VA-ORD GULF WAR RESEARCH : Research Program Overview

Presented to:
National Gulf War Resource Center
Annual Meeting & Informational Health Fair

VHA OFFICE OF RESEARCH AND DEVELOPMENT / Victor Kalasinsky, PhD
September 30, 2016
Arlington, VA
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
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 Funding (2007 – 2016)

<table>
<thead>
<tr>
<th>Fiscal Year (FY)</th>
<th>VA Merit Review</th>
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<td><strong>Total 2007-2016</strong></td>
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Response Statistics for VA-ORD Gulf War Research Requests for Applications (RFAs)

<table>
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<tr>
<th>Period</th>
<th>Proposals Received</th>
<th>Projects Funded</th>
<th>Funds Approved</th>
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<td>Spring 2016 Fall 2016</td>
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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)
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)
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 Competed 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)
Research Advisory Committee on Gulf War Veterans’ Illnesses
San Francisco, August 8-9, 2016

• Tony Wyss-Coray, PhD; Professor of Neurology, Stanford School of Medicine
  ➢ https://med.stanford.edu/profiles/tony-wyss-coray
  ➢ “Blood Proteins as Indicators and Modifiers of Brain Function”

• Sergio E. Baranzini, PhD; Professor of Neurology, UCSF
  ➢ http://baranzinilab.ucsf.edu/
  ➢ “Microbiome: The Gut-Brain Axis, or Neuro-gastroenterology”

• Joe DeRisi, PhD; Professor of Biochemistry and Biophysics, UCSF
  ➢ http://profiles.ucsf.edu/joe.derisi
  ➢ “Pathogen Detection”

• Adam Gazzaley, MD, PhD; Professor of Neurology, Physiology, and Psychiatry, UCSF
  ➢ http://gazzaleylab.ucsf.edu/
  ➢ http://www.nature.com/news/gaming-improves-multitasking-skills-1.13674
  ➢ “Neuromodulation: Video Games meet Neuroscience – The Vision of the Future of Brain Optimization”
Tony Wyss-Coray, PhD
Professor of Neurology, Stanford

Focus Areas
• Age-related diseases; Cognitive Aging
• Neurologic diseases
• Protein biomarkers
• Parabiosis
Genes, Environment, and Aging affect Brain Health

- headache
- sickness feeling
- negative affect
- memory impairment
- neuroinflammation

increased memory and learning function
positive outlook
neurogenesis

A “cold”

physical exercise

Dr. Tony Wyss-Coray, Stanford
Dr. Tony Wyss-Coray, Stanford
“Parabiosis”
Dr. Tony Wyss-Coray, Stanford

- 295 blood samples
- > 100 proteins
- 9 are most significant
Prediction of “Biological Age” using top aging factors in human

r = 0.81
p = < 2.2E x 10^{-16}
Effects of “Rejuvenation” using Parabiosis

- Increased neurogenesis
- Increased synaptic activity
- Increased plasticity-related gene expression
- Increased spine density
- Improved memory and cognition
- Reduce inflammation

Same Effects using Injected Plasma
Application to Alzheimer’s Disease

• **Mouse Model**
  - Amyloid Precursor Protein (APP) – mouse model
  - Injections of “young” plasma improved learning, memory, behavior

• **Human Test**
  - ClinicalTrials.gov - #NCT02256306
  - One unit of “young” plasma per week
  - Molecular tests, cognitive abilities, daily activities (from caregivers)
Plasma Studies in humans (underway or planned)

- Alzheimer’s disease
- Progressive supranuclear palsy
- Parkinson’s disease
- Amyotrophic lateral sclerosis
- Depression
• Circulatory factors from mouse or human blood can modulate aspects of brain aging and cognitive function

• Individual proteins which replicate some of these effects can be identified and used as therapeutic agents or, possibly, as biomarkers.
Sergio E. Baranzini, PhD
Professor of Neurology, UCSF

Focus Areas
• Microbiome of the gut
• Effects of microbiome on the immune system
• Applications to diseases
• Interrelation of the enteric nervous system and central nervous system
Definitions:

- **Microbiota**: A collection of microbial communities living in a specific niche
- **Microbiome**: The collective set of genes from a given microbiota
- **Probiotic bacteria**: Live microorganisms which when administered in adequate amounts confer a health benefit on the host
- **Prebiotics**: Selectively fermented food ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confer benefits upon host health
- **Enteric Nervous System**: Mesh-like system of neurons that controls the gastrointestinal system
Microbiome Characteristics:

