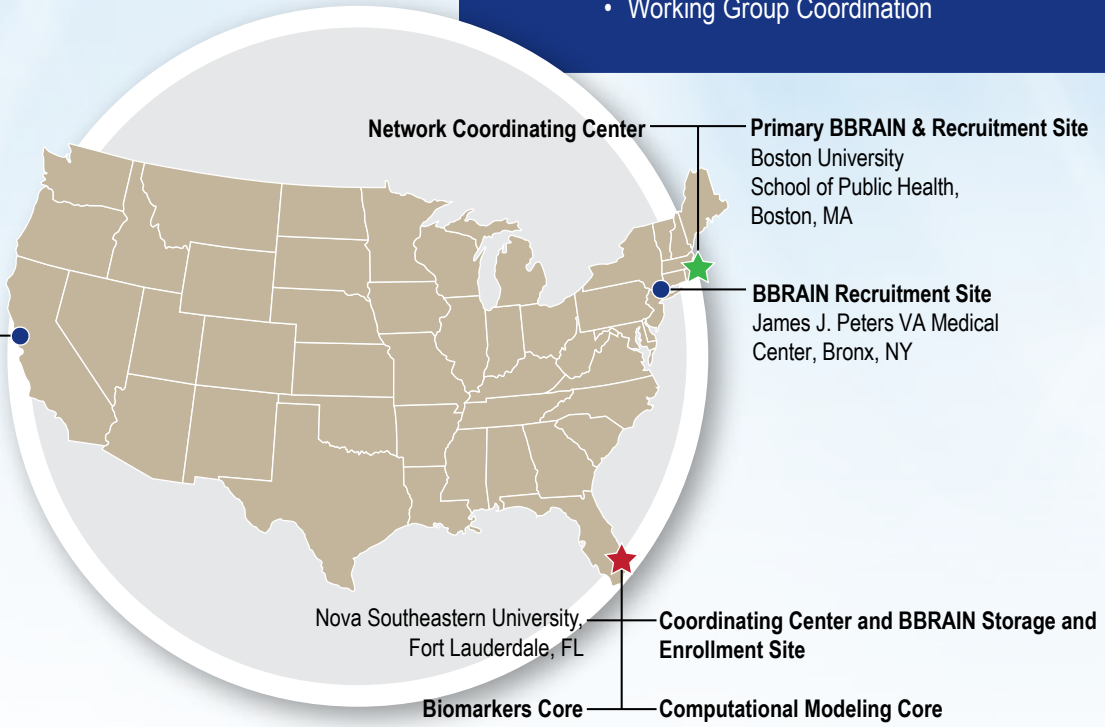
BBRAIN PI, RS, PIs, GWI Advocates

Retrospective Resource Sites

Network Coordinating Center

Network Coordinating Center Tasks

- Institutional Review Board Protocol/ Regulatory Coordination
- Biospecimen Collection, Tracking and Dissemination
- Data Management/Monitoring
- Statistical Management
- Resource Site Performance Evaluation
- Working Group Coordination



**For more details, see http://sites.bu.edu/bbrain/.*

nd Integrated Network for GWI

The BBRAIN is a biorepository network for human GWI research that supports mining of existing BBRAIN contributor specimens and data. It provides centralized holding and cataloguing and coordination of retrospective and prospective biological samples, specimens, and substances related to human GWI research studies contributed by collaborating institutions, along with corresponding cognitive outcomes, brain imaging, demographics, and health symptom surveys. Using the resources of the BBRAIN, researchers can compare biomarkers with medical features of GWI and study outcomes. Features include the use of a common data platform and searchable websites with information about obtaining samples/data for collaborative studies.

