CDMRP

Department of Defense

# Gulf War Illness Research Program





*U.S. Army Medical Research and Materiel Command*

PROTECT · PROJECT · SUSTAIN

## Congressionally Directed Medical Research Programs

### HISTORY

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. The CDMRP has grown to encompass multiple targeted programs and has received over $8.22 billion in appropriations from its inception through fiscal year 2015 (FY15). In response to demonstrated need, targeted funds for the CDMRP are added to the Department of Defense (DoD) budget each year with specific guidance from Congress. These funds are in addition to what the president has laid out for the DoD and, since they are congressionally mandated, cannot be further shaped. Through FY15, nearly 12,000 awards have been made across 25 individual programs. Under the auspices of the U.S. Army Medical Research and Materiel Command (USAMRMC), the CDMRP executes and manages these programs from receipt of funds to competitive selection of applications, through individual project performance to project closeout.

# Gulf War Illness Research Program

## VISION

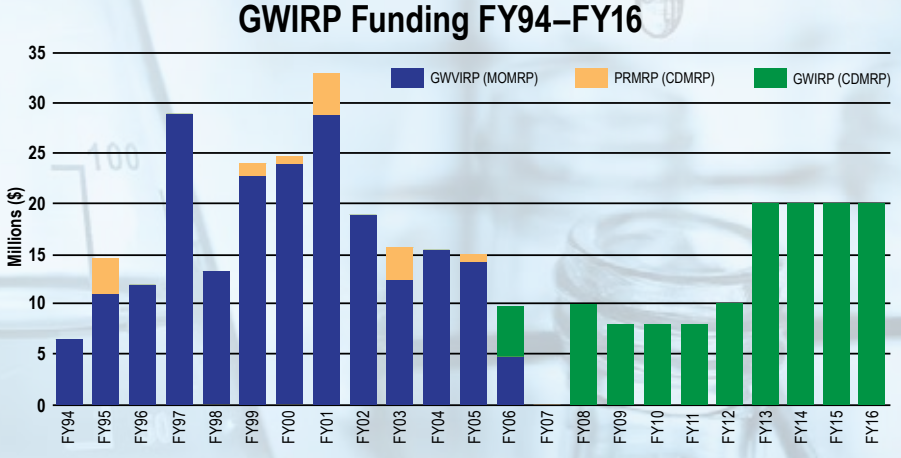
Improve the health and lives of Veterans who have Gulf War Illness

## MISSION

Fund innovative Gulf War Illness research to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms

## ABOUT THE PROGRAM

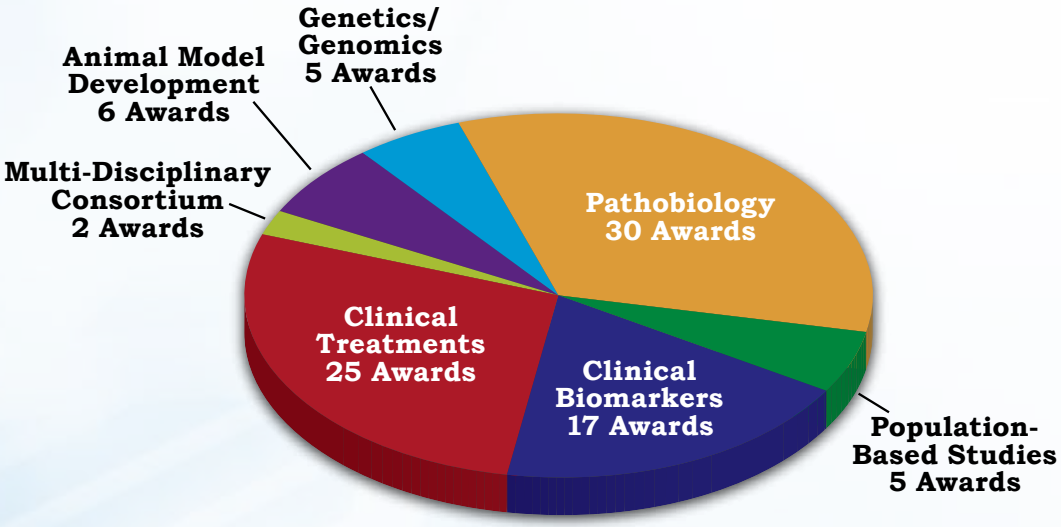
DoD-funded Gulf War Illness (GWI) research began in 1994 with the establishment of the Gulf War Veterans' Illnesses Research Program (GWVIRP) to study the health effects of Service members deployed in the 1990–1991 Persian Gulf War. From FY94 to FY05, the GWVIRP was managed by the USAMRMC Military Operational Medicine Research Program (MOMRP). Research pertaining to GWI also was funded intermittently through the CDMRP's Peer Reviewed Medical Research Program, which supports selected military health-related research topics each fiscal year. The MOMRP shared management responsibility for the GWVIRP with the CDMRP in FY06, with separate $5 million (M) appropriations. Although the GWVIRP did not receive funding in FY07, a $10M appropriation renewed the program in FY08, renamed the Gulf War Illness Research Program (GWIRP), to be managed fully by the CDMRP. Since that time, the GWIRP has been funded by an $8M appropriation each year from FY09 through FY11, $10M in FY12, and $20M in FY13, FY14, FY15, and FY16. The program continues to support innovative, competitively peer-reviewed research to develop treatments addressing the complex symptoms that comprise GWI and its underlying causes, to identify objective markers (biomarkers) improving its diagnosis, and to better understand the pathobiology underlying GWI.



# Moving GWI Research Forward

The program has built a broad research portfolio of over 90 awards featuring clinical trials and basic research as well as studies addressing chemical exposures and GWI symptomatology. The GWIRP continues to challenge the scientific community to design high-impact research that will improve the health and lives of Veterans who have GWI.

