State of the Science GWI: Moving Knowledge to Treatment



NANCY KLIMAS, MD NOVA SOUTHEASTERN UNIVERSITY MIAMI VA MEDICAL CENTER

AND KIM SULLIVAN, PHD BOSTON UNIVERSITY

We Welcome You! Institute for Neuro-Immune Medicine



Mission: "Advance knowledge and care for people with complex neuro-inflammatory illnesses through <u>the integration of research</u>, <u>clinical care and education</u>"



NSU Florida

NOVA SOUTHEASTER

2

The INIM Team

INIM Administration

Dr. Nancy Klimas– Director Ana Del Alamo, MS– Administrative Director Amanpreet Cheema, Ph.D Charles Ramos Nilda Hernandez David Freeman Beth Gilbert, MS Kelly Hilton, Chris Larrimore – Blue Ribbon Research Fellows Coveannda Sumpter

<u>Clinical Systems Biology</u>

Travis Craddock – Director Gordon Broderick (Rochester Health) Mary Jeffrey Rajeev Jaundoo Ricardo Castellanos Tory Toole Francisco Carerra Jacob Hardy Victoria Wyma Jaylen Garcia

Discovery/Diagnostics Lab

Mary Ann Fletcher – Director Lubov Nathanson ,PhD Kristina Aenlle, PhD Maria Abreu, PhD Malay Trivedi, PhD Xiao Rong Zeng, PhD Paula Waziry , PhD Lissette Pierlus Howard Lin Kristy Pinkham Claudia Vizcarra Sandra Yudice Jared Urban Bisha Chen Kristy Pinkham **Michelot Michel** David Freeman

Animal Models and Cardiovascular Research

Mariana Morris, Ph.D. -Director Amanpreet Cheema, Ph.D. Luis Salgueiro Tosta, PhD Rodrigo Schmidt, PhD

NSU and VA Clinical Care and Clinical Research

Alison Bested MD Medical Director Irma Rey MD Maria Vera MD Violetta Renesca. ARNP Irina Rozenfeld, ARNP Nancy Klimas, MD Renan Fernandez Rafael Iglesias Stephen Jaqua Moumita Bishayee,

Amanpreet Cheema, Ph.D. Elizabeth Balbin MA Devra Cohen MPH Precious Leaks-Gutierrez , MBA Jeffry Cournoyer, ATC Fanny Collado RN Lisa Hue, RN Katherine Llosa, RN Jimmy Arocho Shuntae Parnell Zach Barnes Zena Kirby, MA







Boston GWIC and BBRAIN





INIM

4

In this session

- •What is GWI
- What do we know about the cause?
- What research is going on with our group at the Institute for Neuro Immune Medicine, with the GWIC/BBRAIN group from Boston University and nationally?
- How do we move faster, learn more and move it on to clinical trials and accessible treatment?

GWI: Definition, Cause and Diagnosis

- Gulf War Illness (GWI) is a chronic, multi-symptom disorder, that has impacted ~245,000 Veterans who served in the 1990-1991 GW
- Putative cause: Toxic exposures, including nerve agents, pyridostigmine bromide, smoke from oil well fires, pesticides, depleted uranium, and exposure to solvents and corrosive liquids
- **Diagnosis and Disease Presentation:** Veterans deployed to the Persian Gulf between August 8, 1990 through July 31, 1991
 - Most commonly diagnosed by symptom presentation
 - The condition affects multiple organ systems, and as a result patients typically present with fatigue, headaches, joint and muscle pain, gastrointestinal and sleep disturbances, neurologic and neuropsychological symptoms, respiratory issues, and cardiovascular problems

What do we know about the cause?

- Retrospective studies and animal studies explore the potential triggers of the long term illness.
- Toxicants, particularly neurotoxicants seem to play a key role, and pesticide and organophosphate (sarin) animal models are used to study the illness.
- Risk and vulnerability are also explored with studies of genetics, detoxification function, and immune function.
- Illness persistence is the main focus of research what do we know about the illness now, nearly 30 years after its onset?
- Most of the VA and CDMRP research portfolios focus in this area with a goal of discovering targetable areas for treatment, 37 trials listed on clinicaltrials.gov

Inflammation – Brain and Body

Systemic inflammation has been demonstrated in multiple studies, with inflammatory cytokines, activated complement, immune activation. (Reviewed by White et al 2016)

Neuroimaging studies and spinal fluid studies also demonstrate markers of inflammation in the brain (Zeynab Alshelh et al 2020, Jim Baraniuk 2017)



Lubov Nathanson, PhD

Assistant Professor. College of Osteopathic Medicine, Nova Southeastern University

Voluntary Assistant Professor, Dept. of Medicine, University of Miami Miller School of Medicine, Miami, FL

Immuno modulation in GWI (331522)

- Sponsor Georgetown University
- **PI** J Baraniuk
- Collaborator Nathanson
- Status Recruiting
- The goal of this project is to determine changes in the transcriptional regulation in each of the four subtypes of immune cells (helper T cells, cytotoxic T cells, B cells and NK cells) caused by GWI and identify the role of cell-cell communication in pathobiology of GWI. Our studies will reveal potential therapeutic targets of GWI and provide insight into cell-specific disease onset and progression, with the goal of developing better diagnostics tools and therapeutic interventions.

Institute for Neuro-Immune Medicine NOVA SOUTHEASTERN UNIVERSITY | Florida



Oxidative stress, mitochondria, and the brain

Studies have shown depleted antioxidants in the body and in the brain (Golomb et al, Shungu personal communication, others)

In the brain oxidative stress promotes inflammation and vice versa – thus there are a dozen antioxidant based studies in various states of clinical trial. The one phase 2 that showed promise enough to move on to phase 3 is the use of CoQ10 in GWI. The antioxidant in phase 3 trial – the CoQ10 study needs your help! Sign up!

This study is recruiting and needs your help! Please consider volunteering for this study , located in Boston, Bronx, Minneapolis and Miami.

For more information, please contact us at **305-575-7648** or email VHAMIAGWI@va.gov.

