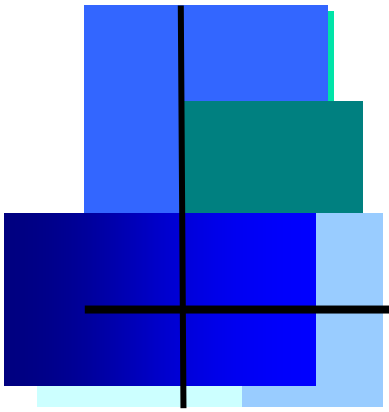
DEPARTMENT OF VETERANS AFFAIRS

ANNUAL SUMMARY

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2016



Annual Summary
FY 2016

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2016

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magnetoencephalography (MEG) scan to assess the strength of brain synchronicity by computing zero-lag crosscorrelations (and their Fisher z transforms) between prewhitened MEG time series. A high-resolution HLA genotyping determined the number of copies, k, of the 6 protective alleles above in each participant. We tested the hypothesis above by regressing NCM, Pain and Fatigue symptom severity against the interaction term, k × z (HLA-related effect), while including z (non-HLA-related effect), gender and age as covariates. The k × z and z terms assessed HLA- and non-HLA-related effects, respectively, of neural synchronicity on symptom severity. The distributions of these effects in sensor space were visualized using statistical heatmaps. Findings: We found significant, graded HLA- and non-HLA-related effects: (a) NCM > Pain > Fatigue for HLA-related effects, (b) NCM > Fatigue > Pain for non-HLA-related effects, and (c) HLA-related > non-HLA-related effects for all symptoms. These effects had widespread but distinct distributions in sensor space that allowed the orderly separation of the 6 terms (3 symptom domains × 2 HLA factors) in a multidimensional plot, where one dimension separated the symptoms and the other the HLA relation. Interpretation: These findings demonstrate the presence of substantial, widespread, distinct and orderly HLA- and non-HLA-related neural influences on NCM, Pain and Fatigue symptom severity in GWI.

Johnson GJ, Slater BC, Leis LA, Rector TS, Bach RR. Blood Biomarkers of Chronic Inflammation in Gulf War Illness. PLoS One. 2016 Jun 28;11(6):e0157855. doi: 10.1371/journal.pone.0157855. eCollection 2016.

BACKGROUND: More than twenty years following the end of the 1990-1991 Gulf War it is estimated that approximately 300,000 veterans of this conflict suffer from an unexplained chronic, multi-system disorder known as Gulf War Illness (GWI). The etiology of GWI may be exposure to chemical toxins, but it remains only partially defined, and its case definition is based only on symptoms. Objective criteria for the diagnosis of GWI are urgently needed for diagnosis and therapeutic research. OBJECTIVE: This study was designed to determine if blood biomarkers could provide objective criteria to assist diagnosis of GWI. DESIGN: A surveillance study of 85 Gulf War Veteran volunteers identified from the Department of Veterans Affairs Minnesota Gulf War registry was performed. All subjects were deployed to the Gulf War. Fifty seven subjects had GWI defined by CDC criteria, and 28 did not have symptomatic criteria for a diagnosis of GWI. Statistical analyses were performed on peripheral blood counts and assays of 61 plasma proteins using the Mann-Whitney rank sum test to compare biomarker distributions and stepwise logistic regression to formulate a diagnostic model. RESULTS: Lymphocyte, monocyte, neutrophil, and platelet counts were higher in GWI subjects. Six serum proteins associated with inflammation were significantly different in GWI subjects. A diagnostic model of three biomarkers-lymphocytes, monocytes, and C reactive protein-had a predicted probability of 90% (CI 76-90%) for diagnosing GWI when the probability of having GWI was above 70%. SIGNIFICANCE: The results of the current study indicate that inflammation is a component of the pathobiology of GWI. Analysis of the data resulted in a model utilizing three readily measurable biomarkers that appears to significantly augment the symptom-based case definition of GWI. These new observations are highly relevant to the diagnosis of GWI, and to therapeutic trials.

Kearney DJ, Simpson TL, Malte CA, Felleman B, Martinez ME, Hunt SC. Mindfulness-based Stress Reduction in Addition to Usual Care Is Associated with Improvements in Pain, Fatigue, and Cognitive Failures Among Veterans with Gulf War Illness. Am J Med. 2016 Feb;129(2):204-14. doi: 10.1016/j.amjmed.2015.09.015. Epub 2015 Oct 28.

BACKGROUND: Many Gulf War I veterans report ongoing negative health consequences. The constellation of pain, fatigue, and concentration/memory disturbances is referred to as "Gulf War illness." Prior research suggests that mindfulness-based stress reduction may be beneficial for these symptoms, but mindfulness-based stress reduction has not been studied for veterans with Gulf War illness. The objective of this trial was to conduct a pilot study of mindfulness-based stress reduction for veterans with Gulf War illness. METHODS: Veterans (N = 55) with Gulf War illness were randomly assigned to treatment as usual plus mindfulness-based stress reduction or treatment as usual only. Mindfulness-based stress reduction was delivered in 8 weekly 2.5-hour sessions plus a single 7-hour weekend session. Pain, fatigue, and cognitive failures were the primary outcomes, assessed at baseline, after mindfulness-based stress reduction, and 6 months follow-up. Secondary outcomes included symptoms of posttraumatic stress disorder and depression. RESULTS: In intention-to-treat analyses, at 6-month follow-up, veterans randomized to mindfulness-based stress reduction plus treatment as usual reported greater reductions in pain (f = 0.33; P = .049), fatigue (f = 0.32; P = .027), and cognitive failures (f = 0.40; P < .001). Depressive symptoms showed a greater decline after mindfulness-based stress reduction (f = 0.22; P = .050) and at 6 months (f = 0.27; P = .031) relative to treatment as usual only. Veterans with posttraumatic stress disorder at baseline randomized to mindfulness-based stress reduction plus treatment as usual experienced significantly greater reductions in symptoms of posttraumatic stress disorder after mindfulness-based stress reduction (f = 0.44; P = .005) but not at 6 months follow-up (f = 0.31; P = .082). CONCLUSIONS: Mindfulness-based stress reduction in addition to treatment as usual is associated with significant improvements in self-reported symptoms of Gulf War illness, including pain, fatigue, cognitive failures, and depression.

Landi A, Broadhurst D, Vernon SD, Tyrrell DL, Houghton M. Reductions in circulating levels of IL-16, IL-7 and VEGF-A in myalgic encephalomyelitis/chronic fatigue syndrome. Cytokine. 2016 Feb;78:27-36. doi: 10.1016/j.cyto.2015.11.018. Epub 2015 Nov 28.

Recently, differences in the levels of various chemokines and cytokines were reported in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) as compared with controls. Moreover, the analyte profile differed between chronic ME/CFS patients of long duration versus patients with disease of less than 3years. In the current study, we measured the plasma levels of 34 cytokines, chemokines and growth factors in 100 chronic ME/CFS patients of long duration and in 79 gender and age-matched controls. We observed highly significant reductions in the concentration of circulating interleukin (IL)-16, IL-7, and Vascular Endothelial Growth Factor A (VEGF-A) in ME/CFS patients. All three biomarkers were significantly correlated in a multivariate cluster analysis. In addition, we identified significant reductions in the concentrations of fractalkine (CX3CL1) and

monokine-induced-by-IFN-γ (MIG; CXCL9) along with increases in the concentrations of eotaxin 2 (CCL24) in ME/CFS patients. Our data recapitulates previous data from another USA ME/CFS cohort in which circulating levels of IL-7 were reduced. Also, a reduced level of VEGF-A was reported previously in sera of patients with Gulf War Illness as well as in cerebral spinal fluid samples from a different cohort of USA ME/CFS patients. To our knowledge, we are the first to test for levels of IL-16 in ME/CFS patients. In combination with previous data, our work suggests that the clustered reduction of IL-7, IL-16 and VEGF-A may have physiological relevance to ME/CFS disease. This profile is ME/CFS-specific since measurement of the same analytes present in chronic infectious and autoimmune liver diseases, where persistent fatigue is also a major symptom, failed to demonstrate the same changes. Further studies of other ME/CFS and overlapping disease cohorts are warranted in future.

Li SJ, Flaxman A, Lafta R, Galway L, Takaro TK, Burnham G, Hagopian A. A Novel Method for Verifying War Mortality while Estimating Iraqi Deaths for the Iran-Iraq War through Operation Desert Storm (1980-1993). PLoS One. 2016 Oct 21;11(10):e0164709. doi: 10.1371/journal.pone.0164709. eCollection 2016.