## GWIRP-Funded Portfolio by Research Topic, FY06–FY14




**GWIRP investments have resulted in treatment and alternative therapy successes including:**

- **Coenzyme Q10 (CoQ10)** – Found to reduce pain, fatigue, and cognitive symptoms in Veterans with GWI
- **Carnosine** – Found to reduce cognitive symptoms in Veterans with GWI (but not to impact their pain, fatigue, or other outcomes)
- **Acupuncture** – Shown to improve GWI symptoms, including pain, fatigue, sleep quality, and cognitive symptoms
- **Nasal irrigation (saline or Xylitol)** – Early results show improvement of sinus and fatigue symptoms
- **Mind-body bridging** – Shown to be an effective intervention in the management of disturbed sleep

## GWIRP Award Mechanisms

# Application Review Process

**FY16 PROGRAMMATIC PANEL:**

**Anthony Hardie,** former Staff Sergeant U.S. Army (Chair), Florida Veterans for Common Sense

**Roberta F. White, Ph.D.,** (Chair Emeritus), Boston University School of Public Health

**Fiona Crawford, Ph.D.,** Roskamp Institute

**Daniel Havlichek, M.D.,** Michigan State University

**Mark Lyles, D.M.D., Ph.D.,** University of Rhode Island

**Carlos Maldonado, Ph.D.,** U.S. Department of Veterans Affairs

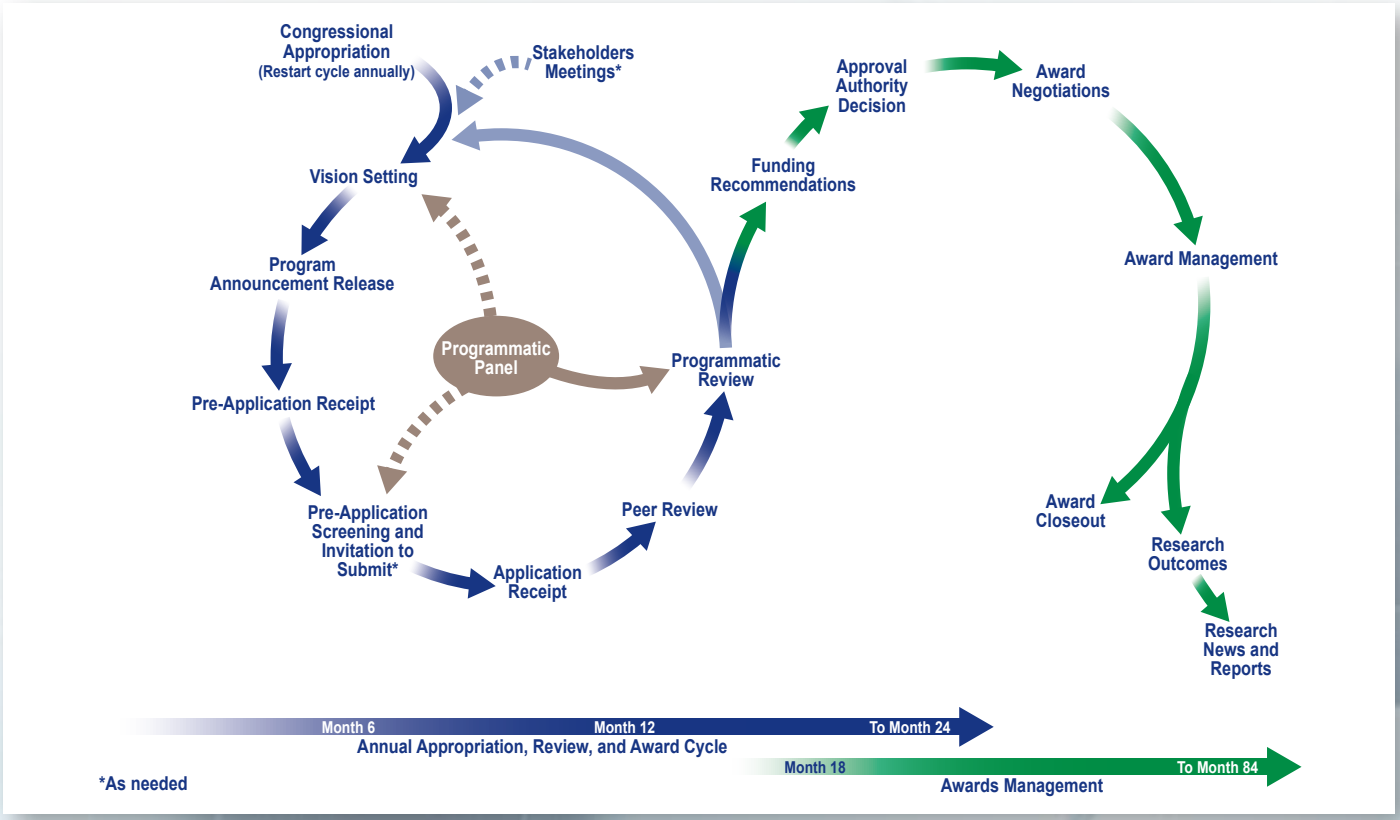
**K. Jeffrey Myers, M.D.,** U.S. Department of Veterans Affairs

**Marni Silverman, Ph.D.,** Henry M. Jackson Foundation for the Uniformed Services University of the Health Sciences

**Andrea White, Ph.D.,** University of Utah

**David K. Winnett, Jr.,** Captain USMC Retired, Veterans for Common Sense

The CDMRP uses a two-tier review process for application evaluation, which is critical to ensuring that each of the research program portfolios reflects not only the most meritorious science, but also the research that best meets the program vision and mission. The first tier of evaluation is a scientific peer review of applications measured against established criteria to determine scientific merit. The second tier is a programmatic review, conducted by a Programmatic Panel composed of leading scientists, clinicians, and GW Veterans with GWI. In this tier of review, the Programmatic Panel compares the applications to each other and makes recommendations for funding based on scientific merit as determined in peer review, potential impact, relevance to program goals, and portfolio composition. The Commanding General of the USAMRMC issues the final approval for funding prior to award negotiations and execution.



# Consumer Advocates and Scientists Working Together

The two-tier review process established by the CDMRP brings together the expertise of scientists with the perspective and experience of "consumers," the GW Veterans themselves. This innovative approach, recommended by the National Academy of Sciences' Institute of Medicine, and adopted by other funding organizations, has proven to be an effective way to evaluate research applications for their potential to meet the program's goals for those we seek to serve.