If successful, this study will move the first GWI treatment forward to the VA formulary

Nancy Klimas, MD and the CoQ10 Study Group

Professor. College of Osteopathic Medicine, Nova Southeastern University

Director. Institute for Neuro-Immune Medicine

Director, Miami VA **Environmental Medicine** Program

Phase 3 placebo control study of Ubiquinol (CoQ10)

- Sponsor Veterans Administration Clinical Research Program
- PI N Klimas, National Coordinator Devra Cohen, MSW
- Collaborators Drs Sullivan, Endahl, Golier, Krengel, Fletcher, Abreu, Aenlle, Deth, Trivedi
- Status Recruiting
- The goal of this project is to prove whether or not CoQ 10 in its most bioactive form, ubiquinol, is an effective treatment of Gulf War Illness





Treating oxidative stress

There are additional antioxidants in phase 2 studies – look at clinicaltrials.gov to look for one in your area.

In South Florida we are also evaluating Glutathione and Curcumin, and will soon initiate a study using Bacopa, which reduces inflammation and quiets oxidative stress in the brain.

The Roskamp Institute in Sarasota is initiating their study "A Randomized, Double-Blind, Placebo-controlled Clinical Trial of Oleoylethanolamide for Targeting Lipid Metabolism in Gulf War Illness" which would impact mitochondrial function. Dr Laila Abdullah leads this research team.

Nationally you will find additional antioxidant trials in Palo Alto California, Waco Texas, and Birmingham Alabama

For more information, please contact us at **305-575-7648** or email VHAMIAGWI@va.gov.

Nancy Klimas, MD

Professor, College of Osteopathic Medicine, Nova Southeastern University

Director, Institute for NeuroImmune Medicine

Director, Miami VA Environmental Medicine Program

Phase 2 placebo control study of liposomal glutathione or curcumin in GWI

Sponsor CDMRP

- PI N Klimas, and the VA Research Team (Fanny Collado, RN, coordinator)
- Collaborators Drs Fletcher, Abreu, Aenlle, Deth, Trivedi
- Status Recruiting
- The goal of this project is to prove whether or not Curcumin or liposomal glutathione is efficacious and safe in Gulf War Illness





Toxicants and detoxification in GWI

Knowing that toxicants appear to be key in the initiation of this illness, scientists are evaluating whether antioxidant pathways are as functional in GWI, as well as studies of the ability of cells to repair cellular damage in other ways.

Clinical trials that promote improved mitochondrial function and balance the energy pathways of the cells also work to improve the cell's ability to rid itself of toxicants.

Stephen Grant, PhD

Professor, College of Osteopathic Medicine, Nova Southeastern University

Persistently evaluated somatic mutation as a bio-marker or clinically relevant exposures in GWI

PI: Stephen G. Grant, PhD **Award #** W81XWH-16-1-0678

Funding Agency: U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012

- 1. Gulf War veterans were exposed to a plethora of toxic agents, including agents that damage DNA, such as smoke from oil field fires
- 2. Are there persistent effects of these exposures that might have long-term consequences on health and quality of life?
- 3. Human cells "induce" or upregulate their DNA repair capacity upon exposure to mutagens (this effect is used to identify mutagenic carcinogens); is there evidence that such a "hormetic" effect occurred in Gulf War veterans?

Institute for Neuro-Immune Medicine NOVA SOUTHEASTERN UNIVERSITY



Lymphocyte DNA repair is elevated in GWI



UNIVERSITY

50 P = 0.01* 45 40 35 30 25 20 15 10 % N = 9N = 45 0 Aged-Matched Control GWI

NER capacity as measured by the UDS assay of four veterans with Gulf War Illness (GWI) compared to nine age matched controls, including one asymptomatic serviceman. NER capacities are expressed as a proportion of concurrently analyzed human foreskin fibroblasts (FF).

from Latimer et al., (2020) Military Medicine 185: e47-e52.

Hormones, hormone regulation and GWI

The neuroendocrine balance in GWI is in a "sick" balance

Hormones that regulate energy (thyroid), stress and inflammation (adrenal), sexual function (Gonadal hormones like testosterone) have been studied individually and in the context of the brain's role in endocrine balance.

Some hormones promote cellular repair, and are the focus of preclinical trials.

Our Reboot study, in human trial, attempts to Reboot the neuroendocrine balance to normal

Luis M Salgueiro-Tosta, PhD

Assistant Professor

Research Associate

College of Osteopathic Medicine, Nova Southeastern University **Title of the project:** "Growth Hormone releasing hormone antagonist evaluation of beneficial effects for GWI."

Principal Investigator: Luis M Salgueiro-Tosta

Status: Active, collecting behavioral and genomic data and analyzing protein (biomarkers of inflammation) data.

Demonstrated that the Synthetic Growth-Hormone Release-Hormone antagonistic analog, MIA-690, has the capacity to modulate the exacerbated neuroinflammatory response present in the tissue of animals exposed to the experimental model of GWI (CORT/DFP/LPS).

Pro-inflammatory cytokines tend to decrease as the anti-inflammatory cytokines increase towards levels favorable for the survival and function of the neural cells. Our next step is to explore the physiological significance of these changes on the cognitive performance, fatigue reduction, and social disruptive stress (anxiety) shown by the experimental animals.

> Institute for Neuro-Immune Medicine NOVA SOUTHEASTERN UNIVERSITY



Gender differences will the eventual treatments be different in men and women?

It is too often assumed that is good for men will work the same way in women, yet studies of autoimmunity, heart disease and other chronic conditions prove this to be untrue. Similarly modest genetic differences seen in ethnic groups or by gender can result in medication differences and drug toxicities.

Studies in GWI are underway to model the illness in women and in men and are resulting in different potential targetable points of treatment.

The model in men has already resulted in an exciting study, our moonshot, attempting to cure the illness. This is the Reboot study and is recruiting now.

The model in women needs additional volunteers to participate in this preclinical study, so that we can offer a treatment study as soon as possible.

For more information, please contact us at **305-575-7648** or email **VHAMIAGWI@va.gov**.

