



VA-ORD GULF WAR RESEARCH : Research Program Overview

Presented to:

Research Advisory Committee on Gulf War Veterans' Illnesses

VHA OFFICE OF RESEARCH AND DEVELOPMENT / Victor Kalasinsky and Robert Jaeger

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San Francisco, CA

VA Office of Research and Development Strategic Plan (2012-2016)

MISSION:

To discover knowledge and create innovations that advance health care for our Veterans and our Nation

VISION:

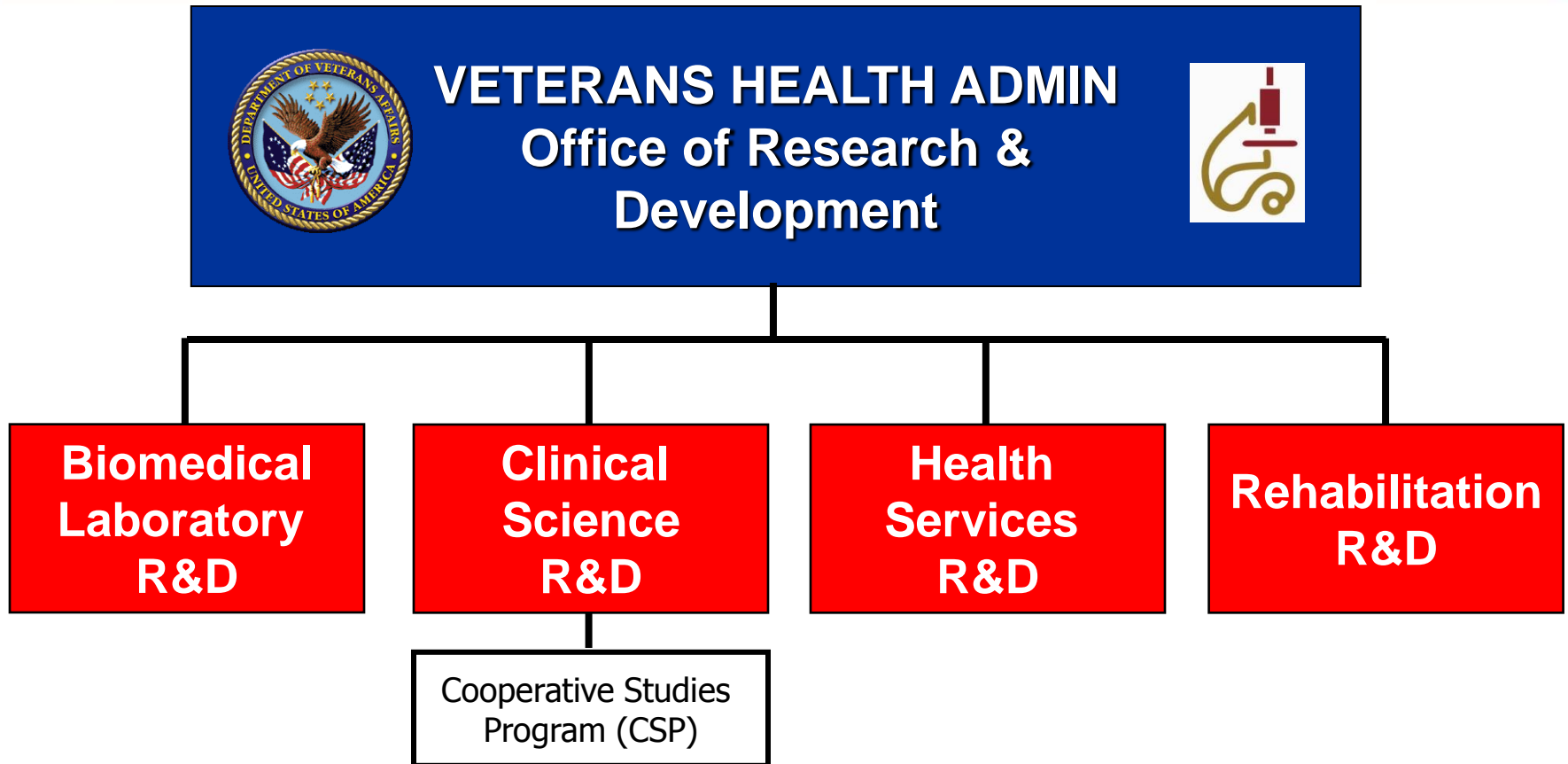
To be the premier research organization leading our Nation's efforts to enhance the health and well-being of Veterans by developing evidence-based clinical care and delivery systems improvements

http://vaww.va.gov/VHAOPP/POPlans/ORD_StrategicPlan2012.pdf

Nationwide VA Intramural Research Program Office of Research and Development

- **116 VAMCs have capacity for research**
 - **More than 90 are funded by VA at any time**
- **More than 2,400 Office of Research and Development (ORD)-funded projects**
- **Community of more than 3,000 VA researchers with a long history of significant research**
- **Broad, extensive research portfolio that balances the needs of all Veterans**