As peer reviewers, consumers evaluate applications for scientific and technical merit as well as the potential successful impact of the research. As Programmatic Panel members, consumers make programmatic recommendations for the GWIRP's vision, investment strategies, and funding selections intended to reflect the needs of the Veteran and research communities.

"With the understanding that quality research and development is a slow painstaking process and that 25 years is a long time for Veterans to wait for answers, I am excited that Gulf War Illness research is moving towards more human subjects studies with practical applications. I have a deep respect for the entire CDMRP team and the fact that Consumer Reviewers are treated as equal partners. Overall, my experience has given me a renewed respect for the scientific process."

***Vera Roddy, Veterans of Foreign Wars, Department of Wisconsin***

"The CDMRP Gulf War Illness Research Program is an extraordinary model for identifying treatments for exposure-related conditions like Gulf War illness. I'm deeply impressed by the quality of the Gulf War illness treatment research proposals we review, and by the engagement, commitment, and passion of the scientists, medical doctors, staff, and consumer reviewers involved with this program. As an affected Gulf War Veteran, I have found my optimism and hopefulness for the future dramatically increased by seeing everything that's coming through this program, and have already gotten some relief from one of the treatments found to be helpful in one of the program's pilot studies. I encourage all my fellow Gulf War Veterans to participate in these research studies, because what's found to help you may help all of us!

***Anthony Hardie, Consumer Reviewer, Programmatic Panel, GWIRP (FY06-FY16); Chair, Programmatic Panel, FY15-16***

"With the recent passing of the 25-year anniversary of the 1991 Persian Gulf War, there remain quite a number of unanswered questions as to why so many of the warriors who participated in that operation are still seriously ill, most likely the result of highly toxic compounds known to have been present within the theater of operations. When compared to the meticulous strategic planning involved in achieving that historic battlefield victory, it now seems very clear that Gulf War Illness is a foe much more evasive and tenacious than the Iraqi military forces we handily defeated in 1991. But thanks to annual funding allocated to the CDMRP Gulf War Illness Research Program, we have recruited legions of the world's finest medical and scientific minds to serve at the tip of the research spear — scientific warriors who are now locked in a fierce battle with this perplexing disease, every last one of whom is committed to nothing less than the complete unconditional surrender of Gulf War Illness in the very near future. Being a part of this very noble endeavor has been one of the most rewarding experiences of my life."

***David K. Winnett, Jr., Captain, USMC (Ret.), Programmatic Review Panelist***

# Establishment of Animal Models

## Neuroinflammatory Pathobiology in Gulf War Illness: Characterization with an Animal Model

**Dr. Stephen Lasley, Ph.D. (pictured top), University of Illinois College of Medicine at Peoria**
**Dr. James O'Callaghan, Ph.D., Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health**

In most illnesses, the inflammatory response and associated sickness behavior are a result of injury or infection, and these usually subside and resolve over time. However, Veterans suffering from GWI have persistent symptoms long after exposure, suggesting that they are suffering from a heightened or chronic neuroinflammatory reaction of unknown etiology. Drs. Stephen Lasley and James O'Callaghan hypothesized that the conditions and exposures that cause chronic neuroinflammation may play a role in the symptoms exhibited by Veterans suffering from GWI. Therefore, experiments were performed using mice to determine if there was a persistent neuroinflammatory pathobiology associated with GWI. Mice were exposed to the acetylcholinesterase inhibitor diisopropyl fluorophosphate (DFP) to mimic nerve agent exposures that may have been experienced by troops in the GW, and to the stress hormone, corticosterone (CORT), to mimic the high physiological stress of the war theater. They found that exposure to a single dose of DFP caused neuroinflammation. Instead of reducing the initial neuroinflammatory response to DFP, they found that prior exposure to CORT "primed" the immune system of DFP-treated animals to mount an exaggerated response. This was unexpected because CORT is known to be immunosuppressive and anti-inflammatory. Taken together, these observations led to the creation of a murine neuroinflammation model of GWI based on combined exposure to physiological stress and a nerve agent. In this mouse model, the non-steroidal anti-inflammatory drug, minocycline, suppressed many of the neuroinflammatory effects, suggesting that anti-inflammatory treatment may be a promising and effective intervention for Veterans suffering from GWI.

## Proteomic Immune Profiling for the Therapeutic Modulation of Cognitive Impairment in a Novel GWI Mouse Model

**Dr. Ghania Ait-Ghezala, Roskamp Institute**

Dr. Ghania Ait-Ghezala hypothesized that combined administration of the GW agents pyridostigmine bromide (PB) and permethrin (PER) will disrupt cross-talk between the central nervous system and the peripheral cholinergic anti-inflammatory pathway. To test her hypothesis, Dr. Ait-Ghezala used a well-characterized mouse model of GW agent exposure and examined tissues for peripheral and central nervous system inflammatory markers at early and late time-points after acute exposure to GW agents. She found that compared to mice that were not exposed to GW chemicals, mice that were exposed to PB+PER had chronic central nervous system inflammation as evidenced by a profound increase in astrogliosis. In addition, mice that were exposed to GW agents had reduced neurogenesis and signs of mitochondrial dysfunction. Taken together, Dr. Ait-Ghezala's data suggest that neuroinflammation and mitochondrial function are important targets to consider

when developing therapeutic intervention for GWI. Currently, she is attempting to clarify the mechanisms behind the pathobiologies she observed in the GW mice in order to pinpoint molecular targets for therapeutic intervention. Her future plans include investigating whether Anatabine, a highly innovative novel treatment that directly targets neuroinflammation, is effective in treating the chronic symptoms including pain, fatigue, and cognitive problems in ill GW Veterans.