Nancy Klimas, MD

Professor. College of Osteopathic Medicine, Nova Southeastern University

Director, Institute for Neuro-Immune Medicine

Director, Miami VA **Environmental Medicine** Program

Gender and Gulf War Illness

A Modeling Study

- Sponsor Veterans Administration Clinical Research Program
- PI N Klimas
- Collaborators Drs Fletcher, Abreu, Aenlle, Nathanson, Craddock, Broderick,
- Status Recruiting
- The goal of this project is to collect data that results in a computational model of the illness, and provide new understanding of targetable treatment points. The data collected is compared to the models that have been developed for men with GWI.

Institute for Neuro-Immune Medicine NOVA SOUTHEASTERN UNIVERSITY | Florida



Lubov Nathanson, PhD

Assistant Professor, College of Osteopathic Medicine, Nova Southeastern University

Voluntary Assistant Professor, Dept. of Medicine, University of Miami Miller School of Medicine, Miami, FL

Genome approach to find female specific mechanisms of GWI pathology (331652)

- PI Nathanson
- Status Recruiting controls, Data analysis
- The goal of this research is to identify novel, female-specific, genomic characteristics of the development of GWI for a better understanding of the causes of disease. Identification of female-specific disease targets will lead to a better design of therapeutic intervention, specifically, it will greatly speed up the identification of promising female-specific biomarkers to improve diagnosis and treatment, which will consider gender differences.

Institute for Neuro-Immune Medicine NOVA SOUTHEASTERN UNIVERSITY



Marianna Morris, PhD

Professor, College of Osteopathic Medicine, Nova Southeastern University

PI, NSU GWIC

Developing a Female Mouse Model for GWI

- PI Morris
- Collaborators: Rodrigo Schmidt, INIM team
- Status Animal Studies underway
- The goal of this research is to develop a female animal model of GWI, using age appropriate animals for use in future testing of modeled treatments. The Model is also being used to better understand the cardia and autonomic mediators of the illness.

Institute for Neuro-Immune Medicine NOVA SOUTHEASTERN UNIVERSITY



Putting it all together: Homeostasis

This has been our team's moonshot vision imitated 10 years ago and the focus of our Gulf War Illness Consortium (GWIC, Morris PI)

Using human studies of men with Gulf War illness, and more recently women with Gulf War Illness studies that explore the relationship of the immune, neuroendocrine, and autonomic nervous system, and its relationship to health, illness and relapse resulted in sophisticated models of illness persistence. The models were so complete, that they could be used to predict treatment, and have resulted in a series of human clinical trials. These include the curcumin, glutathione study, the "reboot "homeostasis moon shot studies, completed in animals and now in human phase 1 study. **(currently recruiting)**

They also allowed sophisticated subgrouping models, and targeted therapies for the autoimmune subset of Gulf war illness (B cell depletion) which **currently recruiting**

For more information, please contact us at **305-575-7648** or email **VHAMIAGWI@va.gov**.

The importance of co-morbid illness: PTSD, TBI, depression

Our modeling work of Gulf War Illness is very sophisticated, and uses an exercise challenge and serial blood draws to map out the series of events that result in relapse. We measure genes that turn on and off, hormones and cytokines that are expressed, cells and their function, all in a very quick time course.

The Computational teams at INIM (Dr Travis Craddock and team) and Rochester (Dr Broderick and colleagues) have used super computing platforms and have developed virtual models able to discern subgroups and the effects of comorbid conditions of predicted treatments.

Travis Craddock, PhD

Director of Clinical Systems Biology, Institute for Neuro-Immune Medicine, Nova Southeastern University

Associate Professor, Department of Psychology and Neuroscience, Computer Science, and Clinical Immunology, Nova Southeastern University

Adjunct Professor, Dept. of Biomedical Sciences, University of Alberta, Edmonton, Canada

Mild Traumatic Brain Injury Association with Gulf War Illness: Evaluation with Established Models (DOD GWIRP)

- Sponsor CDC Morgantown West Virginia
- **PI** O'Callaghan
- Collaborators Craddock (NSU), Sullivan (BU)
- Status Active: Data Collection
- Our objective is to investigate the role of mTBI in GWI symptomology, based upon clinical evaluations that have indicated an increased symptom severity in veterans with GWI who suffered multiple, concurrent mTBIs, computationally model the molecular interactions underlying mTBI and GWI symptomology, and perform preclinical investigation into potential therapeutic interventions for treating GWI in veterans who suffered mTBI.

Disentangling the Effects of PTSD from GWI for Improved Diagnostics and Treatments (DOD GWIRP)

- PI Craddock
- Status Active: Model Construction and Data analysis
- In this work we propose to build on our ongoing research directed at mapping complex inflammatory mechanisms in GWI to improve our understanding of the immunologic underpinnings of GWI, and the compounding effects of co-morbidity with PTSD. Furthermore, we propose to take advantage of our ongoing work in predictive modeling to assess possible changes to putative treatments of GWI in the context of probable PTSD diagnosis.

Improving Diagnostics and Treatments for GWI Females by Accounting for the Effects of PTSD (DOD GWIRP)

- PI Craddock
- Status Active: Model Construction and Data analysis
- In this work we propose to build on our ongoing research directed at mapping complex inflammatory mechanisms in GWI to improve our understanding of the immunologic underpinnings of GWI in women, and the compounding effects of co-morbidity with PTSD. Furthermore, we propose to take advantage of our ongoing work in predictive modeling to assess possible changes to putative treatments of GWI for women in the context of probable PTSD diagnosis

Institute for Neuro-Immune Medicine NOVA SOUTHEASTERN UNIVERSITY



Nancy Klimas, MD

Professor, College of Osteopathic Medicine, Nova Southeastern University

Director, Institute for Neuro-Immune Medicine

Director, Miami VA Environmental Medicine Program

The ReBoot study – Re-booting homeostatic balance to recover from GWI

- Sponsor CDMRP GWIC and GWICTIC
- **PI** N Klimas and the VA Clinical Research Team
- Collaborators Drs Fletcher, Abreu, Aenlle, Nathanson, Craddock, Broderick,
- Status Recruiting
- The goal of this project is to treat GWI using a model predicted by the computational virtual trials program, and test whether patients in the study recover health and homeostatic balance





