Gulf War Research Update

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Director – Gulf War
Office of Research and Development
Department of Veterans Affairs
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Washington D.C.
• 172 VAMCs have the capacity for research
  More than 90 are funded by VA at any given time

• VA Research is an Intramural Program.

• Principle Investigators must have a 5/8th VA appointment.

• Investigators must conduct research in VA space (or request a partial-off site waiver).

• Investigator workforce is ~1:1 clinician- and non-clinician scientist.

• Merit, Pilot, and Career Development awards are investigator initiated projects.

• Broad, extensive research portfolio that balances the needs of all Veterans
Chief Research and Development Officer (CRADO) Priorities

- Increase Veterans’ access to clinical trials
- VA Data as a National Resource
- Increase the real-world impact of VA research
VHA Office of Research and Development (ORD)

Chief Research & Development Officer (CRADO)

- Biomedical Laboratory R&D
- Clinical Science R&D
- Health Services R&D
- Rehabilitation R&D

Cooperative Studies Program (CSP)

Gulf War Program
- RFAs
- Rigor Review Process
Vision

• Improve the health and well-being of Gulf War Veterans through rigor evidence-based science.
• Utilize emerging knowledge to prevent similar war-related illnesses in the future.

Mission

• Develop effective treatments for ill Gulf War Veterans.
• Identify biomarkers and improve diagnosis for conditions affecting Gulf War veterans.
• Continue surveillance/health monitoring for the aging GW Veteran population.
## VA-ORD Funding - Gulf War Research (2008-2018)

<table>
<thead>
<tr>
<th>Fiscal Year (FY)</th>
<th>VA Merit Review</th>
<th>Contract</th>
<th>FY Total</th>
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<td>$6.93 M</td>
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<td><strong>Total 2008-2018</strong></td>
<td><strong>$108.9 M</strong></td>
<td><strong>$24.29 M</strong></td>
<td><strong>$133.2 M</strong></td>
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# VA-ORD Funding - Gulf War Research (2011-2018)

<table>
<thead>
<tr>
<th>FY</th>
<th>Proposals Received</th>
<th>Projects Funded</th>
<th>% Funded</th>
<th>Funds Approved</th>
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<td>2019 (S19)</td>
<td>13</td>
<td>Margin Mtg 7-10-19</td>
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</table>

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 Co-morbid symptoms in GWVI with MDD.
Biomarkers/Mechanisms (12) 37% of total

- Longitudinal assessment of Gulf War veterans with suspected Sarin exposure.
- Multimodal Biological Assessment of Gulf War Illness.
- Women vs. Men with GWI: Differences in Computational Models and Therapeutic Targets.
- A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy.
- Mechanisms of Gulf War Illness.
- Biomarker Candidates in Gulf War Veterans: A 10-year Follow-up Investigation.
- Identification of Plasma Biomarkers of Gulf War Illness Using "omic" Technology.
- The Role of Interleukin-17 cytokines in GWVI patients with IBS.
- Treating GWI immune and metabolic disturbances by targeting lipid metabolism.
- Post Exertional Malaise in GWI: Brain Autonomic and Behavioral Interactions.
- An investigation of the relationship between toxicant exposures during Gulf War deployment and prodromal Parkinson's disease.
- Immune/Inflammatory Priming in Exacerbating Responses to GWVI Stressors: Implications for GWVI Treatments.
Active Gulf War Research Projects, 2019 (3 of 3)
(CFS, Neurological, brain, exposure, IBS, reproductive)

Model Systems/Preclinical (9) 27% of total

- Gulf War Exposures and the Molecular Mechanisms of Paternal Reproductive Risk.
- Novel neurotrophic therapies in an optimized mouse model of GWVI.
- Immune Basis for Hippocampal Cholinergic Deficits in Pyridostigmine-treated Rats.
- Gulf War neuro toxicants and acquired cognitive and neuropsychological dysfunction.
- Maintenance of Telomerase Activity as a Treatment for Gulf War Illness.
- Neuroinflammation and abnormal behavior following combined chemical exposures and bacterial infection.
- Acute exercise tolerance among Veterans with Gulf War Illness (CDA).
- Examining the gut microbiota in Veterans with Gulf War Illness.
- Immune/Inflammatory Priming in Exacerbating Responses to GWVI Stressors: Implications for GWVI Treatments.
- VA Biorepository: Gulf War Veterans' Illnesses Biorepository (Brain and CNS)
Researchers eye probiotics as way of easing Gulf War symptoms

Examining the gut microbiota in Veterans with Gulf War Illness: Safdar, Nasia. Wisc. Summary. They hypothesize that the Veterans with GWI will have less diverse gut bacteria than the Vets without the multi-symptom illness. Safdar and her team expect to be in position to design a clinical trial to investigate probiotics as a way to help Veterans with symptoms of Gulf War illness.