## The Role of Protein Radicals in Chronic Neuroimmune Dysfunction and Neuropathology in Response to a Multiple-Hit Model of Gulf War Exposures

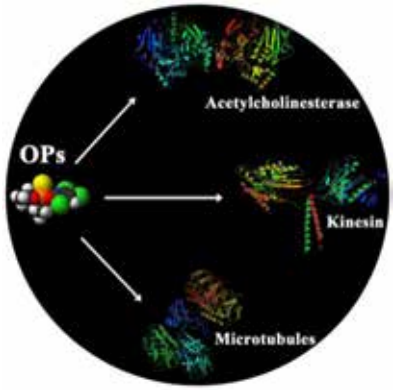
### Dr. Michelle Block, Indiana University School of Medicine

Chronic peripheral inflammation and neuroinflammation have been linked to GWI, but the underlying mechanisms are unknown. In order to elucidate the underlying mechanisms, Dr. Michelle Block is using a "Multiple-Hit" mouse model of GWI-like exposures to study NF-κB p50 in the brain. NF-κB is a redox-sensitive, prototypical pro-inflammatory transcription factor family associated with inflammation-mediated central nervous system pathology. Dr. Block's preliminary results suggest that the hippocampus in NF-κB p50-/- mice is more vulnerable to chronic neuroinflammation at one week after pro-inflammatory insult. Dr. Block and her team also found that the organophosphate (OP) pesticide chlorpyrifos impairs NF-κB p50 function in microglia, suggesting that chlorpyrifos may predispose the hippocampus to chronic neuroinflammation. Currently, Dr. Block is exploring the potential utility of the NF-κB p50 protein radical as an early peripheral biomarker of chronic, delayed, and deleterious central nervous system effects. Dr. Block's long-term goal is to develop new therapeutic avenues for treatment of the brain inflammation component of GWI.

## Organophosphate-Related Alterations in Myelin and Axonal Transport in the Living Mammalian Brain

### Dr. Alvin Terry, Georgia Health Sciences University

Among potential contributing factors to GWI, exposures to OP-based compounds are commonly implicated. OPs are known to attach to the active site acetylcholinesterase, a key protein in nerve signal transmission. In addition to acetylcholinesterase, OPs have been shown to bind proteins essential to axonal transport, a basic and necessary nerve cell process. Dr. Alvin Terry hypothesized that the attachment of OPs to motor proteins following exposure might impede axonal transport and produce neural dysfunction. Using manganese-enhanced magnetic resonance imaging to monitor axonal transport, Dr. Terry found impaired axonal transport in the brains of living rats after treatment with chlorpyrifos, a well-known OP insecticide. Interestingly, the inhibition of transport was evident even 30 days after the OP dosing had ceased. These results indicate repeated exposures to the pesticide chlorpyrifos, at doses below those associated with acute toxicity, can result in persistent alterations in axonal transport. Currently, Dr. Terry is investigating another OP called DFP, with a chemical structure similar to the nerve agent sarin, for effects on axonal transport. Taken together, given the fundamental importance of axonal transport to neuronal function, Dr. Terry's results may help explain some of the long-term neurological effects associated with repeated OP exposure.



# Emerging GWI Pathobiology

## Role of microRNAs in the Pathobiology of Gulf War Illness: Identification of Potential Novel Therapeutic Targets

**Dr. Lisa Pierce, Tripler Army Medical Center**

Dr. Lisa Pierce used an established rat model of GWI to examine short-term and long-term effects of GW-relevant chemical exposures and stress on neuroinflammation and altered microRNA (miRNA) expression in the central nervous system. miRNAs are a recently discovered, highly conserved, important class of small (~22 nucleotide), non-protein-coding RNAs that regulate transcription, messenger RNA stability, and protein expression levels of target genes. Dr. Pierce's most significant finding thus far has been the persistent increase in the expression of a specific miRNA, miR-124, in the hippocampus of GWI rats. Dr. Pierce believes in vivo inhibition of miR-124 function in the hippocampus could be a promising and novel therapeutic approach to improve cognition, emotion regulation, and neuroendocrine dysfunction in GWI. Dr. Pierce has received continued funding in an FY15 GWIRP Investigator-Initiated Research Award to further her research on the therapeutic potential of miR-124 inhibition in treating GWI.

## Restoring the Brain's Lipid Homeostasis as a Therapeutic Avenue for Treating the CNS Symptoms of Gulf War Illness

**Dr. Laila Abdullah, Roskamp Institute**

Evidence suggests that immune and metabolic disturbances are key components of GWI. Lipid metabolism can influence immune responses and metabolic pathways, and pesticides, to which GW veterans were exposed, can alter the expression of nuclear receptors that regulate lipid metabolism. Therefore, Dr. Laila Abdullah is targeting lipid metabolism to identify novel therapies for GWI. In the first year of this project, she developed assays to evaluate lipid changes in her established mouse model of PB and PER (GW agent) exposure, and to monitor the effectiveness of therapies for restoring lipid profiles in GW agent-exposed mice. Preliminary studies showed that GW agent-exposed mice had low brain cardiolipin, a signature mitochondrial phospholipid that is required for electron transport and oxidative phosphorylation. She also observed low omega-3 fatty acids in the brains of exposed mice at a chronic time-point. Her preliminary work showed that short-term treatment with a natural lipid restored the brain phospholipid profile and reduced astroglia activation in exposed mice. Dr. Abdullah is now determining if long-term treatment with such therapies can reduce chronic symptoms and pathologies of GWI in her mouse model. The ultimate goal is to identify translatable therapies for treating GWI.

## Gulf War Illness: Assessment of Bioenergetics in Brain and Muscle

### Dr. Beatrice Golomb, University of California, San Diego

Cell energy impairments are known to produce symptoms profiles consistent with those observed in GWI patients such as fatigue, cognitive issues, muscle problems, gastrointestinal issues, and breathing symptoms. Therefore, Dr. Beatrice Golomb hypothesizes that mechanisms that affect cell energy may also play an important role in GWI. If she is correct, and similar mechanisms are involved, GWI patients could potentially benefit from the therapeutics used to currently treat patients with cell energy impairments. To test her hypothesis, Dr. Golomb will assess whether defects are present in the cell energy of ill GW Veterans and determine whether impaired cell energy correlates to symptoms and function in the corresponding organ. Cell energy will be assessed in 20 GW Veterans with GWI and 20 unaffected matched controls by a noninvasive magnetic resonance approach, termed 31phosphorus magnetic resonance spectroscopy (31P-MRS). 31P-MRS measures phosphorus-containing substances like ATP and phosphocreatine, a backup energy source that is depleted (drops) with exercise. When cell energy is inadequate, recovery of phosphocreatine after exercise is slowed. This study has potential to provide a noninvasive objective approach to aid diagnosis of GWI and offer new treatment options for those suffering from GWI, both of which would greatly enhance the lives of those living with GWI.