OBJECTIVES: We estimated war-related Iraqi mortality for the period 1980 through 1993. METHOD: To test our hypothesis that deaths reported by siblings (even dating back several decades) would correspond with war events, we compared sibling mortality reports with the frequency of independent news reports about violent historic events. We used data from a survey of 4,287 adults in 2000 Iraqi households conducted in 2011. Interviewees reported on the status of their 24,759 siblings. Death rates were applied to population estimates, 1980 to 1993. News report data came from the ProQuest New York Times database. RESULTS: About half of sibling-reported deaths across the study period were attributed to direct war-related injuries. The Iran-Iraq war led to nearly 200,000 adult deaths, and the 1990-1991 First Gulf War generated another approximately 40,000 deaths. Deaths during peace intervals before and after each war were significantly lower. We found a relationship between total sibling-reported deaths and the tally of war events across the period, p = 0.02. CONCLUSIONS: We report a novel method to verify the reliability of epidemiological (household survey) estimates of direct war-related injury mortality dating back several decades.

Maya S, Prakash T, Madhu KD, Goli D. Multifaceted effects of aluminium in neurodegenerative diseases: A review. Biomed Pharmacother. 2016 Oct;83:746-754. doi: 10.1016/j.biopha.2016.07.035. Epub 2016 Jul 29. Review.

Aluminium (Al) is the most common metal and widely distributed in our environment. Al was first isolated as an element in 1827, and its use began only after 1886. Al is widely used for industrial applications and consumer products. Apart from these it is also used in cooking utensils and in pharmacological agents, including antacids and antiperspirants from which the element usually enters into the human body. Evidence for the neurotoxicity of Al is described in various studies, but still the exact mechanism of Al toxicity is not known. However, the evidence suggests that the Al can potentiate oxidative stress and inflammatory events and finally leads to cell death. Al is considered as a well-established

neurotoxin and have a link between the exposure and development of neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease (AD), dementia, Gulf war syndrome and Parkinsonism. Here, we review the detailed possible pathogenesis of Al neurotoxicity. This review summarizes Al induced events likewise oxidative stress, cell mediated toxicity, apoptosis, inflammatory events in the brain, glutamate toxicity, effects on calcium homeostasis, gene expression and Al induced Neurofibrillary tangle (NFT) formation. Apart from these we also discussed animal models that are commonly used for Al induced neurotoxicity and neurodegeneration studies. These models help to find out a better way to treat and prevent the progression in Al induced neurodegenerative diseases.

McAndrew LM, Helmer DA, Phillips LA, Chandler HK, Ray K, Quigley KS. Iraq and Afghanistan Veterans report symptoms consistent with chronic multisymptom illness one year after deployment. J Rehabil Res Dev. 2016;53(1):59-70. doi: 10.1682/JRRD.2014.10.0255.

Many Veterans returning from service in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) experience chronic pain. What is not known is whether for some OIF/OEF Veterans this pain is part of a larger condition of diffuse multisystem symptoms consistent with chronic multisymptom illness (CMI). We use data from a prospective longitudinal study of OIF/OEF Veterans to determine the frequency of CMI. We found that 1 yr after deployment, 49.5% of OIF/OEF Veterans met criteria for mild to moderate CMI and 10.8% met criteria for severe CMI. Over 90% of Veterans with chronic pain met criteria for CMI. CMI was not completely accounted for either by posttraumatic stress disorder or by predeployment levels of physical symptoms. Veterans with symptoms consistent with CMI reported significantly worse physical health function than Veterans who did not report symptoms consistent with CMI. This study suggests that the presence of CMI should be considered in the evaluation of OIF/OEF Veterans. Further, it suggests the pain management for these Veterans may need to be tailored to take CMI into consideration.

Naeser MA, Martin PI, Ho MD, Krengel MH, Bogdanova Y, Knight JA, Yee MK, Zafonte R, Frazier J, Hamblin MR, Koo BB. Transcranial, Red/Near-Infrared Light-Emitting Diode Therapy to Improve Cognition in Chronic Traumatic Brain Injury. Photomed Laser Surg. 2016 Dec;34(12):610-626. doi: 10.1089/pho.2015.4037. Review.

We review the general topic of traumatic brain injury (TBI) and our research utilizing transcranial photobiomodulation (tPBM) to improve cognition in chronic TBI using red/near-infrared (NIR) light-emitting diodes (LEDs) to deliver light to the head. tPBM improves mitochondrial function increasing oxygen consumption, production of adenosine triphosphate (ATP), and improving cellular energy stores. Nitric oxide is released from the cells increasing regional blood flow in the brain. Review of published studies: In our previously published study, 11 chronic TBI patients with closed-head TBI caused by different accidents (motor vehicle accident, sports-related, improvised explosive device blast injury) and exhibiting long-lasting cognitive dysfunction received 18 outpatient treatments (Monday, Wednesday, Friday for 6 weeks) starting at 10 months to 8 years

post-TBI. LED therapy is nonthermal, painless, and noninvasive. An LED-based device classified as nonsignificant risk (FDA cleared) was used. Each LED cluster head (5.35 cm diameter, 500 mW, 22.2 mW/cm^2) was applied for 9 min 45 sec (13 J/cm^2) using 11 locations on the scalp: midline from front-to-back hairline and bilaterally on frontal, parietal, and temporal areas. Testing was performed before and after transcranial LED (tLED; at 1 week, 1 month, and at 2 months after the 18th treatment) and showed significant improvements in executive function and verbal memory. There were also fewer post-traumatic stress disorder (PTSD) symptoms reported. Ongoing studies: Ongoing, current studies involve TBI patients who have been treated with tLED using either 26 J/cm^2 per LED location on the head or treated with intranasal only (iLED) using red (633 nm) and NIR (810 nm) diodes placed into the nostrils. The NIR iLED is hypothesized to deliver photons to the hippocampus, and the red 633 nm iLED is believed to increase melatonin. Results have been similar to the previously published tLED study. Actigraphy sleep data showed increased time asleep (on average one additional hour per night) after the 18th tLED or iLED treatment. LED treatments may be performed in the home. Sham-controlled studies with veterans who have cognitive dysfunction from Gulf War Illness, blast TBI, and TBI/PTSD are currently ongoing.

Nissen LR, Stoltenberg C, Nielsen AB, Vedtofte MS, Marott JL, Gyntelberg F, Guldager B. Danish Gulf War Veterans Revisited: No Evidence of Increased Sickness Absence or Reduced Labor Market Outcome After Deployment to the Persian Gulf. Mil Med. 2016 Nov;181(11):e1644-e1649.

OBJECTIVE: To examine the assumption that postdeployment incidence of sickness and other absence from work are higher among Gulf War Veterans compared with nonveterans. METHODS: A prospective registry study including a cohort of 721 Danish Gulf War Veterans and a control cohort of 3,629 nonveterans selected from the general Danish population. Outcome measures were up to 23 years postdeployment incidence of (1) long-term sickness absence and (2) long-term all types of absence from work. Long term with regard to sickness and other absence was defined as exceeding 8 weeks. The association between outcomes and information on deployment history was studied using time-to-event analysis. The index date was the return date from the last deployment to the Gulf. The follow-up period was the time from index date until April 27, 2014. RESULTS: As the main finding, no difference was found between veterans and nonveterans in the incidence rate of long-term sickness absence. After an initial short period (3 months) with elevated incidence rate of long-term absence from work among veterans, there was no difference between the cohorts. CONCLUSION: Among Danish Gulf War Veterans, no postdeployment increased risk of long-term sickness absence or long-term absence from work was found as compared with nonveterans.

O'Callaghan JP, Michalovicz LT, Kelly KA. Supporting a Neuroimmune Basis of Gulf War Illness. EBioMedicine. 2016 Nov;13:5-6. doi: 10.1016/j.ebiom.2016.10.037. Epub 2016 Oct 26. Commentary; No abstract available.

Phillips KF, Deshpande LS. Repeated low-dose organophosphate DFP exposure leads to the development of depression and cognitive impairment in a rat model of

Gulf War Illness. Neurotoxicol. 2016 Jan;52:127-33. doi: 10.1016/j.neuro.2015.11.014. Epub 2015 Nov 24.