Mouse Models of GWI: Altered microbiome caused significant decrease in tight junction protein Occludin with a concomitant increase in Claudin-2, a signature of a leaky gut: Chatterjee. S. Carolina


Treating GWI immune and metabolic disturbances by targeting lipid metabolism: **Abdullah, Laila.**

**Summary.** This is a preclinical project examining the role and underlying mechanisms of peroxisome- and mitochondrial-lipid metabolism-induced brain glia activation and cognitive impairment in a mouse model of GWI. Accumulation of very long chain fatty acids (VLCFA) in the plasma of GWI Veterans and increased astroglia (β-oxidation) and microglia (inflammation); suggesting peroxisome dysfunction. Using the mouse model of GWI, the dietary supplement, oleoylethanolamide (OEA) restores VLCFA to the normal levels and mitigates neuroinflammation and neurobehavioral deficits in a well-established mouse model of GWI. (VA, CDMRP funding).

Together, this work demonstrates how VA and DoD Gulf War funding translates science from bench to bedside.


Acute exercise tolerance among Veterans with Gulf War Illness (CDA): Jake Lindheimer. **Summary.** This Career Development Award represents an opportunity to train an integrative psycho-physiologist to gain new skills in a clinical environment (WRIISC) whereby the awardee will study exercise dose with post-exercise malaise and how these interact with biological outcomes including cognitive (neuroimaging), pain and inflammation, and behavior.


Oxidative Stress and GWI
Animal Models and GW Veterans


- Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness. Klimas N

**CSP 470: Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans’ Illnesses**

- Cognitive behavioral therapy and aerobic exercise for Gulf War Veterans' illnesses: a randomized controlled trial. Donta ST et al. Cognitive behavioral therapy and exercise, separately and together, can provide modest relief for some of the symptoms of CMI. JAMA, 2003 Mar 19;288(11)

**CSP 585: Gulf War Era Cohort and Biorepository (GWECB)**


**CSP 500a**

- Explore and identify MVP participants that have served in GW, and have GWAS/other genomic data

**CSP 2006**
Project IN-DEPTH

VA - NIH

INVESTIGATIVE DEEP PHENOTYPING STUDY

OF GULF WAR VETERAN HEALTH
NIH Intramural Study: Post-Infectious Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome (ME/CFS).

GWI and ME/CFS have similar clinical phenotypes and comparison may provide insight into shared and distinct modes of disease activity.

VA is preparing a “sister” protocol and recruitment plan.

VA-NIH partnership provides Veteran access to an integrated and comprehensive assessment at an institution that focuses on rare and unexplained illnesses.
VA ADVISORS
Vicky Davey, PhD, MPH

NIH ADVISORS
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Vicky Whittemore, PhD

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Vera Roddy, USAF
David Winnett, USMC (Ret)

SUBJECT MATTER EXPERTS
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Bill Meggs, MD, PhD
Jeffery Nast, JD
Jim O'Callaghan, PhD
Kim Sullivan, PhD

UNDIAGNOSED DISEASE NETWORK
David Adams,
Cynthia Tifft, MD
Project IN-DEPTH: Immunological, Bioenergetic, Neurologic, Homeostatic Regulation of Post-exertional malaise (PEM/CFS).

IN-DEPTH NIH DATA COLLECTION AND STORAGE

NIH DEEP PHENOTYPING VISIT

- History & Physical
- Results of clinical and research labs including whole blood, serum, plasma, saliva, buccal swab, urine and stool samples
- Symptoms assessment - questionnaires
- Psychological assessment – structured interview and questionnaires
- Neurocognitive testing
- MRI thighs, brain
- Muscle strength testing
- Physical activity monitoring and fatigue diary
- Holter monitoring
- Lumbar puncture, sedation or fluoroscopic guided
- Autonomic testing
- Immune cell collection
- Medical, psychiatric, sleep service and/or rehab consultations
- Muscle Biopsy
- Skin Biopsy

- Metabolic chamber
- Body composition measurement by dual energy x-ray absorptiometry
- Metabolic diet and nutritional assessment
- Resting energy expenditure measurements by ventilated hood
- Cardiopulmonary exercise tests (CPET)
- Qualitative measurements of post-exertional malaise
- Blood measurements before and after CPET
- fMRI of muscular fatigue, cognitive fatigue and resting state
- Transcranial magnetic stimulation
- Effort-expenditure for rewards task (EEERT)
- Sleep electroencephalogram

MIAMI TEAM COMPUTATIONAL ANALYSES
All data all subjects

KLIMAS LAB MIAMI
Derived data from sample processing

DURHAM Coordinating Center Crosswalk

NIH CLINICAL AND RESEARCH LABS for analyses

NIH Long Term Storage
- NIH-VA GW BIOREPOSITORY
- ME/CFS Study Data

VA Long Term Storage: MAVERIC
- Copy of all NIH GW Deep Phenotyping data
- Results of all VA computational analyses
+ existing VA recruitment, screening and enrollment data
Gulf War Research – VA-DoD Coordination

- Regular VA:DoD Gulf War Program Manager updates/briefings.

- VA Gulf War Program Manager (PM) attends annual DoD Programmatic Review and Vision Setting meetings.

- DoD Gulf War Program Manager attends VA RACGWVI meetings.

- Regular VA:DoD Gulf War Program Manager contributions to field-, industry-, and government-based meetings.

- DoD Gulf War Program Manager attends coalition forces calls hosted by VA Gulf War Program Manager.
Questions?