Going for the cure: Optimizing treatment course to reset system homeostasis

- ► Key systems:
 - Immune system
 - Endocrine System
 - Nervous System
- All 3 systems intercommunicate.
- ► All systems must be considered.
- Multisymptom illness indicates multiple system involvement.
- <u>One</u> intervention may not be enough









Hypothesis: Complex System – Multiple Homeostatic states

- Complexity gives rise to multiple stable behaviors
- Typical external factors perturb the system, which eventually returns to stability



Fritsch et al. (2013). Exploring the sometimes pathogenic versatility of discrete immune logic. Systems Biomedicine, 1(3), 179-194.



Integrating basic science with clinical data... one-two endocrine-immune punch

3/6/2020



Treatment Trials and Mechanism of Illness Studies: Institute for Neuro Immune Medicine (NSU/VA)

CoQ10 phase 3 study - Miami, Bronx, Boston, and Minneapolis VA (VA funded) **RECRUITING** The Re-Boot Study – Etanercept and Mifepristone in GWI – **RECRUITING** Glutathione vs Curcumin Phase 2 study - Miami VA (CDMRP funded) **RECRUITING** Cells to Therapy – Modeling Treatments in Vitro (VA funded) **RECRUITING** Gender and Models of GWI – (VA funded) **RECRUITING** Microbiome and GWI – (VA funded, Chatterjee PI) **RECRUITING** BBRAIN longitudinal study of GWI **RECRUITING** (also Boston, San Francisco, Bronx) Phase 2 study of B Cell Depletion – the rituximab trial in autoimmune GWI (**RECRUITING**) Project IN Depth VA NIH partnership – deep phenotyping study (recruiting summer 2020)

From Benchtop to Clinical Trials : GWICTIC The Gulf War Illness Clinical Trials and Interventions Consortium

The overall goal of the clinical trials outlined in this consortium is to

- Create an infrastructure to support these trials, but also support future trials in GWI
- Move basic science studies to intervention

In this initial set of studies the investigators plan to capitalize on the two previously funded GWI consortium (GWIC) through CDMRP that takes our benchtop work into clinical trials, and will

- target previously identified markers of disease activity
- reset homeostasis with combination approaches with synergistic mechanisms of action or single agents with multiple disease targets
- to improve outcomes and quality of life for those suffering with Gulf War Illness (GWI)

Understanding GWI: An Integrative Modeling Approach (CDMP # W81XWH-13-2-0085 Morris, NSU)

Brain-Immune Interactions as the Basis of GWI: GWIC) CDMP # W81XWH13-2-0072 Sullivan, BU).



GWICTIC as a resource for future studies

GWICTIC is a CDMRP funded mechanism to develop a national clinical trials consortium.

In addition to the studies funded in the initial application, the GWICTIC offers a infrastructure for clinical trials design and implementation.

Investigators considering an application in the 2020 CDMRP round are encouraged to contact the GWICTIC co PI's (Nancy Klimas, MD and Becky McNeil, PhD) very early in protocol development

GWICTIC The Gulf War Illness Clinical Trials and Interventions Consortium

GWICTIC is the umbrella structure for CDMRP funded trials in South Florida and with the consortium sites: Boston (BU), NJ VA WRIISC, Palo Alto VA WRIISC and Minneapolis VA. It is also supporting other CDMRP work.

Partnered with RTI International, NSU is working with the CDMRP leadership and investigators to provide support of the clinical trials program

South Florida Studies currently recruiting:

Rituximab phase 2 trial (NSU campus)

Soon to begin:

ReBoot study – Etanercept and mifepristone in GWI, Phase 1, then phase 2

Bacopa in GWI, a phase 2 study – design allows participants from anywhere in the USA

Repairing oxidative stress in the brain, a phase 2 study , launch 2021

A Randomized, Double-Blind, Placebo-controlled Clinical Trial of Oleoylethanolamide for Targeting Lipid Metabolism in Gulf War Illness (Roskamp Institute , Sarasota)

Nancy Klimas, MD

Professor. College of Osteopathic Medicine, Nova Southeastern University

Director. Institute for Neuro-Immune Medicine

Director, Miami VA **Environmental Medicine** Program

B Cell Depletion in GWI – CNS autoimmunity subgroup intervention study (Phase 2 placebo control design)

- Sponsor CDMRP
- **PI** N Klimas and the NSU Clinical Research Team
- Collaborators Drs Sullivan, Abou Donia, Abreu, Aenlle.
- Status Recruiting
- The goal of this project is to treat GWI veterans who have demonstrable autoantibodies with a treatment that reduces autoantibody production







CDMRP 2020 Funding cycle

The FY20 Defense Appropriations Act provides funding to the Department of Defense Gulf War Illness Research Program (GWIRP) to support research addressing Gulf War Illness (GWI) pathobiology, diagnosis, and treatment.

Applications submitted to the FY20 GWIRP must address one or more 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
- Communicate: Help veterans, their caregivers, researchers and health care providers communicate effectively about GWI, its symptoms, and potential treatments

Current National VA Trials Portfolio 2018 \$ 13.3 M Total 2008-2018 \$ 133.2 M

Treatments/Clinical Trials (8) 24% of total

Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in GWVI.

Complementary Neurosteroid Intervention in Gulf War Veterans' Illnesses.