Office of Research and Development Organizational Chart



Gulf War Research – Requests for Applications (RFAs)

Biomedical Laboratory Research & Development (BLR&D):

BX-16-011

Award for Research on Gulf War Veterans' Illnesses (GWVI)

BX-16-012

Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)

Clinical Science Research & Development (CSR&D):

CX-16-011

Award for Research on Gulf War Veterans' Illnesses (GWVI)

CX-16-012

Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)

CX-16-013

Award for Research on Treatments for Gulf War Veterans' Illnesses (GWVI) – (clinical trial)

Health Services Research & Development (HSR&D):

HX-16-012

Targeted Solicitation for Service-Directed Research Award on Health Services Research on the Care of Gulf War Veterans

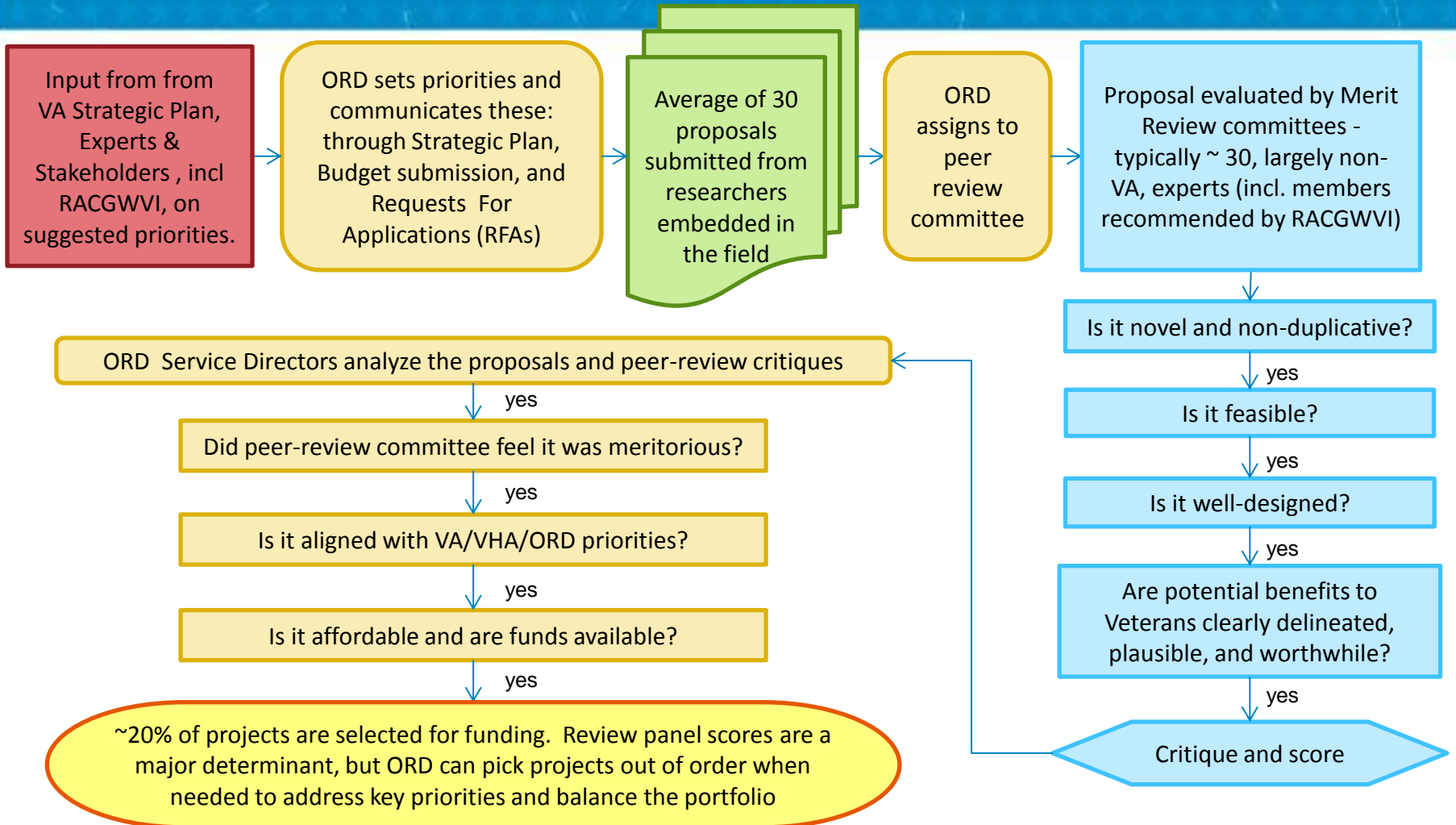
VA Office of Research and Development

- **VA research is driven by improving health care for all Veterans**
 - **Investigator-initiated research (Clinician Researchers)**
 - Pilot projects
 - Merit review
 - Clinical Trials
 - Career Development Awards
 - **Service-directed research**
 - **Cooperative Studies Program (CSP)**
- **Public Access to Information about VA/ORD funded research**
 - <http://clinicaltrials.gov> Information on current and past clinical trials
 - <http://projectreporter.nih.gov/> Information on current and previously funded research projects
 - <http://www.ncbi.nlm.nih.gov/pubmed> Published results of research studies
 - <http://www.rehab.research.va.gov/jour/jourindx.html> Official Journal of ORD

VA Office of Research and Development Application Process

- The clinicians and researchers who treat and interact with ill Gulf War Veterans seeking care in VA Hospitals and Medical Centers are the best and most qualified individuals to propose the research that might be most beneficial to ill Gulf War Veterans.
- ORD invites VA intramural researchers to submit proposals for Gulf War research using the mechanism of “Requests for Applications” (RFAs).
- Since 2011, these RFAs have been issued by ORD twice per year on a consistent basis.
