U.S. Department of Veterans Affairs

Gulf War Research Update

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Office of Research and Development
Department of Veterans Affairs
June 11, 2019
Washington D.C.

VA Office of Research and Development

- **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**

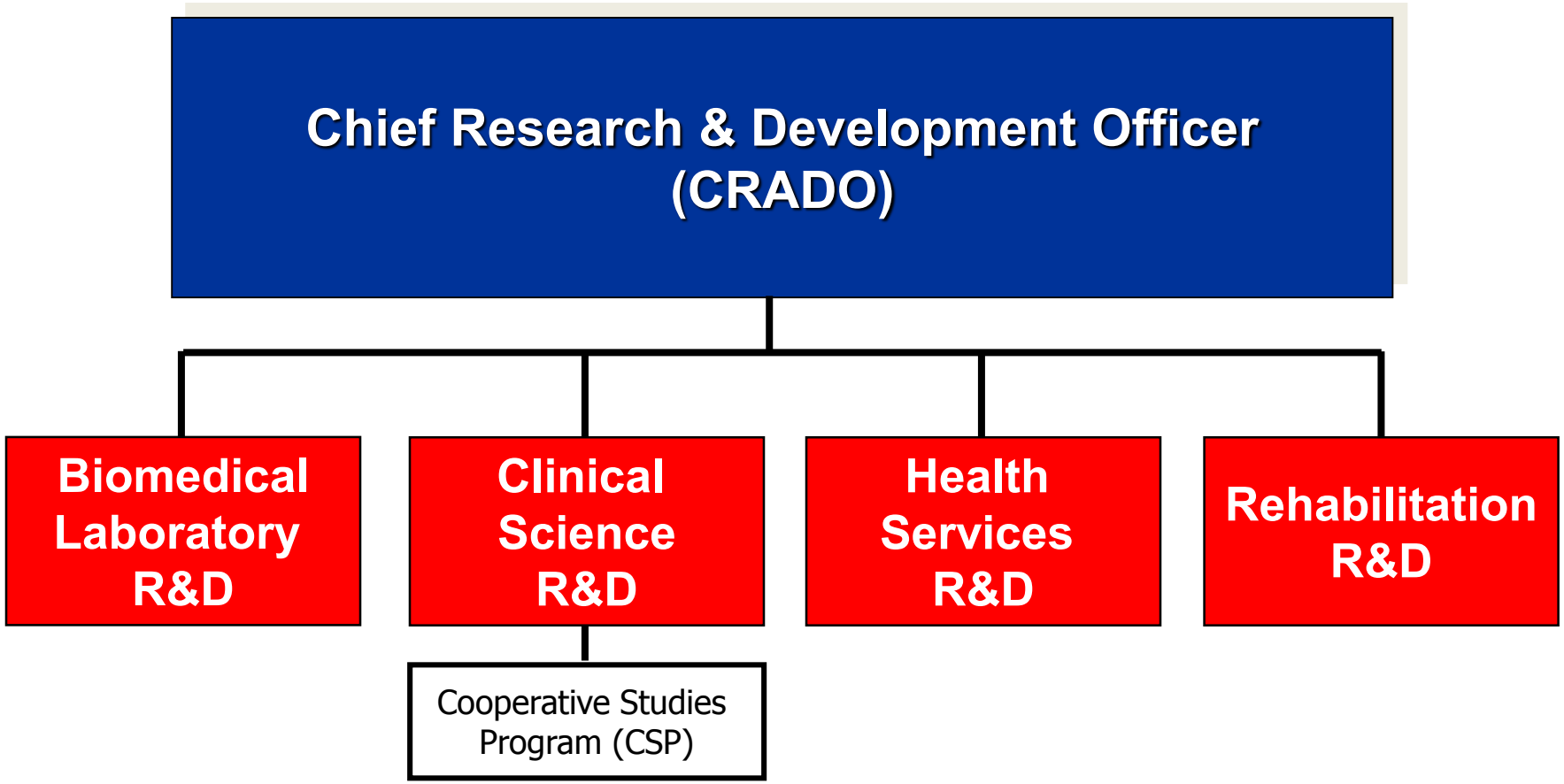
Chief Research and Development Officer (CRADO) Priorities

Rachel B. Ramoni, D.M.D., Sc.D.
CRADO

Wendy Tenhula, Ph.D
DEPUTY CRADO

- **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)



Gulf War Program

- **RFAs**
- **Rigor Review Process**

Mission and Vision: Gulf War Research Program

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)