Approximately 175,000-250,000 of the returning veterans from the 1991 Persian Gulf War exhibit chronic multi-symptom illnesses that includes neurologic co-morbidities such as depression, anxiety and cognitive impairments. Amongst a host of causative factors, exposure to low levels of the nerve agent Sarin has been strongly implicated for expression of Gulf War Illness (GWI). Nerve agents similar to pesticides are organophosphate (OP) compounds. There is evidence from civilian population that exposure to OPs such as in agricultural workers and nerve agents such as the survivors and first-responders of the Tokyo subway Sarin gas attack suffer from chronic neurological problems similar to GWI symptoms. Given this unique chemical profile, OPs are ideal to study the effects of nerve agents and develop models of GWI in civilian laboratories. In this study, we used repeated low-dose exposure to OP agent diisopropyl fluorophosphate (DFP) over a 5-day period to approximate the duration and level of Sarin exposure during the Persian Gulf War. We tested the rats at 3-months post DFP exposure. Using a battery of behavioral assays, we observed the presence of symptoms of chronic depression, anxiety and memory problems as characterized by increased immobility time in the Forced Swim Test, anhedonia in the Sucrose Preference Test, anxiety in the Elevated Plus Maze, and spatial memory impairments in the Object Location Test, respectively. Chronic low dose DFP exposure was also associated with hippocampal neuronal damage as characterized by the presence of Fluoro-Jade staining. Given that OP exposure is considered a leading cause of GWI related morbidities, this animal model will be ideally suited to study underlying molecular mechanisms for the expression of GWI neurological symptoms and identify drugs for the effective treatment of GWIs.

Pierce LM, Kurata WE, Matsumoto KW, Clark ME, Farmer DM. Long-term epigenetic alterations in a rat model of Gulf War Illness. Neurotoxicology. 2016 Jul;55:20-32. doi: 10.1016/j.neuro.2016.05.007. Epub 2016 May 11.

Gulf War Illness (GWI) is a chronic, multisymptom illness that affects 25% of the 700,000 US veterans deployed to the Persian Gulf during the 1990-1991 Gulf War. Central nervous system impairments are among the most common symptoms reported, including memory dysfunction and depression. After 25 years, the diagnosis remains elusive, useful treatments are lacking, and the cause is poorly understood, although exposures to pyridostigmine bromide (PB) and pesticides are consistently identified to be among the strongest risk factors. Epigenetic changes including altered microRNA (miRNA) expression and DNA methylation play an important role in learning, memory, and emotion regulation and have been implicated in various neurological disorders. In this study, we used an established rat model of GWI to determine whether 1) chronic alterations in miRNA expression and global DNA methylation and DNA hydroxymethylation are mechanisms involved in the pathobiology of GWI, and 2) plasma exosome small RNAs may serve as potential noninvasive biomarkers of this debilitating disease. One year after a 28-day exposure regimen of PB, DEET (N,N-diethyl-3-methylbenzamide), permethrin, and mild stress, expression of 84 mature miRNAs and global 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) content were analyzed in the brains of GWI rats and

vehicle controls by PCR array and enzyme-linked immunosorbent assay, respectively. Plasma exosome RNA next-generation sequencing analysis was performed in pooled samples to discover potential noninvasive biomarkers. We found that combined exposure to low doses of GW-related chemicals and mild stress caused epigenetic modifications in the brain that persisted one year after exposure, including increased expression of miR-124-3p and miR-29b-3p in the hippocampus and regional alterations in global 5mC and 5hmC content. GW-relevant exposures also induced the differential expression of two piwi-interacting RNAs (piRNAs) in circulation (piR-007899 and piR-019162). Results from this study implicate a role for epigenetic alterations in GWI. Evaluation of the diagnostic potential of plasma exosome RNAs in veterans with GWI is warranted.

Repine JE, Wilson P, Elkins N, Klawitter J, Christians U, Peters B, Smith DM. Inhalation of two putative Gulf War toxins by mice. J Environ Sci Health B. 2016;51(6):366-73. doi: 10.10 80/03601234.2016.1142318. Epub 2016 Mar 7. Erratum in: J Environ Sci Health B. 2016 Sep;51(9):654.

We employed our inhalation methodology to examine whether biomarkers of inflammation and oxidative stress would be produced in mice following inhalation of aerosols containing carbonaceous particles or the vapor of pesticides prevalent during the first Gulf War. Exposure to two putative Gulf War Illness toxins, fine airborne particles and the pesticide malathion, increased biomarkers of inflammation and oxidative stress in Friend virus B (FVB) female mice. Mice inhaling particles 24 h before had increased lung lavage and plasma Leukotriene B4 (LTB4) (a biomarker of inflammation) and PGF2α (a biomarker of oxidative stress) levels, lung lavage protein and lung lavage lactic dehydrogenase (LDH) levels. These changes were a function of particle density and exposure time. Compared to particle inhalation, mice inhaling malathion 24 h before had small increase in plasma LTB4 and PGF2α levels but no increase in lung lavage LTB4, lung lavage protein, lung lavage LDH, and lung lavage alveolar macrophage (AM) levels compared to unexposed control mice. AM from particle-exposed mice contained phagocytosed particles, while AM from malathion-exposed mice showed no abnormalities. Our results indicate that inhaling particles or malathion can alter inflammatory and oxidative biomarkers in mice and raise the possibility that these toxins may have altered inflammation and oxidative stress biomarkers in Gulf War-exposed individuals.

Rice M, Craddock T, Folcik V, del Rosario R, Barnes Z, Klimas N, Fletcher M, Zysman J, Broderick G. Gulf War Illness: is There Lasting Damage to Endocrine-immune Circuitry? Systems Biomedicine. 2016; (2):80-89.

We reported previously that the persistence of complex immune, endocrine and neurological symptoms that afflict up to one third of veterans from the 1990-91 Gulf War might be supported by a misdirected regulatory drive. Here we use a detailed model of immune signaling in concert with an overarching circuit model of known sex and stress hormone co-regulation to explore how the failure of regulatory elements may further establish a self-perpetuating imbalance that closely resembles Gulf War Illness (GWI). Defects to the model were imparted iteratively and the stable regulatory modes supported by these altered immune-endocrine circuits were identified using repeated simulation

experiments. In each case the predicted homeostatic regimes were compared to experimental data collected in male GWI (n=20) and matched healthy veterans (n=22). We found that alignment of GWI with a new homeostatic regime improved significantly when cortisol's normal anti-inflammatory activity was interrupted. Alignment improved further when this cortisol insensitivity was compounded by the loss of the normal antagonistic effects of Th1 cytokines on Th2 lymphocyte activation. Together these simulation results suggest altered glucocorticoid gene regulation compounded by possible changes in IGF-1 regulation of Th1:Th2 immune balance may be key underlying features of GWI.

Spencer PS, Palmer VS, Kisby GE. Seeking environmental causes of neurodegenerative disease and envisioning primary prevention. Neurotoxicology. 2016 Sep;56:269-283. doi: 10.1016/j.neuro.2016.03.017. Epub 2016 Apr 2.

Pathological changes of the aging brain are expressed in a range of neurodegenerative disorders that will impact increasing numbers of people across the globe. Research on the causes of these disorders has focused heavily on genetics, and strategies for prevention envision drug-induced slowing or arresting disease advance before its clinical appearance. We discuss a strategic shift that seeks to identify the environmental causes or contributions to neurodegeneration, and the vision of primary disease prevention by removing or controlling exposure to culpable agents. The plausibility of this approach is illustrated by the prototypical neurodegenerative disease amyotrophic lateral sclerosis and parkinsonism-dementia complex (ALS-PDC). This often-familial long-latency disease, once thought to be an inherited genetic disorder but now known to have a predominant or exclusive environmental origin, is in the process of disappearing from the three heavily affected populations, namely Chamorros of Guam and Rota, Japanese residents of Kii Peninsula, Honshu, and Auyu and Jaqai linguistic groups on the island of New Guinea in West Papua, Indonesia. Exposure via traditional food and/or medicine (the only common exposure in all three geographic isolates) to one or more neurotoxins in seed of cycad plants is the most plausible if yet unproven etiology. Neurotoxin dosage and/or subject age at exposure might explain the stratified epidemic of neurodegenerative disease on Guam in which high-incidence ALS peaked and declined before that of PD, only to be replaced today by a dementing disorder comparable to Alzheimer's disease. Exposure to the Guam environment is also linked to the delayed development of ALS among a subset of Chamorro and non-Chamorro Gulf War/Era veterans, a summary of which is reported here for the first time. Lessons learned from this study and from 65 years of research on ALS-PDC include the exceptional value of initial, field-based informal investigation of disease-affected individuals and communities, the results of which can provide an invaluable guide to steer cogent epidemiological and laboratory-based research.