- Cognitive Rehabilitation Therapy for Gulf War Veterans.
- Complementary and Alternative Medicine in Veterans with Gulf War Illnesses.
- Novel Interventions for Gulf War Veterans' Illnesses.
- Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness.
- Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness.
- Repetitive transcranial magnetic stimulation (rTMS) in alleviating Pain and Comorbid symptoms in GWVI with MDD

CA WRIISC J Wesson Ashford, MD, PhD

Project Title	Funding	Status
An Evaluation Of The Comparative Efficacy Of Yoga Versus Cognitive Behavioral Therapy For Treating Chronic Pain In Gulf War Illness.	Supported financially by a CDMRP/DoD Gulf War Illness Research Program Innovative Treatment Evaluation Award #11488016 PI Bayley	Project complete. Manuscript under review
Brain and physiological markers of autonomic function are associated with treatment-related improvements in self- reported autonomic dysfunction in veterans with gulf war illness: an exploratory pilot study.	Supported financially by a Stanford Center for Neurobiological Imaging (CNI) Innovation Seed Grant PI, Mathersul, Bayley	Project complete. Manuscript under review
Brainstem Atrophy in Gulf War Illness	Unfunded research project	Manuscript under review
Brainstem Structural Alterations Correlates with Sleep Difficulty and Pain in Gulf War Illness Veterans	Unfunded research project	Manuscript under review

Maheen Mausoof Adamson, PhD

Senior Scientific Research Director, Defense and Veterans Brain Injury Center (DVBIC)

VA Palo Alto Health Care System (PSC/117)

Clinical Associate Professor Neurosurgery, Stanford School of Medicine

Project Title	Funding	Status
rTMS in Alleviating Pain and Co-Morbid Symptoms in GWVI	DOD CDMRP Site PI M M Adamson	2019-2024 Ongoing recruitment
Long Term Efficacy of Neuronavigation-Guided rTMS in Alleviating Headache and Pain in GWI	VA Merit CSR&D Site PI M M Adamson	2019-2024 Ongoing recruitment

Linda L. Chao, PhD

Professor, Departments of Radiology & Biomedical Imaging and Psychiatry, University of California, San Francisco

Research Biologist, San Francisco VA Medical Center

Project Title	Funding	Status
An investigation of the relationship between toxicant exposures during Gulf War deployment and prodromal Parkinson's disease	VA CSR&D Merit Review	Recruiting
Cognitive Behavioral Therapy for Insomnia for Gulf War Illness Clinical Trials Identifier: NCT02782780	VA CSR&D Merit Review	Active, not recruiting
Examination of plasma PON1 paraxonase total activity and genotype in Gulf War Veterans	DOD CDMRP	Data analysis

Dane Cook, PhD

Research Health Scientist, William S. Middleton Veterans Memorial Hospital

Acute exercise tolerance among Veterans with Gulf War Illness

VA Career Development Award/IK2CX001679

Agency: VA CSR&D

Duration: July 1,2018-June 30, 2023

Location: William S. Middleton Veterans Memorial Hospital (Madison, WI)

Short term goal: Determine the dose-response relationship between aerobic exercise intensity and illness severity in Gulf War Illness (n=40)

Long term goal: Develop an evidence-based exercise prescription for Veterans with Gulf War Illness

Status: actively enrolling and testing

http://grantome.com/grant/NIH/IK2-CX001679-01A1

William S. Middleton Memorial Veterans Hospital

Title: Post Exertion Malaise in GWI Brain Autonomic and Behavioral Interactions

PI: Dane B. Cook, PhD

Project # 5101CX001329-04

Status: Ongoing data collection

Publication released:

Lindheimer, J.B., Stegner, A.J., Wylie, G.R., Klein-Adams, J.C., Almassi, N.E., Ninneman, J.V., Van Riper, S.M., Dougherty, R.J., Falvo, M.J. and Cook, D.B., 2020. Post-exertional malaise in veterans with gulf war illness. *International Journal of Psychophysiology*, 147, pp.202-212.

	Project Title	Funding	Status
	A Randomized, Double-Blind, Placebo- controlled Clinical Trial of Oleoylethanolamide for Targeting Lipid Metabolism in Gulf War Illness	DOD GWIRP PI L Abdullah	Starting recruitment soon
The Roskamp Institute	Development of oleoylethanolamide for treating the CNS symptoms of Gulf War Illness	DOD GWIRP PI L Abdullah	Active
Laila Abdullah, PhD	Treating GWI immune and metabolic disturbances by targeting lipid metabolism	VA/RR&D PI L Abdullah	Active
Scientist III, Roskamp Institute Ghania Ait- Ghezala, PhD	Identification of lipid biomarkers of inflammation and metabolic disturbances in GWI	DOD GWIRP PI L Abdullah	Recruiting
Scientist III, head of Molecular Genetics at Roskamp Institute	The Influence of Traumatic Brain Injury on Gulf War Illness Pathogenesis	DOD GWIRP PI B Mouson Co-PI G A Ghezala	Active
	Treatment Strategies in a Mouse Model of Chronic Gulf War Illness	DOD GWIRP PI G A Ghezala	Active

Dikoma C. Shungu, Ph.D

Professor of Physics in Radiology

Affiliation: Weill Cornell Medicine, New York, NY

Biomarkers and Brain Mechanisms of Gulf War Illness

• Project Synopsis:

To use ¹H/³¹P magnetic resonance spectroscopy (MRS), ¹¹C-PK11195 positron emission tomography (PET) neuroreceptor imaging and biochemical techniques to investigate whether neuroinflammation and/or mitochondrial dysfunction and/or oxidative stress play a role in the pathophysiology of Gulf War Illness and to seek an understanding of the underlying brain mechanisms.

• Current Status:

Currently enrolling. Total target enrollment: 40, to consist of 20 Gulf War Veterans with GWI, and 20 Gulf War Veterans without GWI. Total enrollment to date: 20 Gulf War Veterans w/ and w/o GWI.

VA Boston Healthcare System

Title: Novel Interventions for Gulf War Illness

PI: Barbara L. Niles, PhD

Status: Recruiting

ClinicalTrials.gov ID: NCT02661997

Many people who served in the Gulf War in 1990 and 1991 have persistent problems such as:

 Muscle weakness, joint pain, or stiffness

Fatigue

 Mood, memory, or attention concerns

We are recruiting adults who are experiencing these problems for a health promotion study.



Frequently Asked Questions

Q: Who can participate?