# Preclinical Studies
## (Treatments in the Pipeline)

## Monosodium Luminol for Improving Brain Function in Gulf War Illness

### Dr. Ashok Shetty, Texas A&M College of Medicine

Dr. Ashok Shetty is undertaking a study to ascertain the efficacy of a potent anti-inflammatory and antioxidant drug, monosodium luminol-GVT (MSL-GVT, Bach Pharma), for easing cognitive dysfunction and depressive-like behavior in a rat model of GWI. Recently, drugs capable of suppressing oxidative stress and inflammation and/or increasing neurogenesis have received attention in the GWI research community for their potential to alleviate cognitive and mood impairments in Veterans suffering from GWI. Dr. Shetty hypothesizes that oral administration of an optimal dose of MSL-GVT may alleviate both cognitive dysfunction and depression associated with GWI via suppression of inflammation and oxidative stress, and increased neurogenesis in the hippocampus. The data collected thus far suggest that administration of higher doses of MSL-GVT to GWI-rats improved their memory and mood function, decreased the concentration of malondialdehyde (a byproduct of oxidative stress), and normalized expression of oxidative stress responsive genes. These results suggest that cognitive impairment could be reversed through oral administration of relatively higher doses of MSL-GVT in GWI rats. Dr. Shetty's future plans include determining whether oral administration of an apt dose of MSL-GVT for prolonged periods is efficient for alleviating memory and mood dysfunction in GWI rats.

## Novel Therapeutic Approaches for the Treatment of Depression and Cognitive Deficits in a Rodent Model of Gulf War Veterans' Illness

### Dr. Laxmikant Deshpande, Virginia Commonwealth University

Dr. Laxmikant Deshpande used various (repeated low-dose to single high-dose) exposures to OP DFP over a 1- to 10-day period to approximate levels of sarin exposures during the Persian Gulf War. DFP-exposed rats were assessed for neurological impairments at 3 months post-exposure. Rats that were exposed to DFP exhibited symptoms of chronic depression, anxiety, and memory problems as characterized by increased immobility in the Forced Swim Test, anhedonia in the Sucrose Preference Test, anxiety in the Elevated Plus Maze, and spatial and recognition memory impairments in the Object Location/ Recognition Test. Rats that were exposed to DFP experienced neuronal damage in the following regions – hippocampus, piriform cortex, amygdala, and thalamus – the same brain areas that have been reported to be compromised in GW Veterans in clinical, functional, and imaging studies. Taken together, these results are among the first evidence that nerve agent exposure, in the absence of other confounding factors such as stress, pyridostigmine tablets, or other insecticides, can produce neurological morbidities similar to GWI. The Principal Investigator's future plans include deciphering molecular mechanisms with particular emphasis on the role of intracellular calcium dynamics underlying the neuronal damage and neurological deficits in the DFP-exposed rats. Further, his plans also include addressing chronic/latent effects of exposure to GWI compounds with the inclusion of a 1-year assessment end point, and to study the effects of calcium-lowering drugs in an attempt to develop effective therapeutics that target the neurological abnormalities in his rat model.

# Clinical Studies

**(Results from the Clinic)**

## Trial of Naltrexone and Dextromethorphan for Gulf War Veterans' Illness

### Dr. William Meggs, East Carolina University

It has long been suspected that GWI is related to low-grade neuron-inflammation, which led Dr. William Meggs to suspect that symptoms of GWI could be managed therapeutically with anti-inflammatory drugs. In order to test his hypothesis, Dr. Meggs has enrolled 49 subjects in randomized double-blinded study for treating ill GW Veterans with the anti-inflammatory drugs naltrexone and dextromethorphan. Research at the National Institute of Environmental Health and other facilities has proven that naltrexone and dextromethorphan reduce inflammation in the brain. Clinical trials in humans with low-dose naltrexone have established benefits in syndromes related to GWI such as fibromyalgia. Dr. Meggs hopes that his clinical trial will demonstrate the effectiveness of naltrexone and dextromethorphan in improving symptoms of GW Veterans. The clinical outcomes he plans to measure are global clinical impression scale, SF-36 evaluation, Connors Continuous Performance Test, and symptoms scores using visual analogue scales. Currently, Dr. Meggs has identified a sub-group of GW Veterans that are responders to treatment with naltrexone, and he will soon be reporting the results.

## Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness

### Dr. David Rabago, University of Wisconsin, Madison

Veterans afflicted with GWI commonly suffer from chronic upper respiratory symptoms, particularly nasal congestion. In response to this common complaint among GWI patients, Dr. David Rabago has designed a 26-week, three-arm randomized controlled trial to study whether nasal irrigation with xylitol or saline is effective in the treatment of chronic rhinosinusitis and fatigue symptoms in GWI patients. In this study, nasal irrigation using a neti-pot bathes the nasal cavity with either solution.

Dr. Rabago hypothesizes that routine care in addition to either form of nasal irrigation is more effective than routine care alone for sinus symptoms and fatigue. The primary outcome measurement, sinus symptom-related quality of life, is being measured using the Sino-Nasal Outcome Test (SNOT-20), a recommended tool for clinical trial research involving chronic sinus symptoms. Based on preliminary SNOT-20 scores, nasal irrigation with saline appears to be the more promising of the irrigation interventions.

This study is also designed to investigate the mechanism of action of nasal irrigation through the assessment of inflammatory serum and nasal mucosa biomarkers. Dr. Rabago hypothesized that inflammatory processes may contribute to the development and perpetuation of initially infectious illness and to resultant generalized fatigue; data collected will inform this hypothesis.