BBRAIN Team








Boston (Boston University Medical Center):

- Kimberly Sullivan, Ph.D., BBRAIN PI
- Timothy Heeren, Ph.D., Senior Biostatistician and Statistical Core Director
- Ronald Killiany, Ph.D., Imaging Core Director
- Patricia Janulewicz Lloyd, Ph.D., GWIC Study Coordinator and a Co-investigator
- Maxine Krengel, Ph.D., Neurobehavioral Core Director.
- Rosemary Toomey, Ph.D., Co-investigator (neurobehavioral expert)
- Bang-Bon Koo, Ph.D., Assistant Professor
- Joy Ajama, Research Assistant



Miami (Miami VA Medical Center):

- Nancy Klimas, M.D., PI of the Miami site and Laboratory Director
- Maria Abreu, Ph.D., Co-investigator
- Regla Saldana, Study Coordinator


New York (Bronx VA Medical Center)

- Julia Golier, M.D., PI of the New York site
- Danielle DiGirolamo, Study Coordinator


San Francisco
(San Francisco VA Medical Center):

- Linda Chao, Ph.D., PI of the San Francisco site
- Steven Martinez, Study Coordinator

GWIRP Research Highlights

Veterans with Gulf War Illness: Understanding the Spectrum of Experiences Related to Aging and Demographics

Girija Kaimal, Ed.D., M.A., ATR-BC, Drexel University;
Rebekka Dieterich-Hartwell, Ph.D., BC-DMT, LPC, Drexel University; and
Bryann DeBeer, Ph.D., Texas A&M University

Despite nearly three decades since the Gulf War, GWI's pathophysiology remains poorly understood, leaving patients and health care providers with little to no guidance on appropriate diagnosis measures, treatment options, and care opportunities. To address this gap, Dr. Girija Kaimal received a GWIRP-funded FY17 Qualitative Research Award to conduct a grounded theory study of Veterans and healthcare providers over 2 years to examine the individual perspectives and understand the overall impact of the illness. This information will be used to construct effective strategies for communicating information on symptoms and treatments to Veterans and health care givers.

Since its initiation, this study has focused on documenting the unique experiences and perceptions of individuals regarding their physical health, cognitive functioning, quality of life, or quality of care received. Preliminary findings suggest a marked knowledge gap in understanding the relationship between toxic exposures and the resulting symptoms and struggles affecting this Veteran population. As the study progresses, the data collected will undergo a series of coding and analysis to identify recurring patterns and themes to create a grounded theory framework. Dr. Kaimal and a team of subject matter experts will utilize the framework, narrative experiences, and visual representations to prepare a curriculum for a Massive Open Online Course, providing a resource to educate healthcare providers on the definition and symptoms of GWI and detail the prevalence and incidence of the disease.

Alleviating Headache and Pain in GWI and Neuronavigation-Guided rTMS

Albert Leung, M.D., Veterans Medical Research Foundation of San Diego

Headache and pain are some of the most common debilitating symptoms in Veterans with GWI. Conventional pharmacological treatments for these symptoms have proven ineffective and often result in a number of negative side effects. Previous research has shown that non-invasive brain stimulation such as rTMS can ameliorate the symptoms of a number of chronic pain conditions and headaches when applied to specific regions of the brain. With funding from an FY15 GWIRP Innovative Treatment Evaluation Award, Dr. Albert Leung conducted a pilot randomized, controlled clinical trial to validate case reviews from a small group of Gulf War Veterans that suggested improvements in headache following treatment with rTMS.

The study examined 40 Gulf War Veterans with GWI and 20 healthy Gulf War Veteran controls from the VA San Diego Healthcare System and Naval Medical Center San Diego who were given four rTMS or sham treatments over a period of 1 week and were assessed during treatment and at 1, 4, and 8 weeks post-treatment. A comparison of the Gulf War Veterans who received rTMS to those in the sham group demonstrated that rTMS treatment resulted in significant improvements in muscle pain, concentration, and fatigue.

Dr. Leung received funding from the VA Clinical Science Research and Development for a larger-scale, multi-center treatment trial in FY18. In addition, he also received funding from a GWIRP Clinical Trial Award for a complementary multi-center, two-arm clinical trial to address a sub-population, meeting the GWI diagnostic headache and pain criteria, but with different comorbid symptom severities than those addressed in the VA trial.