- VA/ORD has a specific Merit Review Panel, with expertise in Gulf War issues, to insure high quality, independent, and unbiased reviews of Gulf War research proposals submitted to ORD.

How ORD selects GWVI projects for funding



VA/ORD-Based FACA Committees (Federal Advisory Committee Act)

- **National Research Advisory Council (NRAC)**
 - To provide advice to the Under Secretary for Health and the Secretary of Veterans Affairs on research and development sponsored and/or conducted by the Veterans Health Administration, to include policies and programs of the Research and Development Office
- **Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI)**
 - To provide advice and make recommendations to the Secretary of Veterans Affairs on proposed research plans and strategies related to understanding and treating the health consequences of military service in the Southwest Asia theater of operations during the 1990 - 1991 Gulf War
 - Mandated by Congress in 1998; first chartered in January, 2002
- **Genomic Medicine Program Advisory Committee (GMPAC)**
 - To provide advice to the Secretary on the scientific and ethical issues related to the establishment, development, and operation of the Program in order to further VA's medical research in providing Veterans with Medical care and treatment.

VA/ORD Gulf War Research Strategic Plan (2013-2107)

- **Process to develop Plan began in January, 2011**
- **Submitted for concurrence within VA in August, 2012**
- **Internal VA approval in February, 2013**
- **Public release by VA in May, 2013**
- <http://www.research.va.gov/resources/pubs/docs/GWResearch-StrategicPlan.pdf>
- **Subject to future updates as needed (2015 Update)**
- <http://www.research.va.gov/pubs/docs/GWResearch-StrategicPlan.pdf>
- **Plan is comprehensive, with particular emphasis on Treatments and Diagnosis**

VA/ORD Gulf War Research Strategic Plan (2013-2107)

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VA/ORD Gulf War Research Strategic Plan (2013-2107)

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VA/ORD Gulf War Research Strategic Plan (2013-2107)

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- 5.4 Genetics/Genomics/Systems Biology
 - etc.