Fiscal Year (FY)	VA Merit Review	Contract	FY Total
2008	$ 6.93 M	$ 15.00 M	$ 21.93 M
2009	$ 9.63 M	$ 6.97 M	$ 16.60 M
2010	$ 11.57 M	$ 2.29 M	$ 13.86 M
2011	$ 5.54 M	$ 0.03 M	$ 5.57 M
2012	$ 6.72 M		$ 6.72 M
2013	$ 7.94 M		$ 7.94 M
2014	$ 9.73 M		$ 9.73 M
2015	$ 11.63 M		$ 11.63 M
2016	$ 12.34 M		$ 12.34 M
2017	$ 13.56 M		$ 13.56 M
2018	$ 13.3 M		$ 13.3 M
Total 2008-2018	$ 108.9 M	$ 24.29 M	$ 133.2 M

VA-ORD Funding - Gulf War Research (2011-2018)

FY	Proposals Received	Projects Funded	% Funded	Funds Approved
2011	**26**	**3**	**11.50%**	**$04.0M**
2012	**32**	**7**	**21.80%**	**$11.4M**
2013	**35**	**7**	**20.00%**	**$12.6M**
2014	**40**	**5**	**12.50%**	**$ 07.5M**
2015	**33**	**8**	**24.20%**	**$13.2M**
2016	**26**	**4**	**15.30%**	**$02.5M**
2017	**29**	**5**	**17%**	**$05.3M**
2018	**27**	**5**	**19%**	**$02.6M**
2019 (S19)	**13**	**Margin Mtg 7-10-19**		

Active Gulf War Research Projects, 2019 (1 of 3)
(Oxidative Stress, Cognitive, Inflammation, QOL, Pain)

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.

Active Gulf War Research Projects, 2019 (2 of 3)
(CFS, Inflammation, Gender, Exposure, Neurological, stress)

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)

VA Research Outcomes – Model Systems
Gut Brain Barriers and Chaos

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

- Seth RK, Kimono D, Alhasson F, Sarkar S, Albadrani M, Lasley SK, Horner R, Janulewicz P, Nagarkatti M, Nagarkatti P, Sullivan K, Chatterjee S. Increased butyrate priming in the gut stalls microbiome associated-gastrointestinal inflammation and hepatic metabolic reprogramming in a mouse model of Gulf War Illness. Toxicol Appl Pharmacol. 350:64-77, 2018

- Alhasson F, Das S, Seth R, Dattaroy D, Chandrashekaran V, Ryan CN, Chan LS, Testerman T, Burch J, Hofseth LJ, Horner R, Nagarkatti M, Nagarkatti P, Lasley SM, Chatterjee S. Altered gut microbiome in a mouse model of Gulf War Illness causes neuroinflammation and intestinal injury via leaky gut and TLR4 activation. PLoS One. 12:e0172914, 2017.

VA Research Outcomes VA:DoD Synergy

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 (b-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.

- Joshi U, Evans JE, Joseph R, Emmerich T, Saltiel N, Lungmus C, Oberlin S, Langlois H, Ojo J, Mouzon B, Paris D, Mullan M, Jin C, Klimas N, Sullivan K, Crawford F, Abdullah L. Oleoylethanolamide treatment reduces neurobehavioral deficits and brain pathology in a mouse model of Gulf War Illness. Sci Rep. 8:12921, 2018.

- Emmerich T, Zakirova Z, Klimas N, Sullivan K, Shetty AK, Evans JE, Ait-Ghezala G, Laco GS, Hattiangady B, Shetty GA, Mullan M, Crynen G, Abdullah L, Crawford F. Phospholipid profiling of plasma from GW veterans and rodent models to identify potential biomarkers of Gulf War Illness. PLoS One. 12:e0176634, 2017.

- Abdullah L, Evans JE, Montague H, Reed JM, Moser A, Crynen G, Gonzalez A, Zakirova Z, Ross I, Mullan C, Mullan M, Ait-Ghezala G, Crawford F. Chronic elevation of phosphocholine containing lipids in mice exposed to Gulf War agents pyridostigmine bromide and permethrin. Neurotoxicol Teratol. 40:74-84. 2013

VA Research
Training tomorrow's leaders in Gulf War Research

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.

- Wylie GR, Genova H, Dobryakova E, DeLuca J, Chiaravalloti N, Falvo M, Cook D. Fatigue in Gulf War Illness is associated with tonically high activation in the executive control network. Neuroimage Clin. 2018.
- Falvo MJ, Chen Y, Klein JC, Ndirangu D, Condon MR. Abnormal rheological properties of red blood cells as a potential marker of Gulf War Illness: A preliminary study. Clin Hemorheol Microcirc. 68:361-370, 2018.
- Falvo MJ, Lindheimer JB, Serrador JM. Dynamic cerebral autoregulation is impaired in Veterans with Gulf War Illness: A case-control study. PLoS One. 2018
- Van Riper SM, Alexander AL, Koltyn KF, Stegner AJ, Ellingson LD, Destiche DJ, Dougherty RJ, Lindheimer JB, Cook DB. Cerebral white matter structure is disrupted in Gulf War Veterans with chronic musculoskeletal pain. Pain. 158:2364-2375, 2017.
- Chen Y, Meyer JN, Hill HZ, Lange G, Condon MR, Klein JC, Ndirangu D, Falvo MJ. Veterans with GWI exhibit greater mtDNA damage which is consistent with mitochondrial dysfunction. PLoS One 2017 12:e0186711.