Sripada RK, Lamp KE, Defever M, Venners M, Rauch SA. Perceived Social Support in Multi-era Veterans With Posttraumatic Stress Disorder. J Nerv Ment Dis. 2016 Apr;204(4):317-20. doi: 10.1097/NMD.0000000000000476.

Low social support is associated with greater prevalence and severity of posttraumatic stress disorder (PTSD). However, the factors that explain the association between social

support and PTSD are not well understood. In the current study, 741 VA patients who presented to a PTSD clinic between 2005 and 2013 completed assessments of symptom severity and social support. Analysis of variance and linear regression tested the associations between social support, sociodemographic characteristics, and PTSD symptom severity. In adjusted analyses, social support was robustly associated with PTSD severity ($\beta = -0.30$, $p < 0.001$). After stratification by combat era, this association remained significant for all era veterans except veterans of the post-Vietnam/Desert Storm era. Other sociodemographic characteristics did not affect the association between social support and PTSD. Our findings suggest that the detrimental effects of poor social support pervade across sociodemographic groups and that efforts to improve social support in veterans with PTSD are needed.

Turner MP, Hubbard NA, Himes LM, Faghihahmadabadi S, Hutchison JL, Bennett IJ, Motes MA, Haley RW, Rypma B. Cognitive Slowing in Gulf War Illness Predicts Executive Network Hyperconnectivity: Study in a Population-Representative Sample. Neuroimage Clin. 2016 Aug 26;12:535-541. eCollection 2016.

Cognitive slowing is a prevalent symptom observed in Gulf War Illness (GWI). The present study assessed the extent to which functional connectivity between dorsolateral prefrontal cortex (DLPFC) and other task-relevant brain regions was predictive of GWI-related cognitive slowing. GWI patients (n = 54) and healthy veteran controls (n = 29) were assessed on performance of a processing speed task (the Digit Symbol Substitution Task; DSST) while undergoing functional magnetic resonance imaging (fMRI). GWI patients were slower on the DSST relative to controls. Bilateral DLPFC connectivity with task-relevant nodes was altered in GWI patients compared to healthy controls during DSST performance. Moreover, hyperconnectivity in these networks predicted GWI-related increases in reaction time on the DSST, whereas hypoconnectivity did not. These results suggest that GWI-related cognitive slowing reflects reduced efficiency in cortical networks.

White RF, Steele L, O'Callaghan JP, Sullivan K, Binns JH, Golomb BA, Bloom FE, Bunker JA, Crawford F, Graves JC, Hardie A, Klimas N, Knox M, Meggs WJ, Melling J, Philbert MA, Grashow R. Recent research on Gulf War illness and other health problems in veterans of the 1991 Gulf War: Effects of toxicant exposures during deployment. Cortex. 2016 Jan;74:449-75. doi: 10.1016/j.cortex.2015.08.022. Epub 2015 Sep 25. Review.

Veterans of Operation Desert Storm/Desert Shield - the 1991 Gulf War (GW) - are a unique population who returned from theater with multiple health complaints and disorders. Studies in the U.S. and elsewhere have consistently concluded that approximately 25-32% of this population suffers from a disorder characterized by symptoms that vary somewhat among individuals and include fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints. Gulf War illness (GWI) is the term used to describe this disorder. In addition, brain cancer occurs at increased rates in subgroups of GW veterans, as do neuropsychological and brain imaging abnormalities. Chemical exposures have become the focus of etiologic GWI research because nervous system symptoms are prominent and many neurotoxicants were present

in theater, including organophosphates (OPs), carbamates, and other pesticides; sarin/cyclosarin nerve agents, and pyridostigmine bromide (PB) medications used as prophylaxis against chemical warfare attacks. Psychiatric etiologies have been ruled out. This paper reviews the recent literature on the health of 1991 GW veterans, focusing particularly on the central nervous system and on effects of toxicant exposures. In addition, it emphasizes research published since 2008, following on an exhaustive review that was published in that year that summarizes the prior literature (RACGWI, 2008). We conclude that exposure to pesticides and/or to PB are causally associated with GWI and the neurological dysfunction in GW veterans. Exposure to sarin and cyclosarin and to oil well fire emissions are also associated with neurologically based health effects, though their contribution to development of the disorder known as GWI is less clear. Gene-environment interactions are likely to have contributed to development of GWI in deployed veterans. The health consequences of chemical exposures in the GW and other conflicts have been called "toxic wounds" by veterans. This type of injury requires further study and concentrated treatment research efforts that may also benefit other occupational groups with similar exposure-related illnesses.

Yee MK, Seichepine DR, Janulewicz PA, Sullivan KA, Proctor SP, Krengel MH. Self-Reported Traumatic Brain Injury, Health and Rate of Chronic Multisymptom Illness in Veterans From the 1990-1991 Gulf War. J Head Trauma Rehabil. 2016 Sep-Oct;31(5):320-8. doi: 10.1097/HTR.0000000000000173.

BACKGROUND: Traumatic brain injury (TBI) was not considered to be common in the 1990-1991 Gulf War (GW). Therefore, the relationship between TBI and chronic health symptoms experienced by GW veterans is unknown. Health symptoms reported by veterans deployed more recently to this region (Operations Enduring and Iraqi Freedom) are similar to those of GW veterans and have been primarily attributed to TBI. OBJECTIVE: To examine the relationships among self-reported TBI, health symptoms, chronic multisymptom illness (CMI), and health-related quality of life among GW veterans. PARTICIPANTS: Participants included 1 274 GW veterans from the Devens Cohort Study, 156 of whom self-reported a history of TBI (12.2% of the sample). DESIGN: Cross-sectional retrospective analysis of existing survey data. MAIN MEASURES: A 52-item health symptom checklist and the RAND 36-Item Health short Form Survey. RESULTS: Self-reported TBI in GW Veterans is related to increased rates of health symptoms, CMI, and poorer health-related quality of life. CONCLUSIONS: Gulf War veterans' self-reported exposure to TBI is related to increased rates of chronic health symptoms and CMI, which interfere with everyday activities of daily living.

Zakirova Z, Crynen G, Hassan S, Abdullah L, Horne L, Mathura V, Crawford F, Ait-Ghezala G. A Chronic Longitudinal Characterization of Neurobehavioral and Neuropathological Cognitive Impairment in a Mouse Model of Gulf War Agent Exposure. Front Integr Neurosci. 2016 Jan 12;9:71. doi: 10.3389/fnint.2015.00071. eCollection 2015.

Gulf War Illness (GWI) is a chronic multisymptom illness with a central nervous system component that includes memory impairment as well as neurological and musculoskeletal

deficits. Previous studies have shown that in the First Persian Gulf War conflict (1990–1991) exposure to Gulf War (GW) agents, such as pyridostigmine bromide (PB) and permethrin (PER), were key contributors to the etiology of GWI. For this study, we used our previously established mouse model of GW agent exposure (10 days PB+PER) and undertook an extensive lifelong neurobehavioral characterization of the mice from 11 days to 22.5 months post exposure in order to address the persistence and chronicity of effects suffered by the current GWI patient population, 24 years post-exposure. Mice were evaluated using a battery of neurobehavioral testing paradigms, including Open Field Test (OFT), Elevated Plus Maze (EPM), Three Chamber Testing, Radial Arm Water Maze (RAWM), and Barnes Maze (BM) Test. We also carried out neuropathological analyses at 22.5 months post exposure to GW agents after the final behavioral testing. Our results demonstrate that PB+PER exposed mice exhibit neurobehavioral deficits beginning at the 13 months post exposure time point and continuing trends through the 22.5 month post exposure time point. Furthermore, neuropathological changes, including an increase in GFAP staining in the cerebral cortices of exposed mice, were noted 22.5 months post exposure. Thus, the persistent neuroinflammation evident in our model presents a platform with which to identify novel biological pathways, correlating with emergent outcomes that may be amenable to therapeutic targeting. Furthermore, in this work we confirmed our previous findings that GW agent exposure causes neuropathological changes, and have presented novel data which demonstrate increased disinhibition, and lack of social preference in PB+PER exposed mice at 13 months after exposure. We also extended upon our previous work to cover the lifespan of the laboratory mouse using a battery of neurobehavioral techniques.