Prevalence and Patterns of Symptoms Among Female Gulf War Veterans

Steve Coughlin, Ph.D., M.P.H., Augusta University;
Kimberly Sullivan, Ph.D., Boston University School of Public Health

Women comprised 7% of the military personnel who served in the 1990–1991 Gulf War. In 2015–2016, the VA Cooperative Studies Program conducted the Gulf War Era Cohort and Biorepository (GWECB) study, which tallied questionnaire responses from 1,318 Gulf War-deployed and -era Veterans concerning their health status and symptoms. Dr. Steven Coughlin at Augusta University and a team of GWI researchers, including Dr. Kimberly Sullivan at Boston University, are using an FY15 GWIRP Gulf War Illness Epidemiology Research Award to take a deeper look at the results of this survey as they relate to female Veterans' health issues. They hypothesized that symptoms associated with the diagnostic pattern of GWI would be higher in female Gulf War Veterans.

The results indicate that women Veterans who were deployed to the Gulf War continued to report a variety of symptoms at a higher frequency than female Veterans of the same era who were not deployed to the Gulf. The diminished quality of life associated with high symptom burden reported in this study is likely to account for at least some of the psychiatric symptoms such as depression and anxiety. Despite limitations and potential distortions associated with elective participation, symptom self-reporting, and no stratification for toxic exposures during deployment, these findings contribute to the knowledge base to develop biological markers of GWI and effective treatments for this condition that may be gender-specific.

Tau Pathology as a Contributor to Gulf War Illness and a Basis for Potential Therapy

Liang Qiang, Ph.D., Drexel University and Boston University

Dr. Liang Qiang recognized the need for effective therapies to treat GWI and, with the support of an FY16 GWIRP New Investigator Award, led a multicenter study to elucidate mechanisms by which neurotoxins could cause cognitive deficits among Veterans suffering from GWI. Hyper-phosphorylation of Tau, one of the most abundant microtubule (MT)-associated proteins in neurons, causes it to dissociate from the MT lattice, rendering MTs unstable and unable to support the transport of organelles including mitochondria. The study used a repository of human-induced pluripotent cells (hiPSCs) derived from Gulf War Veterans to investigate how Diisopropylfluorophosphate (DFP), a sarin surrogate, might cause Tau pathology. Preliminary studies indicated that DFP significantly upregulated Tau expression and induced early Tau phosphorylation in cortical glutamatergic neuronal cultures derived from hiPSCs. The team conducted additional molecular analyses to characterize the effects of neurotoxin exposure in GWI by using a regimen combining the stress hormone cortisol with DFP. Synaptic transmission recordings exhibited increased activity in neurons derived from Veterans with GWI compared to those derived from Veterans without GWI. Preliminary findings reported pronounced activation of neuroinflammation, which is posited as one of the main drivers of GWI.

This project is the first to utilize the biobank of hiPSCs that have been developed from Gulf War Veterans and is leading the way among proof-of-principle studies to reveal the capabilities of hiPSC 2D and 3D models in the GWI research community.

GWIRP Research Highlights

Gulf War Illness and Inflammation: Association of Symptom Severity with C-Reactive Protein

Apostolos P. Georgopoulos, M.D., Ph.D., Brain Sciences Center, Minneapolis VA Health Care System

Despite years of research, GWI etiology remains unclear, but evidence suggests that many GWI symptoms are linked to immune-related inflammation. With support from an FY14 Investigator-Initiated Research Award, Dr. Georgopoulos is studying the abnormal features of the immune system in Veterans with GWI. Dr. Georgopoulos and his team examined levels of a molecule called C-reactive protein (CRP) in the blood of Veterans with GWI.[1] CRP is mainly produced in the liver, and elevated levels in blood accompany any sort of inflammation ranging from an ankle sprain to cancer. Dr. Georgopoulos' team recruited Veterans with GWI but no comorbidities. They measured CRP levels and body mass index and then administered a self-report checklist to evaluate the presence and severity of symptoms across six domains characteristic of GWI as well as drug and alcohol use. They found that elevated CRP levels were associated with elevated symptom severity in all domains, especially pain, fatigue, and mood/ cognition. This evidence further implicates inflammation in GWI symptomatology, adding credence to the persistent antigen hypothesis, which states that genetic variations in immune systems make large fractions of the population susceptible to chronic inflammatory irritation by antigens that their immune systems are unable to process and destroy. Dr. Georgopoulos' results may support this theory of GWI etiology, which, if true, would mean that therapies based on identifying and clearing persistent antigens should reduce the symptoms of GWI.