Oxidative Stress and GWI
Animal Models and GW Veterans

- Shetty GA, Hattiangady B, Upadhya D, Bates A,.Attaluri S, Shuai B, Kodali M, Shetty AK. Chronic Oxidative Stress, Mitochondrial Dysfunction, Nrf2 Activation and Inflammation in the Hippocampus Accompany Heightened Systemic Inflammation and Oxidative Stress in an Animal Model of Gulf War Illness. Front Mol Neurosci. 2017

- Kodali M, Hattiangady B, Shetty GA, Bates A, Shuai B, Shetty AK. Curcumin treatment leads to better cognitive and mood function in a model of Gulf War Illness with enhanced neurogenesis, and alleviation of inflammation and mitochondrial dysfunction in the hippocampus. Brain Behav Immun. 69:499-514, 2018.

- Golomb BA, Allison M, Koperski S, Koslik HJ, Devaraj S, Ritchie JB. Coenzyme Q10 benefits symptoms in Gulf War veterans: results of a randomized double-blind study. Neural Comput. 26:2594-651, 2014. ***Q100 conferred benefit to physical function and symptoms in veterans with Gulf War illness.***

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

- Baraniuk JN, El-Amin S, Corey R, Rayhan R, Timbol C. L-Carnosine treatment for gulf war illness: a randomized controlled trial. Glob J Health Sci. 5:69-81, 2013.

Cooperative Studies Gulf War Projects
Multi-Center Clinical Trials and Epidemiology Studies

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)***

- Khalil L, McNeil RB, Sims KJ, Felder KA, Hauser ER, Goldstein KM, Voils CI, Klimas NG, Brophy MT, Thomas CM, Whitley RL, Dursa EK, Helmer DA, Provenzale DT. The Gulf War Era Cohort and Biorepository: A Longitudinal Research Resource of Veterans of the 1990-1991 Gulf War Era. Am J Epidemiol. 187:2279-2291, 2018.

CSP 500a

CSP 2006

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

GWI PROTOCOL: VA"SISTER" PROTOCOL

Project IN-DEPTH

VA - NIH

INVESTIGATIVE **DE**EP **P**HENO**T**YPING STUDY

OF GULF WAR VETERAN **H**EALTH

PROJECT IN-DEPTH

NIH Intramural Study: Post-Infectious Myalgic Encephalomeylopathy/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.

PROJECT IN-DEPTH: PLANNING COMMITTEE

VA ADVISORS
Vicky Davey, PhD, MPH

NIH ADVISORS
Avi Nath, MD
Vicky Whittemore, PhD

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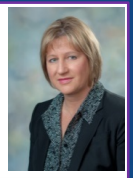
David Winnett, USMC (Ret)

UNDIAGNOSED DISEASE NETWORK
David Adams,
Cynthia Tifft, MD

U.S. Department of Veterans Affairs

PROJECT IN-DEPTH
Study Structure

VA Gulf War Program Director



K. Block, PhD

VA Study Team

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Study Co-Chair, Washington DC

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Local Site, East Orange NJ

D. Helmer, MD

Local Site, Palo Alto CA

W. Ashford, MD

Local Site, Seattle WA

S. Hunt, MD

NIH Study PI

NIH/NINDS, Principal Investigator

B. Walitt, MD

Durham Coordinating Center

D. Provenzale, MD

Cooperative Studies Program Data and Specimen Repository

D. Provenzale, MD

MAVERIC

Biorepository

G. Sugumaran

Massachusetts Veterans Epidemiology Research and Information Center

Project IN-DEPTH: Immunological, Bioenergetic, Neurologic, Homeostatic Regulation of Post-exertional malaise (PEM/CFS).

National Institutes of Health
Turning Discovery Into Health

IN-DEPTH NIH DATA COLLECTION AND STORAGE

NIH DEEP PHENOTYPING VISIT

NIH CLINICAL AND RESEARCH LABS for analyses

- 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 (EEfRT)
- Sleep electrocephalogram

MIAMI TEAM COMPUTATIONAL ANALYSES All data all subjects

KLIMAS LAB MIAMI

Derived data from sample processing

DURHAM Coordinating Center
Crosswalk

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 Manger (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.

VA-ORD Gulf War Research Strategic Plan

Questions?