IV. RESEARCH FUNDING TRENDS

This section provides a quantitative overview of the current research portfolio on GWVI and the evolution of the portfolio since 2007. Topics that are covered include research expenditures by VA, DoD, and HHS from FY 2007-2016, and the number of research projects in which the Federal Government has invested.

The appropriated funds for FY 2007 through 2016, centrally obligated to each project, are shown in Appendix C and summarized in Table IV-1. Federal funding for GW research totaled almost $280 million during this period. Funds obligated for these projects prior to FY 2007 are not shown in either Table IV-1 or Appendix C. Since many projects are multi-year efforts for which funds are obligated at the beginning of the project period, projects that received all of their funds prior to FY 2007 are listed with no associated obligation ($0) in Appendix C. Federal funds for these earlier projects were reported in prior annual reports.

Table IV-1. 10-Year (FY 2007-2016) Funding Trends for GW Research in Millions of Dollars

Department	FY '07	FY '08	FY '09	FY '10	FY '11	FY '12	FY '13	FY '14	FY '15	FY '16	Total Costs FY '07-'16
DoD	$ 3.4	$ 11.7	$ 10.4	$ 10.4	$ 10.3	$ 11.7	$ 19.5	$ 22.5	$ 23.8	$ 24.3	**$ 148.0**
HHS	$ 0.5	$ 0.4	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0	**$ 0.9**
VA	$ 22.1	$ 21.9	$ 16.6	$13.9	$ 5.6	$ 6.7	$ 7.9	$ 9.7	$ 11.6	$ 12.4	**$ 128.4**
Total	**$ 26.0**	**$ 34.0**	**$ 27.0**	**$ 24.3**	**$ 15.9**	**$ 18.4**	**$ 27.4**	**$ 32.2**	**$ 35.4**	**$ 36.6**	**$ 277.3**

The funding level for FY 2015 in the table above differs from the value reported in the 2015 Annual Summary due to the delayed start of 28 projects funded through the FY 2015 appropriation for the Gulf War Illness Research (GWIRP) managed by the Congressionally Directed Medical Research Programs (CDMRP) at DoD. DoD did not receive final approval until after the 2015 Annual Summary was prepared.

VA, DoD, and HHS sponsored a total of 544 distinct research projects on GWVI during the period of FY 1992 through FY 2016. Appendix A lists all of the research and development projects and programs supported now or in the past by each of the three Federal agencies. Nine projects have been dual-funded by VA and DoD, and each agency has given the project its own unique project number (DoD-115/VA-062; DoD-116/VA-063; DoD-116A/VA-063A; DoD-116B/VA-063B; D0D-118/VA-061; DoD-119/VA-055; DoD-125/VA-074; DoD-143/VA-078; and DoD-154/VA-088). In prior annual reports to Congress, the total number of funded projects was corrected for the number of dual-funded projects. Starting with the 2005 annual report to Congress, this practice has been discontinued since VA and DoD may start or end funding of their portion of these projects independent of each other. Any dual-funded project would, therefore, be treated as two distinct projects.

The numbers of new, ongoing, and completed projects for FY 2007 - FY 2016 are shown in Figure IV-1. As of September 30, 2016, 404 projects (74 percent of the 544 projects) were completed, and 140 projects (26 percent) were new or ongoing.

The annual distribution of new and ongoing projects within the five major Research Focus Areas is shown in Figure IV-2.

Figure IV-1. Cumulative Number of Funded Projects (FY 2007 - FY 2016)

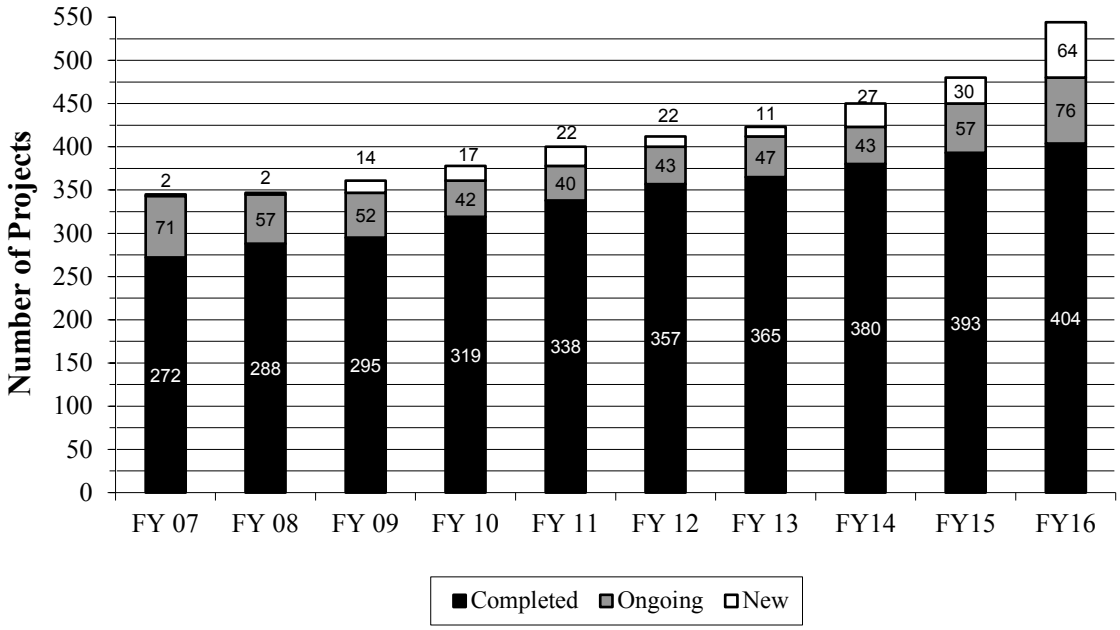
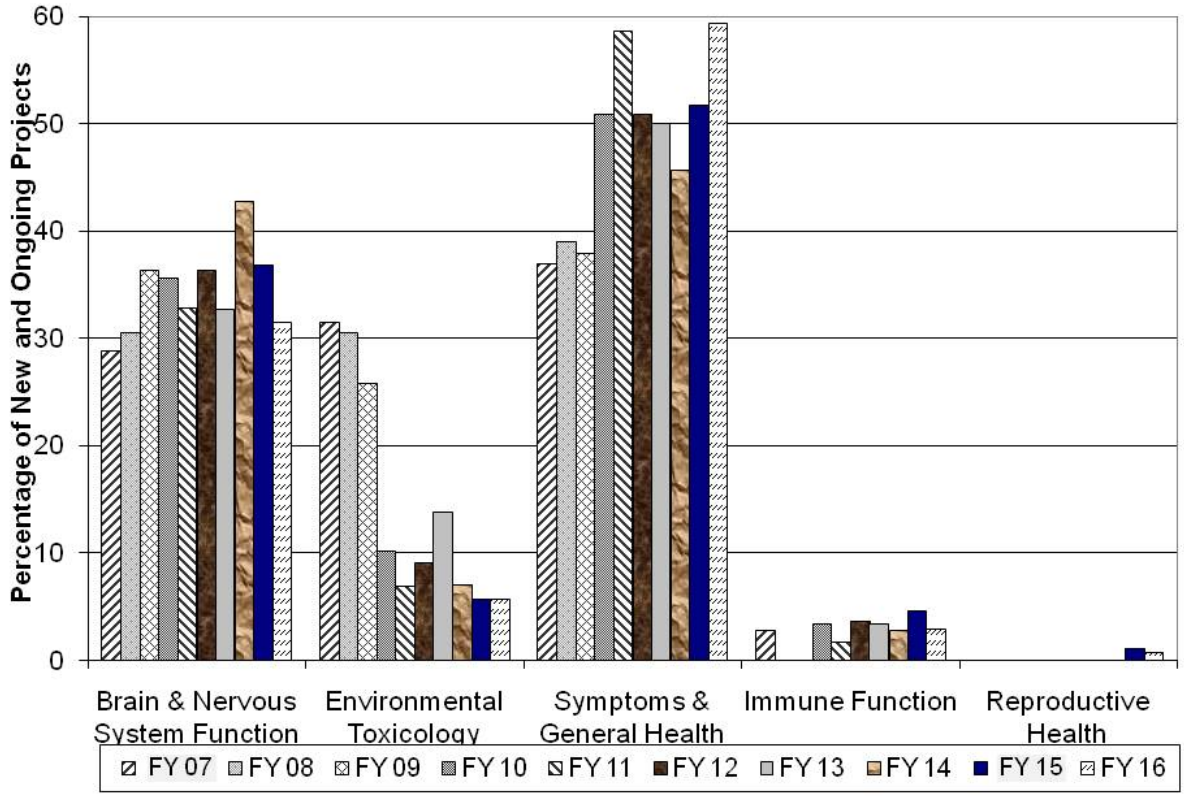


Figure IV-2. Annual Distribution of Topic Areas for New and Ongoing Projects



V. NEW RESEARCH PROJECTS AND INITIATIVES

A. New Initiatives

Program Announcements (PAs) and Requests for Applications (RFAs) were issued by CDMRP and VA in FY 2016. Proposals received for review in response to these PAs and RFAs were reviewed, and projects selected for funding will begin in FY 2017. As more investigators engage in GW research, there has been an increase in applications for funding and increases in the number of newly-approved treatment trials and biomarker studies. In 2016, 36 newly awarded projects were added to the 76 ongoing projects and 28 additional projects were selected for funding.