- Composition of human gut microbiota: $10^{13} – 10^{14}$ microorganisms
- Collective microbiome is 100 to 150 times the human genome
- Microorganisms in the gut affect immune responses through the interaction of their metabolism with that of humans

Microbiome:

- Varies with anatomical location of human body, but metabolic pathways remain constant
- Varies with ethnicity
- Correlates with diet
Examples of Research Studies

- Microbiota and Obesity
- Microbiota and Cancer Therapy
- Normal Gut Microbiota modulates brain development and behavior
- Lactobacillus modulates emotional behavior via vagus nerve
- Microbiota and Autism
- Microbiota and Immune System
Effect of Gut Microbiota in Autoimmune Demyelination

- Cells cultured with gut bacteria from multiple sclerosis (MS) patients show reduced immune response (58 patients)
- Experimental Autoimmune Encephalomyelitis (EAE) induces brain inflammation & demyelination in mice (model for Multiple Sclerosis)
- Mice fed MS bacteria show higher EAE scores
- DNA of individual microorganisms is being sequenced to identify those found in MS patients
- Testing MS-associated bacteria in mice
- The International MS Microbiome Study
Joseph DeRisi, PhD
Professor of Biochemistry and Biophysics, UCSF

Focus Areas
- Identify disease-causing microorganisms by analyzing DNA or RNA
- Small amount of DNA/RNA from microorganisms in a large amount of human DNA (“needle in a haystack”)
- Develop techniques isolate DNA/RNA from microorganisms
- Variety of specimens (blood, tissue, cerebrospinal fluid (CSF), intraocular fluid)
Examples of Microorganisms Detected/Diagnosed:

- Herpes Simplex 1 (HSV-1)
- Rubella virus
- West Nile virus (renal transplant)
- Malaria (Plasmodium falciparum)
- Amoeba (Balamuthia mandrillaris)
- Fungus (Cryptococcus neoformans)
- Tapeworm (Taenia solium)
- Protozoan (Toxoplasma gondii)
Focus Areas

- Enhance cognitive abilities in healthy patients or those with neurological diseases
- Educational – help young minds develop
- Improve how the brain functions
- Improve neuroplasticity (the brain’s ability to modify itself)
Treating Neurological Problems:
• Targeted
• Personalized
• Multimodal
• Closed-loop

Using Consumer-Level Information Technology:
• Virtual Reality
• Augmented Reality
• Wearable Physiological Devices
• 3-D Video Games Engines
• Artificial Intelligence
• Motion Capture
Neuroracer (Dr. Gazzaley, UCSF)
Neuroracer (Dr. Gazzaley, UCSF)

EEG

Nature, 2013 (Sep 5); 501(7465):18
http://www.nature.com/news/gaming-improves-multitasking-skills-1.13674
Couple the Video Games with:

- EEG (electroencephalogram) topology plots
- MRI (magnetic resonance imaging)
- Cognitive testing
- Blood tests
  (inflammatory markers, hormones, proteins, etc.)
• **New Video Games**
  - **Meditrain** - Concentrated meditation with feedback to learn how to control internal distractions
  - **Rhythmicity** - Using the rhythm of music to help the rhythms of the brain to improve cognitive function
  - **Virtual Attention** - Learning to focus and broaden one’s attention over space and time
  - **Body-Brain Trainer** - Combines cognitive and physical feedback to modify the game to keep your heart rate in an optimum range

• **Enhance the Effects of Video Games**
  - Neuromodulation
  - Neurofeedback
Research Over the Next Ten Years
(Dr. Gazzaley, UCSF)

- PTSD – (in conjunction with VA)
- Traumatic Brain Injury
- Alzheimer’s Disease
- Parkinson’s Disease
- Multiple Sclerosis
- Attention Deficit Disorder
- Anxiety Disorder
- Schizophrenia
- Depression
- Addiction
- Autism
Websites of Interest
Gulf War Research

- [http://clinicaltrials.gov](http://clinicaltrials.gov) Information on current and past clinical treatment trials
- [http://www.publichealth.va.gov/](http://www.publichealth.va.gov/) VA’s Post-Deployment Health Service website
- [http://www.va.gov/rac-gwvi/](http://www.va.gov/rac-gwvi/) Research Advisory Committee on Gulf War Veterans’ Illnesses
Gulf War Research Activities

QUESTIONS?