Gulf War Research Strategic Plan (2013-2017)

Eight Focus Areas

(<http://www.research.va.gov/pubs/docs/GWResearch-StrategicPlan.pdf>)

- **5.1 Symptomatic and Specific Treatments**
- **5.2 Databases and Continued Surveillance**
- **5.3 Establish an Evidence-Based Case Definition of Chronic Multisymptom Illness in Gulf War Veterans**
- **5.4 Genetics, Genomics, and Systems Biology**
- **5.5 Biomarkers**
- **5.6 Animal Models**
- **5.7 Improve Coordination and Communication**
- **5.8 Translate Research Findings into Practice**

VA/ORD Gulf War Research Strategic Plan (2013-2107)

5.1.2 IOM Recommendations (Treatments)

The IOM recommended that “future studies funded and conducted by the Department of Veterans Affairs to assess treatments for chronic multisymptom illness should adhere to the methodologic and reporting guidelines for clinical trials, including appropriate elements (problem– patient–population, intervention, comparison, and outcome of interest) to frame the research question, extended follow-up, active comparators (such as standard-of-care therapies), and consistent, standardized, validated instruments for measuring outcomes.” [6, p. 191]

Additionally, “the Department of Veterans Affairs should fund and conduct studies of interventions that evidence suggests may hold promise for treatment of chronic multisymptom illness. Specific interventions could include biofeedback, acupuncture, St. John’s wort, aerobic exercise, motivational interviewing, and multimodal therapies.” [6, p. 191]

VA/ORD Gulf War Research Strategic Plan (2013-2107)

5.1.3 RACGWVI Recommendations (Treatments)

“The Committee believes that the first priority of federal Gulf War illness research must be the identification of effective treatments to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures.” [20, p. 77]

The RACGWVI recommended pursuit of treatment approaches based on known mechanistic pathways of Gulf War illness, which could also lead to significant breakthroughs in the treatment of other exposure-related occupational health problems.

Although the perfect animal model of Gulf War illness has not yet been developed, the RACGWVI recommended preclinical animal models be used to develop and test new treatments focused on pathobiological mechanisms of Gulf War illness and the effects of Gulf War theater exposures.

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Additional recommendations from the RACGWVI include:

- Use of Center- and consortium based treatment research efforts to capitalize on multi-disciplinary expertise and multi-pronged approaches to treatment targets and pre-clinical trials.
- Support, through the VA Cooperative Studies Program, for confirmation validation of safety and efficacy from initial Phase I/II trials conducted by the DoD CDMRP.
- Publication of data on effective treatments from VA's 2005 longitudinal survey.
- Reconducting the IOM review of treatments by Gulf War Veterans' medical practitioners ordered by Congress in 2010 (Public Law 111-275, 2010, Section 805)
- Ensure that VA annual reports to Congress on Gulf War illness research funded by VA include only studies and treatment trials in which the health of Gulf War Veterans is the central focus and the study participants are primarily Gulf War Veterans.

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5.5.3 RACGWVI Recommendations (Biomarkers)

Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they clarify the physiological basis of the disorder and may help to determine treatment targets for Gulf War illness and other health problems in Gulf War veterans. The RACGWVI recommended that VA research in this area include the following elements:

- Objective markers of exposure should be utilized whenever possible. These include environmental sampling and modeling of conditions in theater.
- Identification of biomarkers of exposure and downstream effects of exposures since the war that are present years after the exposure occurred have strong potential for understanding the physiological effects of Gulf War theater exposures and the relationship of these exposures to Gulf War illness. Applicable methods might include genomic, genetic, epigenetic, proteomic, lipidomic and metabolomic assays to explore suspected physiological effects and to identify novel, unsuspected pathways of illness.

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5.5.3 RACGWVI Recommendations (continued; Biomarkers)

- Research and statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposures as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection, and other environmental stressors. [20, p. 56]

Research on the pathobiological underpinnings of Gulf War illness and ill health in Gulf War veterans should continue to focus on the central and autonomic nervous systems and on immunological and neuroendocrine outcomes. RACGWVI recommended that:

- Clear, operationalized case definitions are needed. Findings may differ in differing patient populations, either defined with different Gulf War illness criteria or experiencing different health problems. For example, non-veteran

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5.5.3 RACGWVI Recommendations (continued; Biomarkers)

patients with multisymptom illnesses like chronic fatigue syndrome or fibromyalgia may show different patterns of immunological or neurological function than veterans who have Gulf War illness and meet criteria for these disorders.

- Gulf War theater exposures, age, and other variables likely moderate pathobiological effects and should be carefully addressed in research.
- Gender should be considered whenever possible in mechanistic and treatment research on Gulf War illness.
- Since the pathobiological mechanisms underlying Gulf War illness are poorly understood, exploratory probes such as genomics, metabolomics, lipidomics, and proteomics may yield useful information that can lead to more focused research.
- Epigenetic and genetic approaches to research on Gulf War illness pathobiology are likely also to be informative.