In addition to the RFAs for Biomedical Laboratory Research &Development and Clinical Sciences R&D, a VA RFA in Health Services R&D asked researchers to propose ways of determining if GW Veterans are satisfied with their health care at VA and to propose solutions to any problems they identify. Thus far, five projects have been recommended for funding.

Two CDMRP-funded research consortia combine the talents and expertise of GW researchers who focus on different aspects of GWI. One consortium studies brain-immune interactions to monitor neurotoxic and neuroinflammatory reactions as the investigators try

to understand the underlying causes of the health problems in GW Veterans. The other consortium is focused on a "systems biology" approach to combining basic research with clinical results to identify biomarkers and possible treatments for GW Veterans.

The National Academy of Medicine (NAM; formerly the Institute of Medicine) released a study for VA entitled "Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War, 2016" on February 11, 2016. A follow-up study, "Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War," was contracted by VA in 2016 with an expected completion date in 2018. An NAM report entitled "Evaluation of the Congressionally Directed Medically Research Programs Review Process" and released on November 15, 2016, was requested by the Defense Health Agency (DHA) to evaluate the review process and to determine the extent of coordination between CDMRP and other agencies like NIH and VA. The CDMRP Gulf War program was part of this NAM review.

B. Portfolio Review

VA and DoD each review their portfolios of GW research on a regular basis in order to determine research gaps and to expand successful research topic areas. The Federal GW research portfolio is increasingly focused on identifying potential new treatments (clinical trials, including complementary medicine approaches) for ill GW Veterans and identifying new diagnostic markers of disease and potential therapeutic targets to develop new therapies. VA and DoD program managers meet regularly to share information regarding funded GW research projects and coordinate activities, whenever possible, to maximize combined program impact. To formalize this process, the GW research programs have been integrated into the ongoing Department-wide VA-DoD Review and Analysis meetings. The third such GW review was held in September 2017, and the next review will be in 2018.

C. New Projects

This section highlights the new research projects that have been approved since last year's 2015 Annual Summary; these projects represent an investment of more than $30 million by the time they are completed. They are described below and incorporated into the tables in Appendices A, B, and C.

DoD Projects

Fifty-six new projects were recommended for funding through the FY 2016 appropriation or in CY 2015 after the previous annual summary was submitted for the GWIRP managed by CDMRP. These projects focused on Brain and Nervous System Function (13), Environmental Toxicology (4), Symptoms and General Health (38), and Immune Function (1).

*DoD-269, "The Role of Desert-Dust Metals in the Pathobiology of Gulf War Illness" is designed to determine if exposure to pyridostigmine bromide (PB), permethrin (PM), or

DEET, followed by exposure to metals shown to be associated with desert dust, results in an ability of those metals to cross the blood-brain barrier. An in vitro model that mimics the blood-brain barrier will be used for these studies. If PB, PM, or DEET exposure results in metals crossing the blood-brain barrier, it suggests that a previously uninvestigated multi-exposure scenario may play a role in the manifestation of Gulf War illness.

*DoD-270, “Examination of Plasma PON1 Paraoxonase Activity and Genotype in Gulf War Veterans” will investigate the extent to which genetic variability in PON1, specifically the ability of PON1 to neutralize different types of organophosphates (OPs), and GW Veterans' exposure to those OPs contribute to their risk for developing GWI. A model that explains why certain GW Veterans developed GWI while others with similar deployment experiences and exposures remained healthy will be tested using a large (> 800) sample of existing/ongoing GW cohorts.

*DoD-271, “Neuroepidemiologic Case Definition of Gulf War Illness from Neuroimaging and EEG in a Population-Representative Nested Case-Control Sample of Gulf War Veterans” will continue to develop a population-representative comparative epidemiologic description of the rates of GWI symptomatology and clinical diagnoses in an established cohort of deployed and non-deployed GW veterans.

*DoD-272, “Examination of Neuroimaging, Cognitive Functioning, and Plasma Biomarkers in a Longitudinal Cohort: Fort Devens” is designed to improve understanding of the pathobiology for the chronicity of symptoms in GWI. The goal is to develop brain imaging and peripheral blood plasma biomarkers of oxidative stress that correlate with cognitive and health symptom outcomes in a well-established GWV cohort.

*DoD-273 Partenered award to DoD-272, “Examination of Neuroimaging, Cognitive Functioning, and Plasma Markers in a Longitudinal Cohort of Gulf War Deployed Veterans: The Fort Devens Cohort” is designed to improve understanding of the pathobiology for the chronicity of symptoms in GWI. The goal is to develop brain imaging and peripheral blood plasma biomarkers of oxidative stress that correlate with cognitive and health symptom outcomes in a well-established GWV cohort.

*DoD-274, “Stress Hormone Enhancement of OP-Induced Neuroinflammation as an Animal Model of GWI: The Role of Toll-Like Receptors and Plasticity” will build on prior findings related to the effect of physiological stressors and exposure to irreversible organophosphate (OP) cholinesterase inhibitors as a basis for developing GWI, and extend key findings with diisopropyl fluorophosphate (DFP) to the additional GWI-relevant OPs, chlorpyrifos (CPF), and dichlorvos (DDVP). Also, a greater understanding of the basis of the corticosterone (CORT) "priming" effect is needed to identify targets for therapeutic intervention. Toll-like receptor 2 (TLR2) pathways in the signaling underlying neuroinflammatory "priming" have been implicated, and the role of TLR2 in the development of CORT-OP-induced neuroinflammation will be investigated. This study will also define the extended duration of the synaptic and behavioral effects resulting from CORT and OP-induced neuroinflammation and attempt to diminish this condition with pharmacological trophic factors that affect neurogenesis and plasticity.

*DoD-275 Partnered award to DoD-274, “Stress Hormone Enhancement of OP-Induced Neuroinflammation as an Animal Model of GWI: The Role of Toll-Like Receptors and Plasticity” will build on prior findings related to the effect of physiological stressors and exposure to irreversible organophosphate (OP) cholinesterase inhibitors as a basis for developing GWI, and extend key findings with diisopropyl fluorophosphate (DFP) to the additional GWI-relevant OPs, chlorpyrifos (CPF), and dichlorvos (DDVP). Also, a greater understanding of the basis of the corticosterone (CORT) "priming" effect is needed to identify targets for therapeutic intervention. Toll-like receptor 2 (TLR2) pathways in the signaling underlying neuroinflammatory "priming" have been implicated, and the role of TLR2 in the development of CORT-OP-induced neuroinflammation will be investigated. This study will also define the extended duration of the synaptic and behavioral effects resulting from CORT and OP-induced neuroinflammation and attempt to diminish this condition with pharmacological trophic factors that affect neurogenesis and plasticity.

*DoD-276, “Identification of Lipid Biomarkers of Inflammation and Metabolic Disturbances in GWI” will examine the possible usefulness of omega-6 and omega-3 fatty acid, mitochondria specific lipids (cardiolipin and acylcarnitines), and peroxisome function specific very long chain fatty acids (VLCFA) and branched chain fatty acids (BCFA) as biomarkers of GWI. Lipids will be examined in blood samples from three mouse models of GWI using liquid chromatography/mass spectrometry (LC/MS). Lipids that indicate differential response to GW exposure and are altered at several chronic post-exposure time points across the mouse models will be examined in blood samples collected from Veterans with GWI and controls from the GW era.

*DoD-277, “Treatment of Memory Disorders in Gulf War Illness with High-Definition Transcranial Direct Cortical Stimulation” is designed to determine if 1-milliamp anodal HD tDCS is an effective treatment for verbal retrieval deficits in GWI. This study will attempt to entrain the verbal retrieval circuit using HD tDCS to target the pre-supplementary motor area in order to improve retrieval in impaired GWI patients, using behavioral and electrophysiological markers to assess outcomes.