- Veterans who served in the Gulf in 1990- 1991 and
- Have pain and other symptoms of Gulf War Illness.

Q: What are the treatments?

- You will be randomly assigned to either a Wellness or Tai Chi group
- <u>Wellness Group</u>: A skills based class promoting wellness by focusing on exercise, surroundings, personal
- tion growth, diet, sleep habits, relationships, practice and goal setting are discussed in every meeting.
 - <u>Tai Chi Group</u>: A Tai Chi class for beginners that teaches movements, forms, and philosophy. Tai Chi is a slow moving martial art that combines flowing postures with breathing, meditation, and stretching.
 - Both groups meet twice a week for 12 weeks.

Q: What is involved in the study?An initial assessment involving an

- interview, questionnaires and assessment of your physical and mental health
- A final assessment after the last session of the program
- 3 and 9 month follow-up assessments

Q: Will I be compensated?

 Yes. If you qualify and complete the study, you will receive up to \$515 for your time and transportation.



Q: Where will this study take place?

 This study will take place at the VA Boston Healthcare System located in Jamaica Plain.

Q: Will medications be prescribed?

No, this study does not involve medications.

To learn more, please contact:

(857) 364-6262

Our staff will answer any questions you may have, and help you to decide if our Novel Interventions for Gulf War Illness study is a good fit for you. If so, you will be scheduled for your first appointment. You may choose not to participate at any time.

Centers for Disease Control and Prevention

Investigators:

K A Kelly

S M Lasley

J P O'Callaghan

Project Title	Funding	Status
Brain-Immune Interactions as the Basis of Gulf War Illness	CDMRP PI K Sullivan	2013 – 2020 Research ongoing
Therapeutic Intervention of Glial- Mediated Enhancement of Neuroinflammation in an Established Model of GWI.	CDMRP PI K A Kelly	2016 – 2020 Research ongoing
Stress Hormone Enhancement of OP- Induced Neuroinflammation as an Animal Model of GWI: The Role of Toll- Like Receptors and Plasticity	CDMRP PIs: SM Lasley & JP O'Callaghan	2016 – 2020 Research ongoing
Stress Hormones Affect the Neuroinflammasome and Neurotoxicity	CDC Intramural PI JP O'Callaghan	2017 – 2021 Research ongoing
Neuroinflammation-Related Phosphoprotein Signaling Pathways as Potential Therapeutic Targets for GWI Using an Established Animal Model	CDMRP PI JP O'Callaghan	2017 – 2021 Research ongoing
Preclinical Investigation of Non-Fatal Work-Related Traumatic Brain Injury	CDC Intramural PI JP O'Callaghan	2018 – 2022 Research ongoing
Mild Traumatic Brain Injury Association with Gulf War Illness: Evaluation with Established Models	CDMRP PI JP O'Callaghan	2019 – 2023 Recruiting personnel

Creating more efficient processes for scientists to progress

- **BBRAIN** Building Scientific Collaborations across the GWI Research Community
- **GWI Veteran Research Clearing House** working with veterans to move the pace of science
- **GWICTIC** moving basic science to clinical intervention



Boston Biorepository and Integrative Network for Gulf War Illness (BBRAIN)

KIMBERLY SULLIVAN, PHD

BBRAIN as a core Resource for future biomarker studies



- The established infrastructure developed for BBRAIN will provide much needed repository samples and data mining for other studies to be successful in their biomarker and translational studies.
- We have a strong track record of translating biomarkers from the animal/cell to the clinic and BBRAIN will build upon this expertise. In this way, BBRAIN and GWICTIC will provide infrastructure for Biomarker Development and Targeted Treatment Trials
- In the 2019 CDMRP program announcement, investigators were given the option to share samples with BBRAIN or to request BBRAIN resources for their studies.
- BBRAIN has developed a "menu" of available samples/data that investigators can request on our website and that will be sent to our steering committee for approval of sample/data sharing.
- Year one was used to develop our website and SOPs for sample/data requests and to obtain institutional approvals for sample sharing and new subject recruitment for our 10 sites.
- In this year, we will formalize this request system and provide a web link and contact information that investigators can use to engage BBRAIN prior to their preproposals and throughout protocol development.



About the Repository

- We are collecting blood, plasma, serum, saliva, stool, and urine samples from 500 Gulf War veterans as well as demographic surveys and cognitive test data as part of the BBRAIN study.
- We will combine demographic, health, and exposure data with cognitive test outcomes and brain imaging data (MRI, DTI, fMRI, PET imaging) from 10 collaborating institutions into a centralized catalog available for data mining and sharing. GWICTIC studies will also share samples with BBRAIN.
- We will also be including de-identified previously collected survey, clinical, and preclinical data compiled from the 10 participating GWI investigators to be made available to the BBRAIN repository.





Year 1 Specific Goals:

- 1. OBTAIN INSTITUTIONAL APPROVALS
- 2. ENGAGE VETERAN ADVOCATES
- 3. COMMON DATA ELEMENTS PROJECT
- 4. CENTRALIZED RECRUITMENT AND OUTREACH EFFORTS

5. CENTRALIZED OPERATIONS DESIGN USING REDCAP AND OTHER DATA MANAGEMENT TOOLS

6. CENTRALIZED CATALOGUING AND COORDINATION OF BIOREPOSITORY RESOURCES TO SHARE WITH MILITARY RESEARCH COMMUNITY





COMPLETED APPROVALS

















NEARLY COMPLETED APPROVALS





- DUA and MTA agreements are in process with these sites.
- HRPO approval pending for Miami VA and Bronx VA

Veteran Outreach Efforts













The Institute for Neuro-Immune Medicine at Nova Southeastern University will be hosting the 2020 Sustained Homeostatic Imbalance due to Environmental-exposure Linked to Deployment (SHIELD) Conference. This free event is open to all Gulf War Veterans.