[1] *James LM, Engdahl BE, Johnson RA, and Georgopoulos AP. 2019. Gulf War Illness and Inflammation: Association of Symptom Severity. J Neurol Neuromed 4(2):15-19.*

A Preliminary Report on the Gut Microbiome in Gulf War Veterans

Saurabh Chatterjee M.Sc., Ph.D., University of South Carolina

Gastrointestinal (GI) disturbances are a frequently reported symptom of GWI, suggesting an imbalance in the gut microbiome. Moreover, immune/neuroinflammatory dysfunction is now a recognized hallmark of GWI, and the gut microbiome is thought to be intimately tied to the state of the immune/ neuroimmune system, further implicating its involvement in GWI. With support from a GWIRP Investigator-Initiated Focused Research Award, Dr. Chatterjee collaborated with a team from the GWIRP-supported Boston University Gulf War Illness Consortium to study gut microbiome dysbiosis in Veterans with GWI. This first-of-its-kind study in Veterans was inspired by observations of gut microbiome dysbiosis in animal models of GWI. The team recently reported preliminary results from the analysis of fecal samples from Veterans.[2] They found that, compared to controls, both groups of Veterans with GWI had a reduced abundance of microbes from the phylum Firmicutes, the family Lachnospiraceae, and the genuses Dailister and Roseburia. GFW+GI Veterans had higher abundances of the phyla bacteroidetes, actinobacteria, euryarchaeota, and proteobacteria and the families Bacteroidaceae, Erysipelotrichaceae, and Bifidobacteriaceae than either controls or the GWI-GI group. In biome research, similar differences have been observed in inflammatory bowel diseases and Roseburi specifically (reduced in both GWI groups) is known to help digest complex carbohydrates and generate butyric acid, effects that play several beneficial roles in the GI tract. In incidental findings, the team found higher levels of the pro-inflammatory molecule TNF-R1 in the blood of both GWI groups. Such findings can lead to novel treatments and diagnostic markers for GWI, and the team expects to discover more interesting findings as the study progresses.

[2] *Janulewicz PA, Seth RK, Carlson JM, et al. 2019. The Gut-Microbiome in Gulf War Veterans: A Preliminary Report. Int J Environ Res Public Health 16:3751.*

Molecular Mechanisms for Mood-Altering Effects of Ketamine in a DFP-Based Rat Model for Gulf War Illness-Related Depression

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The etiology of GWI is multi-factorial, and exposure to organophosphates (OP) during deployment is one of the factors underlying GWI development. Gulf War Veterans suffer from a cluster of symptoms, including mood-related conditions, and treating GWI symptoms with existing therapies is challenging. With support from an FY16 Investigator-Initiated Focused Research Award - Tier 1 - Discovery, in a series of two papers, Dr. Deshpande's research team investigated ketamine (KET), a drug that initiates a rapid and sustained antidepressant response, as an effective treatment for GWI-related depression. Dr. Deshpande observed that rats exposed to a repeated low-dose of diisopropyl fluorophosphates (DFP), a compound that mimics Gulf War OP exposure, expressed chronic depressive characteristics during behavioral assessment and decreased Brain-Derived Neurotrophic Factor (BDNF) levels within the hippocampus. In agreement with Dr. Deshpande's previous findings, calcium levels were elevated in hippocampal neurons of DFP-exposed rats. Interestingly, rats treated with KET 3-months post-DFP exposure exhibited antidepressive characteristics during behavioral assessment 1-hour post-KET treatment. These antidepressive characteristics persisted for 24 hours post-KET treatment, suggesting activation of mechanisms involved in long-term synaptic plasticity. BDNF expression levels were also significantly increased 24 hours post-KET treatment. Conversely, hippocampal calcium levels in DFP-exposed mice were significantly lower 1-hour post-KET treatment, but not 24 hours post-KET. These findings suggest that KET-induced inhibition of hippocampal calcium triggers rapid onset of antidepressive behavior while persistent antidepressive actions are modulated by BDNF expression. Dr. Deshpande's research provides a starting point for further assessment of KET for GWI-related depression.

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