*DoD-278, “Metabolomics Distinguish Veterans with Gulf War Illness: Replicating and Expanding Promising Results” will follow up a prior study that identified a spectrum of critical, previously unidentified objective changes in Gulf War Veterans with Gulf War illness (GWI). Previously identified changes match pathways reported to be altered in reports of metabolomic and lipid alterations in mitochondrial dysfunction. Use of this approach completely separated GWV with GWI from controls matched in age, sex, and ethnicity. This study will expand key insights into pathways and mechanisms in GWI and may provide an objective means to diagnose GWI.

*DoD-279, “Neurodegenerative Changes after Exposure to Gulf War Insults” will use an established mouse model of Gulf War exposures to identify induced changes in the CNS connectivity/neuroprotective pathway followed by administration of a dietary treatment to upregulate activity of the Nrf2 transcription factor to improve neuronal health.

*DoD-280, “Curcumin Nanoparticle Therapy for Gulf War Illness” will test oral administration of an optimal dose of curcumin encapsulated in biodegradable polymer nanosystems (nCUR) and its ability to alleviate cognitive, memory, and mood impairments associated with GWI via suppression of oxidative stress and inflammation and increased neurogenesis in the hippocampus.

*DoD-281, “Exploring Mechanisms Underlying Impaired Brain Function in Gulf War Illness through Advanced Network Analysis” is designed to map the whole-brain resting state network architecture of GWI Veterans and compare them with age-matched Veteran controls.

*DoD-282, “Gulf War Women's Health Cohort” will focus on (1) establishing a large sample of women Veterans who served in the 1990-1991 Gulf War, and a comparison group of women who served in other locations during that period, (2) providing current, comprehensive data on the health status of these women, and (3) identifying any specific conditions that affect GW women Veterans at excess rates.

*DoD-283, “Therapeutic Inhibition of microRNA-124 for the Treatment of Gulf War Illness” will investigate the therapeutic efficacy of a locked nucleic acid (LNA)-antisense oligonucleotide (LNA-antimiR-124) to improve learning and memory impairments, depressive-like behavior, and neuroendocrine dysfunction in an established rat model of GWI.

*DoD-284, “Alleviating Headache and Pain in GWI with Neuronavigation-Guided rTMS” is a clinical trial that will compare the effect of active repetitive transcranial magnetic stimulation (rTMS) at the left motor cortex with sham rTMS to reduce symptoms of GWI-related headaches and pain (GWI-HAP). The study will compare the treatment effect in improving joint and muscle pain, attentional cognitive function, fatigue, depression, and sleep disturbance as secondary outcome measures.

*DoD-285, “Disentangling the Effects of PTSD from GWI for Improved Diagnostics and Treatments” is designed to perform a secondary systems biology analysis based on resources, methodology, and results from ongoing GWI research initiative to (1) isolate bio-behavioral profiles that are specific to GWI alone, (2) evaluate how immune regulation in GWI is modified in the presence of probable PTSD diagnosis, and (3) use ongoing work in predictive modeling to assess possible changes to treatment of GWI in the context of probable PTSD diagnosis.

*DoD-286, “Persistently Elevated Somatic Mutation as a Biomarker for Clinically Relevant Exposures in GWI” will compare military Veterans deployed to the Gulf to those who were not deployed using a glycophorin A (GPA) mutation assay to identify an association of somatic mutation frequency with both common and rare components of GWI, such as chronic fatigue syndrome and cancer.

*DoD-287, “Improving Cognitive Function in Veterans with Gulf War Illness by Improving Cerebral Vascular Function” is designed to link the reduced ability of cerebrovascular

dilation to cognitive impairments seen in GWI. Researchers will determine if Veterans with GWI that have cognitive impairment also demonstrate an impaired ability to dilate their cerebral vessels. This study will also determine if low cerebrovascular reactivity can be restored by blocking COX and as a result, improve cognitive function.

*DoD-288, “Pyridostigmine Bromide, the Enteric Nervous System, and Functional Gastrointestinal Disorders in Gulf War Illness” will attempt to understand how the anti-nerve gas drug PB contributes to the development of functional GI disorders in Gulf War illness. Investigators propose that controlling reactive gliosis in the enteric nervous system with the anti-inflammatory drug palmitoylethanolamide (PEA) is a novel therapeutic approach that will improve gut dysfunction induced by PB.

*DoD-289, “Investigating Increased Glutamate Transporter EAAT2 Function as a Potential Therapeutic Approach for Gulf War Illness” will study the hypothesis that chronic exposure to GWI-related chemicals and stress results in an increase in extracellular glutamate levels and the dysfunction of the glutamatergic system leading to hippocampal damages and subsequent cognitive and mood deficits. Enhanced glutamate uptake function by increased expression of the glutamate transporter EAAT2 is proposed to normalize the dyshomeostasis of the glutamatergic system and subsequently restore normal synaptic and astrocytic function. This, in turn, may result in improvement of cognitive functions and amelioration of depression and anxiety symptoms.

*DoD-290, “Mitochondrial Dysfunction and Gulf War Illness” will investigate the hypothesis that mitochondrial dysfunction is an important contributor to GWI. An important corollary hypothesis is that mitochondrial parameters measured in peripheral blood mononuclear cells (PBMCs) are a biomarker for mitochondrial dysfunction in affected tissues. In a small preliminary cohort, these investigators have obtained strong data supporting the hypothesis that mitochondrial health is impaired in PBMCs of Veterans with GWI. To test the hypothesis, mitochondrial parameters in PBMCs of a larger cohort of GWI cases and controls will be measured. The stability of mitochondrial parameters over time as well as the role of multiple factors as drivers of mitochondrial function will be investigated.

*DoD-291, “Identification of Causes and Treatments for Chronic Pain in a Model of Gulf War Illness” will investigate whether musculoskeletal pain, which is mediated by neuroinflammatory signaling in a GWI rat model, can be successfully treated by clinically relevant, systemically administered drugs targeting key sites along the neuroinflammatory pathway. The success of these drugs in advanced preclinical development and/or with Food and Drug Administration (FDA) approval will expedite their translation to successful clinical application.

*DoD-292, “Therapeutic Intervention of Glial-Mediated Enhancement of Neuroinflammation in an Established Model of GWI” will characterize the contribution of different durations of high physiological stress and glial cell types on the phenotype of an established corticosterone (CORT)-primed diisopropyl fluorophosphate (DFP) model of Gulf War illness (GWI) and test the therapeutic potential of Food and Drug Administration (FDA)-approved inflammatory and cell-type specific inhibitors anakinra and etanercept.

*DoD-293, “Evaluation of Treatment Efficacy with a Potent Novel Immunomodulatory Glycan Conjugate in Gulf War Illness Models” will test a novel immunotherapeutic, a glycan conjugate, which is a component of human milk, in two different mouse models of GWI. One of the models consists of a 10-day pyridostigmine bromide/permethrin (PB/PM) treatment; the other model utilizes PB, the insect repellent DEET, the sarin surrogate DFP, and stress (PB/DEET/DFP/stress), with the exposure paradigm spanning 15 days. Investigators propose that in both GWI models, glycan (LNFPIII) conjugate treatment, even when initiated months after exposure to the GWI chemicals has ended, will restore immune system balance in the periphery and in the brain.

*DoD-294, “Improving Diagnostics and Treatments for GWI Females by Accounting for the Effects of PTSD” will build on ongoing research directed at mapping complex inflammatory mechanisms in GWI to improve understanding of the immunologic underpinnings of GWI in women and the compounding effects of comorbidity with PTSD. The current proposal focusing on women is intended to serve as a complementary study to a similar ongoing analysis in men.

*DoD-295, “GWI: Molecular Analysis of Disease Endophenotypes and Response to Acupuncture Treatment” will undertake a comprehensive plasma proteomics analysis using a recently developed and highly sophisticated screening technology (SOMAscan) that multiplexes 1,310 proteins. By applying bioinformatics and machine learning tools in combination with systems biology approaches, investigators will generate signatures, classifiers, and disease interactive networks that define GWI. A thorough validation process will follow the identification of differentially expressed proteins. The goal is not only to devise a highly sought diagnostic test for GWI, but also to gain, via the study of the GWI proteome, insights about disease mechanisms that will pave the way to develop targeted therapies. In parallel, the PI will take advantage of the fact that in the parent GWI cohort patients were treated with acupuncture and will search for the elusive "acupuncture biological signature". Finally, intra-patient variability in symptom experience, psychosocial variables and response to acupuncture will be captured with specific sets of serum proteins.