- Learn about Gulf War illness
- Connect with fellow Gulf War Veterans
- Learn about life-changing research that is helping Veterans
- Special Guest Panel of Operation Desert Storm/Desert Shield Patient Advocates

Questions? Contact Zena Kirby 954-262-2870 or zkirby@nova.edu







At BU and Beyond, Gulf War Veterans Still Suffer from Toxic Wounds



http://www.bu.edu/articles/2019/gulf-war-illnessresearch/?fbclid=IwAR3pmSWTxYXbbC9JHOJ8LxQXJYytgtcj--RwGEQTd6TtGzEhZH2dFOiu3GA

Common Data Elements

- GWI Common Data Elements (CDE) workshops
- Publication of CDEs on CDMRP GWIRP website
- Publication of Cognitive outcome CDEs in Jeffrey et al. 2019
- Plans for additional CDE publications
- Plans for GWI Case Criteria Meeting







OPEN ACCESS

Center, United States

Center, United States

Saurabh Chatterjee, University of South Carolina,

Correspondence:

tcraddock@nova.edu

Specialty section:

a section of the journal Frontiers in Psychology

This article was submitted to

Psychology for Clinical Settings,

Kimberly Sullivan

tty@bu.edu Travis J. A. Craddock

Kennuerder Oulf Wer illnesse ner

United States

Reviewed by:

Brandon Roberg.

Wm. Jennings Bryan Dorn VA Medical

Wm. Jennings Bryan Dom VA Medical

Edited by: J. P. Ginsberg, REVIEW published: 26 September 2019 doi: 10.3389/fpsvg.2019.02088



Neuropsychological Findings in Gulf War Illness: A Review

Mary G. Jeffrey¹, Maxine Krengel², Jeffrey L. Kibler³, Clara Zundel², Nancy G. Klimas^{1,4,5}, Kimberly Sullivan⁶⁺ and Travis J. A. Craddock^{1,4,7,8+}

¹ Institute for Neuro-Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States, ² VA Boston Healthcare System, Boston, MA, United States, ³ Department of Clinicial and School Psychology, Nova Southeastern University, Fort Lauderdale, FL, United States, ⁴ Obpartment of Clinicial Immunology, Nova Southeastern University, Fort Lauderdale, FL, United States, ⁸ Marri VA Medical Contor, Marni, FL, United States, ⁸ Department of Environmental Health, Boston University School of Public Health, Boston, MA, United States, ⁸ Department of Psychology and Neuroscience, Nova Southeastern University, Fort Lauderdale, FL, United States, ⁸ Department of Computer Science, Nova Southeastern University, Fort Lauderdale, FL, United States

This review paper summarizes the accumulation of research investigating neuropsychological outcomes in veterans with Gulf War illness (GWI). Earlier research focused on Gulf War veterans (GW) who were deployed versus non-deployed, as well as those who were symptomatic versus asymptomatic, or compared neuropsychological test results to published norms. Further research became more sophisticated, investigating specific GWI criteria, as well as the result of neurotoxicant exposure and the relationship to possible neurocognitive outcomes. As the early research supported both psychological and physiological effects on GWI; current research as summarized in this literature review supports the presence of neuropsychological deficits, particularly in the domains of attention, executive functioning, memory, and motor functioning related to chemical exposures that can be exacerbated by comorbid mood-related conditions. The same test battery has not been used consistently making it difficult to compare results among studies. Therefore, researchers created a resource to provide recommendations for the recently listed Neuropsychological Tests for Common Data Elements (CDEs) for use in all future GWI studies. Future research is necessary to further understand patterns of neuropsychological test data and how these decrements may relate to immunological or other biological markers, and the impact of trauma from physical and psychological stressors. In conclusion, there is consistent evidence that GWI is characterized by neuropsychological decrements - with future research these findings may aid in the diagnosis and assessment of treatment trial efficacy of GW veterans.



Research Dissemination



Presentations/Publications

K. Sullivan; N. Klimas. Military Biorepositories. National Academy of Science (NAS) Workshop on Gulf War Respiratory Health Committee (Invited Speaker), Washington, DC, October 3, 2019.

K. Sullivan. Military Occupational Health and Toxicology. American Academy of Environmental Medicine annual meeting. (Invited keynote speaker), Louisville, KY, October 12, 2019.

N. Klimas. Can We "Reboot" Human Homeostasis to Cure Chronic Illness? What We Are Learning from Gulf War Illness and ME. American Academy of Environmental Medicine annual meeting. (Invited keynote speaker), Louisville, KY, October 12, 2019.

Jeffrey MG, Krengel M, Kibler JL, Zundel C, Klimas NG, Sullivan K, Craddock TJA. Neuropsychological Findings in Gulf War Illness: A Review. Front Psychol. 2019 Sep 26;10:2088. doi: 10.3389/fpsyg.2019.02088. eCollection 2019. Review. PMID: 31616335. Link: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.02088/full



Home

Calling Gulf War Veterans...



ide, NYC 1991. (Joseph Sohm, Visions America)

We are looking for veterans of the 1990-1991 Gulf War to take part in a one-day study in Boston, New York, Miami, or San Francisco. Our study is for both healthy veterans and veterans suffering from Gulf War Illness. To learn more about the study, please visit our page about BBRAIN. If you are interested in participating, please call us at 617-358-1717 or email us at <u>bbrain@bu.edu</u>!



Investigators

If you are a researcher looking to request data or samples, please visit our page for investigators.





BBRAIN: a repository for GWI investigators

Veterans of the 1991 Gulf War continue to experience chronic symptoms including fatigue, memory and concentration problems, muscle and joint pain, headaches and gastrointestinal problems known as Gulf War Illness (GWI). Preliminary evidence shows that GWI is related to immune dysfunction, neuroinflammation, cognitive decrements, CNS autoantibodies, lipidomics/ proteomics, axonal transport/ microtubule stability, mitochondrial function and oxidative stress, gut microbiome and genetic/genomic/epigenetic susceptibility.