## Use of a Portable Stimulator to Treat GWI

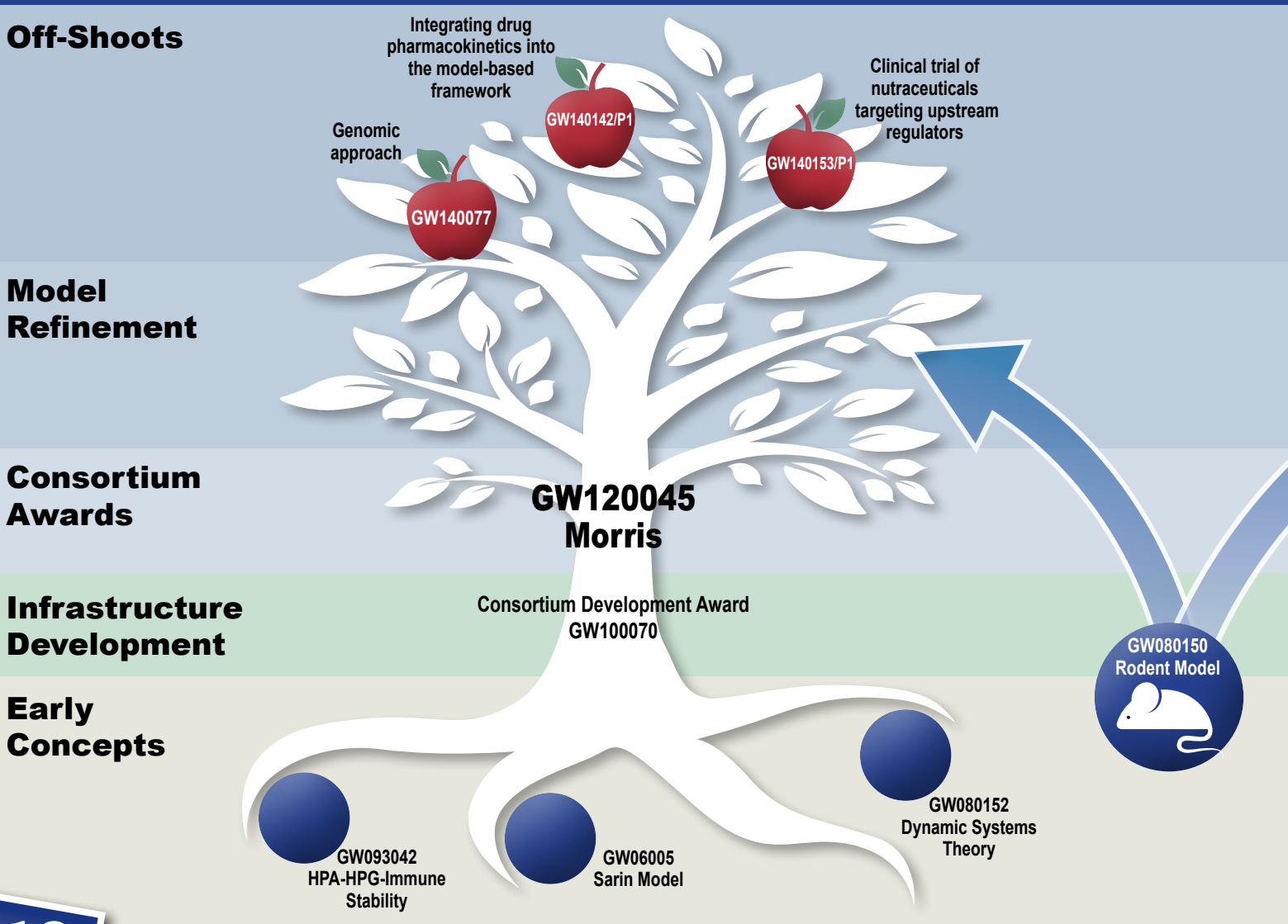
### Dr. Jorge Serrador, Veterans Biomedical Research Institute, Inc.

GW Veterans regularly report symptoms of nausea and dizziness, both of which are associated with vestibular (balance system) damage. In order to help GW Veterans suffering with dizziness and/or balance dysfunction, Dr. Jorge Serrador has designed double-blind, cross-over, sham-controlled trials of subsensory electrical stimulation in order to improve vestibular function in GW Veterans suffering from GWI. The proposed stimulator is portable and is similar to a hearing aid that can be worn behind the ear. Dr. Serrador plans to address three different aims over the next two years: (1) determine the level of vestibular dysfunction in a group of Veterans with GWI, (2) determine the ability of subsensory electrical stimulation to improve balance function in the laboratory, and (3) determine if enhancement of vestibular function using stochastic stimulation will result in long-term effects. If subsensory galvanic stimulation is found to be of benefit in this population, the application of a portable stimulator for home use may improve accessibility to treatment and decrease cost of services through reduced need for repeated appointments with clinicians.