VA/ORD Gulf War Research Strategic Plan (2013-2107)

5.5.3 RACGWVI Recommendations (continued; Biomarkers)

- In order to effectively pursue “omics” and genetic research, standardized sample collections in research that uses biological specimens can expedite exploratory and hypothesis-driven research. Standard protocols for sample collections should be established and followed.
- Increased emphasis should be placed on the study of alterations in regulatory dynamics both within and across the principal regulatory axes, including the endocrine, immune and nervous systems. These should include response to standardized challenges at different time scales, i.e., acute response to exercise, circadian rhythm, and monthly cycles as well as long-term illness progression. Analysis should be integrative and deployed across these interacting systems whenever possible using methodologies that formally acknowledge regulatory control.
- Animal models may be appropriate to investigate mechanistic hypotheses and illness or exposure effects. [20, p. 71]

VA-ORD Gulf War Research Funding (2007 – 2016)

Fiscal Year (FY)	VA Merit Review	UTSW Contract	FY Total
2007	\$ 7.06 M	\$ 15.00 M	\$ 22.06 M
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*	\$ 14 M		\$ 14 M
Total 2007-2016	\$ 90.75 M	\$ 39.29 M	\$ 130.04 M

* Estimated

Response Statistics for VA-ORD Gulf War Research Requests for Applications (RFAs)

	Proposals Received	Projects Funded	Funds Approved
Spring/Fall 2011	26	3	\$ 4.0 M
Spring/Fall 2012	32	7	\$ 11.4 M
Spring/Fall 2013	35	7	\$ 12.6 M
Spring/Fall 2014	40	5	\$ 7.5 M
Spring/Fall 2015	33	8	\$ 13.2 M
Spring 2016	11	1	\$ 0.3 M
Fall 2016	Sep 2016	Dec 2016	

Gulf War Research Projects Active in 2015-2016 (slide 1 of 3)

Treatments/Clinical Trials

- Impact of exercise training on pain and brain function in Gulf War Veterans (5.1)
- Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in GWVI (5.1)
- Complementary Neurosteroid Intervention in Gulf War Veterans' Illnesses (5.1)
- Cognitive Rehabilitation Therapy for Gulf War Veterans (5.1)
- Complementary and Alternative Medicine in Veterans with Gulf War Illnesses (5.1)
- RCT of Duloxetine and Pregabalin for the treatment of GWI in Veterans (5.1)
- Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness (5.1)

Gulf War Research Projects Active in 2015-2016 (slide 2 of 3)

Biomarkers/Mechanisms

- Diagnostic Utility of mtDNA Content and Exercise Challenge in Vets with GWI (5.1, 5.4)
- Examination of Cognitive Fatigue in Gulf War Illness Using fMRI (5.5)
- Longitudinal assessment of Gulf War veterans with suspected Sarin exposure (5.4, 5.5)
- Multimodal Biological Assessment of Gulf War Illness (5.5)
- National Health Survey of Persian Gulf Veterans and their Families (5.2)
- Somatic hypersensitivity in Veterans with IBS (5.1)
- Vascular and Skeletal Muscle Function in Gulf War Veterans Illness (5.1, 5.4)
- Women vs. Men with GWI: Differences in Computational Models and Therapeutic Targets (5.1, 5.4)
- Genomics of Gulf War Illness in Veterans (5.4)

Gulf War Research Projects Active in 2015-2016 (slide 3 of 3)

Model Systems

- Central Mechanisms Modulating Visceral Sensitivity (5.4, 5.6)
- Immunoregulation of Myelin Specific T Lymphocytes (5.4, 5.6)
- Neuroprotection and Myelin Repair Mechanisms in Multiple Sclerosis (5.4, 5.6)
- Sleep Neurobiology and Circuitry (5.4, 5.6)
- Prevention of Hippocampal Neurodegeneration Due to Age and Apnea (5.6)
- Epigenetic Mechanisms Relevant to the Pathogenesis of ALS (5.4, 5.6)
- Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans (5.1, 5.6)
- Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF (5.5, 5.6)
- Memory and Mood Enhancing Therapies for Gulf War Illness (5.1, 5.6)
- Identification of Plasma Biomarkers of Gulf War Illness Using "omic" Technology (5.5, 5.6)
- Gulf War Exposures and the Molecular Mechanisms of Paternal Reproductive Risk (5.6)
- Novel neurotrophic therapies in an optimized mouse model of GWVI (5.1, 5.6)
- Neuroinflammation, Oxidative Stress, and Hippocampal Defects in GWI (5.5, 5.6)
- Immune Basis for Hippocampal Cholinergic Deficits in Pyridostigmine-treated Rats (5.6)