BBRAIN is designed to act as a retrospective and prospective biorepository for GWI through a collaboration of investigators at our resource sites (Boston University School of Public Health, the Bronx VA, the San Francisco VA, and the Miami VA). We are collecting blood, plasma, serum, saliva, stool, and urine samples from 500 Gulf War veterans as well as demographic surveys and cognitive test data. We will combine demographic, health, and exposure data with cognitive test outcomes and brain imaging data (MRI, DTI, fMRI, PET imaging) from 10 collaborating institutions into a centralized catalog available for data mining and sharing. We will also be including de-identified previously collected survey, clinical, and preclinical data compiled from the 10 participating GWI investigators to be made available to the BBRAIN repository.

BBRAIN Inventory

Biological Samples

 •Whole blood
 •Serum

 •Stem cells
 •Fecal samples

 •CSF
 •Urine

 •Saliva
 •PBMC

 •DNA
 •Buffy coat

 •Plasma

Clinical Data

Fitbit measures (heart rate, sleep, exercise)
 Cognitive tests (executive functioning: attention, vigilance, and tracking: motor function: visuospatial function; memory; motivation; mood; general intellectual abilities)
 Brain imaging (PET, MRI, DTI, fMRI)

Data Sharing

Requests to access data in our repository can be made through our website: sites.bu.edu/bbrain

Contact Us Principal Investigator: Kimberly Sullivan, PhD

tty@bu.edu 617-358-2598



Repository Sample Request Form

Sample Request

Type of Sample:	Blood Products	
	O Whole Blood	
	O PBMC	
	O Plasma	
	○ Serum	
	 Buffy Coat 	
	O Plasma	
	Salivary Products	
	o Saliva	
	 Salivary Cortisol 	
	Other Products	
	o CSF	
	o Stem Cell	
	o DNA	
	o Urine	
	• Stool	
Total Number of Samp	oles Requested	
Minimum Volume of S	ample Needed per Subject	
Gender Requested	# of Females:	
	# of Males:	
Status Requested	# of GWI Cases:	
	# of No GWI Veterans:	

Additional notes about sample requirements:

GWI Veteran Research Clearing House – working with veterans to move the pace of science: Partnering with the Veteran Community to Move Science Forward

> Chronic Multi-Symptom Illnesses (CMI): Operation Desert Shield/Desert Storm Clinical Research Web Based Study

> > This study and service is funded through private donation

STUDY PI: ELIZABETH BALBIN COORDINATOR: PRECIOUS LEAKS-GUTIERREZ DATA MANAGEMENT: ARNALDO TERCERO



Study Information

The purpose of this study is it to gather initial health and exposure information regarding veterans and contract workers who may have had exposures during the Gulf War, operation Desert Storm Desert Shield (ODS). Many of these individuals may be experiencing symptoms associated with Gulf War Illness (GWI) or Chronic Multi-Symptom Illness (CMI). Information gathered will be analyzed.

In addition a registry of individuals interested in future studies is being collected, **to be used as a recruitment tool** with prescreened veterans who have requested notification about study opportunities. Thus we are creating a data base for notification of current and future research.

Participants will receive newsletters on research advances , notices of events and other ways to network with the scientific community

What to expect if you sign up

The Clearing house consists of a database of information about veterans, service members, and contract workers, who were in service or deployed during Operation Desert Storm/Desert Shield, and or continued Gulf War. Information collected is via questionnaire and stored in the NSU REDCap platform. Data collected includes; basic demographic information, service and deployment, exposures, medical symptoms, and contact information. Each participant is consented and issued a unique ID number.

Survey takes approximately 30 minutes to complete. At the start of the survey, participants have the ability to give permission for contact regarding current and future clinical research for Gulf War Illness., and also give permission to be informed by newsletter and email about events and research progress. Participants are contacted by the study coordinator of this study for further information.

Current Numbers

Study began 3rd quarter 2019

Individuals who took/started the survey: 1,395 (760 ODS)

- Male: 730 (629 ODS)
- Female: 157 (126 ODS)
- Did not answer: **505**

Completed the survey: 790 (704 ODS)

- 98% have CMI/GWI symptoms
- 724 met the Kansas Definition
- 707 were deployed
- ODS/DS: Subjects range from **45-77 yrs**.

Individuals who would like to participate in current and future studies: **813** (**696 ODS**)

Current Numbers cont.

Divided by zones:

- South: 438 (50%)
- Midwest: 191 (22%)
- West: 157 (18%)
- Northeast: 87 (9%)
- US Territories: 15 (1%)

*507 participants did not answer

Survey Participants Self Report

Of the 790 (704 ODS) participants who completed the survey:

- •Have you been diagnosed with GWI or CMI?
 - Yes: 228 (212)
 - No: 386 (348)
 - Unsure: 146 (138)
 - Did not answer 21 (13)
- •Where you in good health prior to Gulf War?
 - Yes: 755 (693)
 - No: 4 (4)
 - Unsure: 2 (2)
 - Did not answer: 4 (12)

Using the Clearing House – Scientists and Veterans

There has been a positive response by study participants to our web based study platform, with many individuals wishing to continue further involvement if more studies were available.

We have the ability to expand the study to include the collection of cognitive testing, activity (steps), heart rate (HR), and sleep. In addition biological samples would be collected and processed.

Nutraceutical studies such as the Bacopa or the ongoing VA sponsored phase 3 CoQ10 study would benefit from a "virtual" trial relying on the web based platform. Laboratory prescreening/other assays, as well as distribution of study nutraceutical, can be easily coordinated through the study coordinator on site.

We will help any investigator with an approved study communicate with you, the potential study participant through the newsletter or directed mailings by region.

BOTTOM LINE: Please sign up this is the single best way to participate in clinical trials and the single most important predictor of success is recruitment

https://www.nova.edu/nim/research-studies/research-studies-pages/gwi-studies/gwi-survey-study-page.html

Rolling out the platform

SHEILD Conference February 28th - free streamed conference to the GWI veteran community

Partnering with large veteran organizations – we need you to be successful!

Thought leaders, asking veterans with social media outreach to engage veterans in the process

You tube station – developing modules for veterans with GWI to manage the illness and learn more about the role of research in their care.

Engaged a full time social media expert to manage the social media

roll out of this project and related outreach efforts.





Funded by



Thank You