# FY12 Consortium Awards

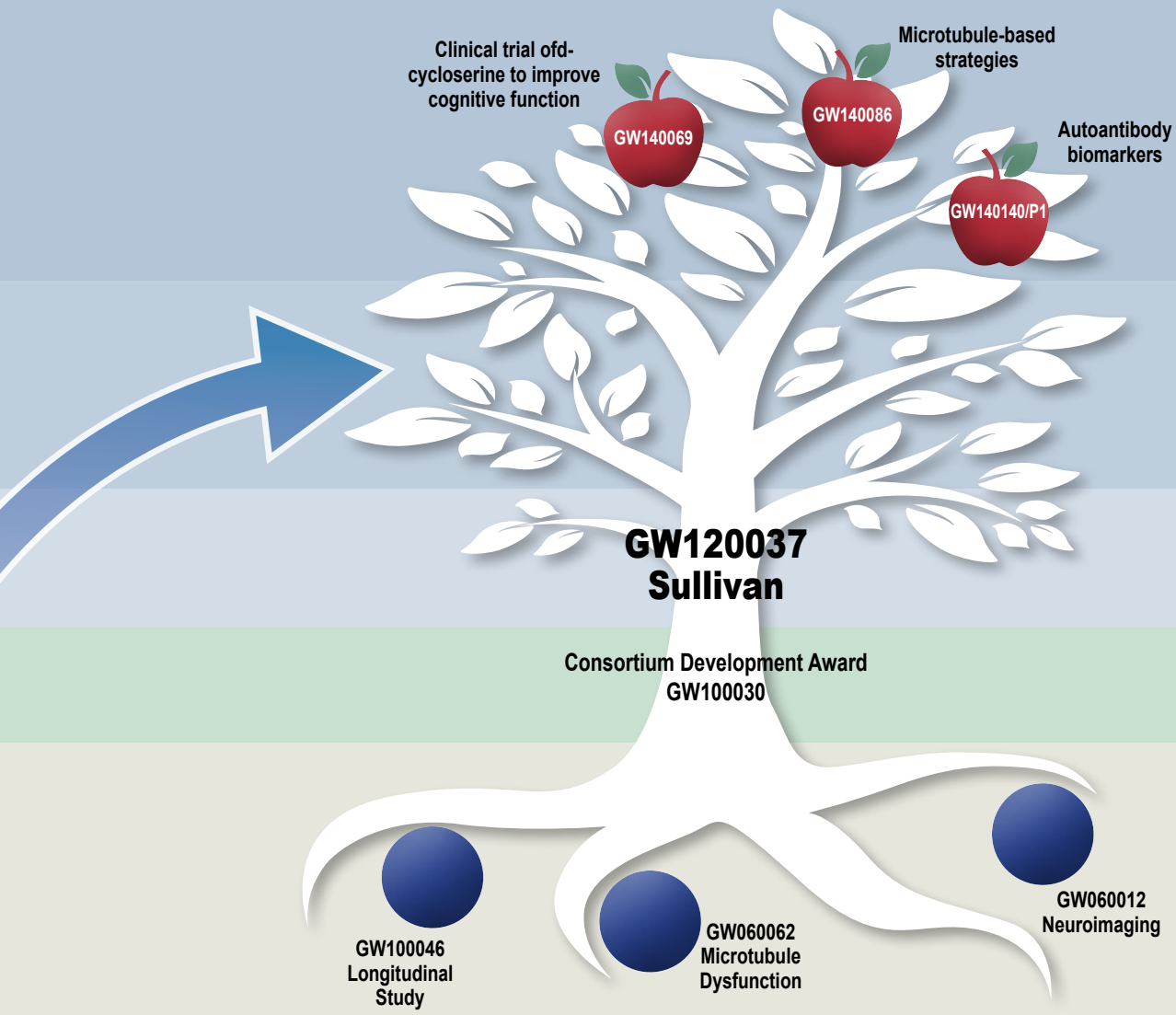
**The FY12 GWIRP Consortium Awards are intended to support major multi-institutional research efforts, conducted by leading GWI investigators, focused on overarching challenges in GWI.**

***Understanding Gulf War Illness: An Integrative Modeling Approach*** **(GW120045) establishes a consortium aimed at developing translational models of GWI that integrate basic and clinical research through computational modeling. The consortium is led by PI Mariana Morris, Ph.D., at Nova Southeastern University. To date, early model-based optimization has predicted two-phase delivery of an anti-inflammatory intervention followed by a glucocorticoid receptor blockade may deliver the highest probability of remission under idealized conditions. Work is ongoing to increase model fidelity.**



To ensure standard practices and the translation of results, these consortia are sharing resources and actively collaborating. Both teams are making use of a common rodent model of OP-induced neuronal inflammation initially developed in a preceding CDMRP award to Drs. Lasley and O'Callaghan. Investigators from both consortia have successfully obtained funding to expand various lines of research initiated under the consortia.

***The Gulf War Illness Consortium*** **(GW120037) brings together established GWI researchers to investigate the pathobiological mechanisms responsible for symptoms as they relate to brain-immune interactions. Boston University serves as the coordinating center for the consortium, which is led by Dr. Kimberly Sullivan. Findings to date include a new and important mechanism related to myelination and remodeling of the node of Ranvier that provides insight into mechanisms of white matter damage in GWI, a potential biomarker, and possible treatment using drugs that are currently approved for vascular disorders.**



# Expansion of Successful Research

Starting in FY14, the GWIRP instituted the Investigator-Initiated Research Expansion Award to support continued investigation and further development of high-impact research ideas that were previously investigated under GWIRP Investigator-Initiated Research Awards.

### Dr. Kimberly Sullivan, Boston University & Dr. Mohamed Abou-Donia, Duke University

***Original***: Showed that neurotoxicant exposures were strongly associated with the symptoms of GWI and specific CNS damage. (GW060012)

***Follow-on***: Will attempt to correlate these findings with plasma proteins. (GW140140)

### Dr. Gordon Broderick, Nova Southeastern University & Dr. Darrell Whitley, Colorado State University

***Original***: Constructed computer models to simulate stable but abnormal regulation in GWI and Chronic Fatigue Syndrome. Completed some comparisons with human data. (GW093042)

***Follow-on***: Will expand the computer model and use simulation to identify potential real-world treatments. (GW140142)

### Dr. Beatrice Golomb, University of California at San Diego

***Original***: Uncovered evidence of oxidative stress and impaired mitochondrial function in GWI; pilot-tested coenzyme Q10 as a remedy. (GW060036, GW093063)

***Follow-on***: Will test a complex, bioenergetic-boosting cocktail in a clinical trial. (GW140146)

### Dr. Nancy Klimas, South Florida Veterans Affairs Foundation & Dr. Richard Deth, Nova Southwestern University

***Original***: Mapped exercise stress in GWI using physiological measures and blood-borne biomarkers. Predicted that down-regulation of NF-κB bring the GWI network back to a more normal state. (GW080152)

***Follow-on***: Phase I/II study to compare two nutraceuticals known to down-regulate NF-kB. Repeat the dynamic modeling to assess the fidelity of the model. (GW140153)