Gulf War Research Projects Selected for funding

- Models of Care for Gulf War Veterans (5.1)
- Exercise and Autonomic Dysfunction (5.1, 5.5)
- Translational Approaches to Treating Gulf War Illness (5.1, 5.8)
- Healthcare Utilization Patterns for Gulf War Era Veterans (5.1)
- Gulf War Toxicants and Neurological dysfunction (5.6)
- Integrative Medicine for Gulf War Veterans (5.1)
- Treatments for Sleep Disorders in Gulf War Veterans (5.1)
- Gastrointestinal Pain in Gulf War Veterans (5.5, 5.8)
- Aging as a Risk Factor for GWI (5.1, 5.4, 5.6)

Recently Completed Gulf War Research Projects

- Autonomic Functions of Gulf War Veterans with Unexplained Illnesses (5.1, 5.4)
- Motor Neuron Function of Gulf War Veterans with Excessive Fatigue (5.1, 5.4, 5.5)
- Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans (5.1)
- Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP (5.1)
- Behavior of Neural Stem Cells in a Rat Model of GWS (5.6)
- Multiple Sclerosis in Gulf War Veterans (5.3)
- A Randomized Controlled Trial of a Mindfulness-Based Intervention for Gulf War Syndrome (5.1)
- Bacterial Overgrowth Associated with Chronic Multi-Symptom Illness Complex (5.1)
- Multiple Antigenic Peptides to Alter the Course of Autoimmune Disease (5.4, 5.6)
- Host Defense Mechanisms in Polyaromatic Hydrocarbon Carcinogenesis (5.5, 5.6)
- MEG Synchronous Neural Interactions (SNI) in Gulf War Veterans (5.5)
- rTMS for the Treatment of Chronic Pain in GW1 Veterans (5.1)

Gulf War Research Biorepositories

- **Gulf War Veterans' Illnesses Biorepository (5.2, 5.4, 5.5)**
 - Began operations – July, 2012
 - Enrolling Veterans to obtain medical records
 - Brain and spinal cord tissue to be collected post-mortem
 - Review of pilot project in November, 2014
 - http://www.research.va.gov/programs/tissue_banking/gwvib/default.cfm
- **CSP #585 Gulf War Era Cohort and Biorepository (5.2, 5.4, 5.5)**
 - Deployed and non-deployed Veterans
 - Users of VA health care and non-users
 - Surveys and blood collection
 - September, 2014 – May 2016: enrolled 1276 participants
 - <http://www.research.va.gov/programs/csp/585/default.cfm>

CSP 585: Gulf War Era Cohort and Biorepository Update

- **Phase 1 of the pilot ended May 2, 2016 (1276 participants)**
- **Repository data request process is being finalized**
- **Cohort maintenance begins early Fall 2016**
- **Phase 2 – qualitative analysis of Phase 1**
 - Up to 12 focus groups and 30 telephone interviews with Veterans
 - Up to 20 interviews with subject matter experts
 - Recruitment for focus groups and SMEs has begun
 - First focus group will take place tomorrow at the SF VAMC (12 Veterans)
 - Tuesday, August 9, 2016; 2:00 – 4:00pm
 - HR Training Room, Building 7, Room 218
 - Share your thoughts about research projects
 - Speak to MaryBeth Grewe or Kristina Felder

Gulf War Research Activities Institute of Medicine (IOM) Reports

Recent IOM project

- **Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War**
 - **Sep 9, 2014 – Mar 16, 2016; IOM briefing, Feb 10, 2016**
 - **Updated previous IOM studies (Volumes 4 and 8)**
 - **Emphasis on:**
 - **Neurological disorders**
 - **Cancer (especially brain cancer and lung cancer)**
 - **Chronic multisymptom illness**
 - **Listening Sessions (Apr 29; Jun 9)**
 - **RAC teleconference (Jun 25) & letter to Secretary of Veterans Affairs**

Gulf War Research – VA-DoD Coordination

- **Regular briefings/updates between Gulf War Program Managers in VA/ORD and DoD/CDMRP**
- **Periodic review of proposals submitted/funded between agencies**
- **Annual Report to Congress (jointly with DoD)**
 - <http://www.research.va.gov/pubs/GulfWarRpt14.cfm>
- **Joint VA/DoD Working Groups (Deployment Health and Medical)**

Gulf War Research Activities

QUESTIONS ?