### Dr. Robert Haley, Dr. Edward Wakeland, University of Southwest Texas Medical Center at Dallas

***Original***: Found three distinct phenotypic variants of GWI with supporting evidence from imaging. (GW100073)

***Follow-on***: Attempt to create a diagnostic tool by correlating gene expression with phenotype. (GW140158)

### Dr. Anne Louise Oaklander, Massachusetts General Hospital & Dr. Jorge Serrador, Veterans Biomedical Research Institute

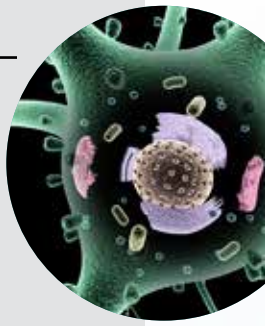
***Original***: Found significant frequency of early-onset small-fiber polyneuropathy (eoSFPN) in Veterans with GWI. (GW093049)

***Follow-on***: Will develop technologies for eoSFPN screening and diagnosis. (GW140169)

# New Investigator Awards

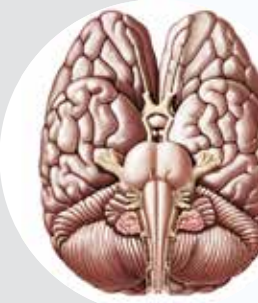
The GWIRP views recruitment of new investigators with fresh ideas and exciting new research techniques as an important means of furthering research into GWI. The New Investigator Award mechanism is structured to fund both newly-independent investigators at the start of their careers and established investigators who are new to the field of GWI research.

### Microtubule Abnormalities Underlying Gulf War Illness in Neurons from Human-Induced Pluripotent Cells, *Dr. Peter Baas, Drexel University*



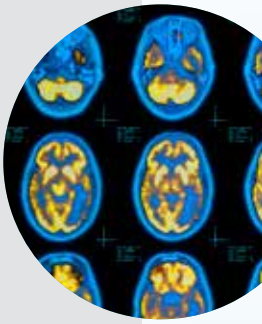
Microtubules are structures within neurons that handle the transport of proteins and organelles up and down the long axis of the neuron. Dr. Peter Baas hypothesizes that toxic exposure of neurons and/or neuroinflammatory cells during the GW caused long-lasting microtubule defects in neurons. He will develop new immortal lines of pluripotent cells derived from the blood of GW Veterans themselves, and differentiate neurons and glial cells from these so that microtubule defects can be assessed in them as a test of his hypothesis. Moreover, these cells will provide a resource for further investigations of nerve cell abnormalities in GW Veterans.

### Vagus Nerve Stimulation as a Treatment Strategy for Gulf War Illness, *Dr. Lee Shapiro, Texas A&M University System Health Science Center*



The vagus nerve is the tenth cranial nerve. It regulates the autonomic nervous system and mediates cholinergic pathways that function to modulate the inflammatory response and ultimately to preserve homeostasis. These are precisely the systems that appear to be affected in GWI, so Dr. Lee Shapiro hypothesizes that stimulation of the vagus nerve will reverse GWI symptomology. He will test this theory by seeing if either short- or long-term vagus nerve stimulation will reverse cognitive, behavioral, pain sensitivity, and pathobiological deficits in a mouse model of GWI.

### Biomarkers and Brain Mechanisms of Gulf War Illness, *Dr. Dikoma Shungu, Cornell University, Weill Medical College*



Popular hypotheses explaining GWI include neuroinflammation, oxidative stress, and mitochondrial dysfunction. Dr. Dikoma Shungu will attempt to measure these effects directly in the central nervous systems of Veterans with GWI by Magnetic Resonance Imaging and positron emission imaging techniques to measure the levels of several markers of neuroinflammation, oxidative stress, and mitochondrial dysfunction, including the peripheral benzodiazepine receptor. In addition, some of these markers will be assayed directly in cerebral spinal fluid.

### Preclinical Treatment of an Organophosphate Model of Gulf War Illness, *Dr. Haley Speed, University of Texas Southwestern Medical Center at Dallas*

In previous work, Dr. Haley Speed has observed a delayed decrease in synaptic strength and synaptic spine density in the hippocampus in a mouse model of GWI, and she believes treatment with the FDA-approved neurotrophic factor IGF-1 might help reverse these effects. Dr. Speed will conduct a preclinical efficacy trial in a mouse model to determine the effectiveness of IGF-1 in reversing the morphological changes and loss of synaptic strength.

## Ongoing GWIRP Therapeutic Evaluations

Many treatments and alternative therapies are currently being investigated in the clinic. In addition to making an impact on finding treatments for GWI, these investigations are establishing cohorts of GW Veterans which are valuable resources for future investigations.

- Dr. Vernon Lin, Cleveland Clinic Foundation – Acupressure
- Dr. Peter Bayley, Palo Alto Institute for Research and Education – Yoga for chronic pain
- Dr. Ashok Tuteja, Western Institute for Biomedical Research – FODMAP + diet for irritable bowel syndrome symptoms
- Dr. Benjamin Natelson, Beth Israel Deaconess Medical Center – Vagus nerve stimulation device
- Dr. Julia Golier, Bronx Veterans Medical Research Foundation – Intranasal insulin
- Dr. Jarred Younger, University of Alabama at Birmingham – Botanical anti-inflammatories
- Dr. Jon Kaiser, KPAX Pharmaceuticals – Methylphenidate+nutraceuticals for cognitive deficits
- Dr. Giulio Pasinetti, Mount Sinai School of Medicine – Dietary polyphenols for fatigue and cognitive function
- Dr. Ronald Bach, Minnesota Veterans Medical Research and Education Foundation – Prednisone (anti-inflammatory)
- Dr. Rosemary Toomey, University of Minnesota at the Twin Cities – D-cycloserine
- Dr. Fiona Crawford, Roskamp Institute – Anatabine (anti-inflammatory)
- Dr. Beatrice Golomb, University of California at San Diego – Mitochondrial/antioxidant cocktail
- Dr. Nancy Klimas, South Florida Veterans Affairs Foundation for Research and Education – Liposomal glutathione and curcumin

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