*DoD-296, “Susceptibility of Cathepsin A to Organophosphate Pesticides and Nerve Agents” will investigate the hypothesis that fibromyalgia syndrome (FMS)-like symptoms of GWS may arise from organophosphate (OP)-inhibition of the serinyl cathepsin, CatA. Investigators will characterize the organophosphate inhibitor susceptibilities of CatA, using a set of OP pesticides and simulants. They will confirm nerve agent inhibition by demonstrating effects of OP-inhibition on the activity and stability of NEU1/CatA and beta-galactosidase(bGal)/CatA complexes.

*DoD-297, “Quantitative Acute and Chronic Assessments of Gulf War Chemical Toxicity in Rats Using Neuroelectrophysiological Measurements and PBPK Models” will characterize CNS function using multiple electrophysiological (EP) approaches and calculate the time course and concentrations of Gulf War chemicals DEET, pyridostigmine bromide (PB), and permethrin in the brain using physiologically based pharmacokinetic (PBPK) models.

Investigators will develop an in vitro model of GWI using brain slices exposed to Gulf War chemicals, at concentrations similar to those predicted by the PBPK model. An asssessment of the effectiveness of potential countermeasures (e.g., luteolin) to mitigate the neuronal dysfunction induced by Gulf War chemicals will be performed.

*DoD-298, “Computer-Aided Decoding of Brain-Immune Interactions in Gulf War Illness (GWI): A Joint Embedding on Brain Connectomic and Immunogenomic Markers” will employ a novel classification framework based on a combination of brain connectomics and immuno-genetic (genomic) approaches of GWI to develop novel computer-based diagnostic systems and features.

*DoD-299, “Sigma-1 Receptor Agonists as a Novel Therapeutic for Brain Mitochondrial Dysfunction in Gulf War Syndrome” will investigate the therapeutic efficacy of selected S1R agonists in relieving cognitive degradation in an established GWI mouse model. Investigators hypothesize that S1R agonists improve cognitive abilities through effectively restoring mitochondrial energy metabolism in neurons and enhancing neuroplasticity in GWI mice.

*DoD-300, “A Pilot RCT on the Effect of Resveratrol on Mood, Memory Deficits, Hippocampal Inflammation, and Neurogenesis in Veterans with Gulf War Illness (GWI)” will evaluate the effect of the over-the-counter antioxidant supplement resveratrol (RESV), a polyphenol found abundantly in the skin of red grapes and that is known to have robust antioxidant and anti-inflammatory properties, on cognitive function, memory, functional status, and mood in Veterans who suffer from GWI. Investigators will also evaluate the effects of RESV on neurogenesis, functional connectivity, and functional status in the hippocampus and examine any anti-inflammatory and antioxidant effects.

*DoD-301, “Growth Hormone-Releasing Hormone (GHRH) Antagonist: Evaluation of Beneficial Effects for Gulf War Illness” will use an existing model of GWI to evaluate new therapeutic alternatives to alleviate GWI based on the beneficial effects of highly biologically active analogs (antagonists) of GHRH.

*DoD-302, “Investigating Gene-Environment Interactions in Multiple Cohorts of 1990-1991 Gulf War Veterans” will determine the contribution of BChE genotype to the development of GWI overall, in relation to PB and other cholinergic exposures in theater, and in combination with effects of PON1-192 genetic status.

*DoD-303, “Direct Current Stimulation for Pain Treatment of Gulf War Illness” will conduct a prospective, double-blind, placebo controlled, randomized, parallel-group study to evaluate the efficacy and safety of a novel therapy to treat pain complaints for Veterans diagnosed with Gulf War illness. A new treatment option using tDCS has been developed by this group for the management of fibromyalgia complaints. This approach is being directly translated to Gulf War Veterans with pain symptoms since they report a similar disability, meet the criteria for fibromyalgia, and seem to have a similar neural mechanism underlying the pathology.

*DoD-304, “Human Leukocyte Antigen in Gulf War Veterans: Association with Symptoms and Inflammatory Markers” will evaluate the association of genotype, GWI symptomatology, and biomarkers of immune system dysfunction, inflammation, and autoimmunity in a large sample of Gulf War era Veterans to better understand the pathogenesis and pathophysiology of GWI and ultimately inform treatment decisions for affected Veterans.

*DoD-305, “Glutamate Receptor and Kynurenine Pathway Functioning in the Pathobiology of Gulf War Illness” will characterize CNS kynurenine pathways (KP) and glutamatergic N-methyl-D-aspartate receptor (NMDAR) functioning in a well-characterized sample of 1991 Gulf War Veterans. Associations with other markers of central inflammation, and with GWI symptom severity, will be investigated. Investigators hypothesize higher quinolinic acid or protective kynurenic acid (KYNA) kynurenines produced by KP and more pronounced NMDAR activity will be seen in GWI cases than in Gulf War Veteran controls.

*DoD-306, “Mitochondrial Dysfunction and Aberrant Immune Activation in the Pathobiology of Gulf War Illness” will investigate the etiology of GWI in terms of mitochondrial dysfunction and subsequent immune activation. Investigators hypothesize that persistent mitochondrial dysfunction is an important driver of GWI pathobiology, and propose that mitochondrial dysfunction aberrantly engages the innate immune system to enhance inflammatory and interferon responses, thus exacerbating GWI symptoms. This study will test whether bezafibrate, a Food and Drug Administration-approved, lipid-lowering drug that boosts healthy mitochondrial function and lowers inflammation, will alleviate neuropathology and cognitive dysfunction in a rodent model of GWI.

*DoD-307, “Identification of Causes and Treatment for Chronic Depression in a Rodent Model of Gulf War Illness” is designed to probe the molecular basis of GWI depression by addressing the hypothesis that chronic DFP exposure upregulates NMDA-Rs (N-methyl-D-aspartate receptors), which activate Ca2+ induced Ca2+ release mechanisms leading to sustained neuronal Ca2+ elevations, and treatment with KET will revert these elevated Ca2+ levels to baseline, thereby exerting a rapid and long-lasting antidepressant effect with minimal toxicity in GWI rodents.

*DoD-308, “Genetic Basis of Individual Differences in Susceptibility to Gulf War Illness” will measure genetic variation in neuroinflammatory gene expression response to corticosterone, DFP, and their combination in 40 BXD recombinant mouse strains. Investigators will conduct genetic mapping to identify candidate genes underlying differential transcriptional response to DFP and corticosterone + DFP. Investigations will include gene network and gene ontology analysis.

*DoD-309, “Gene Expression to Advance Understanding, Aid Diagnosis, and Define Treatment Targets in Gulf War Illness” will use recombinant mice strains to test whether genes play a role in determining who develops GWI. Investigators will treat mice with a combination of DFP and CORT, will measure symptoms and brain changes, and correlate genes that are involved in these differences.

*DoD-310, “Melatonin for Reversing Brain Dysfunction in Gulf War Illness” is designed to test whether increased oxidative stress, chronic inflammation, and declined neurogenesis in the hippocampus along with systemic inflammation are amid the major causes underlying cognitive, memory, and mood impairments in GWI. Investigators propose to test the efficacy of oral administration of melatonin (MEL; a hormone synthesized mainly by the pineal gland and having robust antioxidant and sleep-inducing properties) for easing cognitive, memory, and mood dysfunction in a rat model of GWI.

*DoD-311, “The Role of Oxidative Stress and Mitochondrial Dysfunction in Cognitive Impairments in Gulf War Illness” will use an established mouse GWI model to investigate the pathogenic mechanism of GWI, with the ultimate goal of identifying effective therapeutic approaches to improve the neurocognitive functions in GWI Veterans. This project proposes two specific aims. Aim 1 will determine how Gulf War agents affect mitochondrial functionality in the CNS over time following exposure and identify the root causes that perpetuate mitochondrial dysfunction. Aim 2 will evaluate therapeutic strategies, focusing on improving mitochondrial functions, using genetic and pharmacological approaches, and evaluate their efficacies against cognitive impairments in GWI.

*DoD-312, “Identification of Epigenetic Signatures as Biomarkers of Gulf War Illness” will use integrated approaches to investigate epigenetics changes of GWI and correlate the epigenetic changes with GW-relevant exposures (including pyridostigmine bromide [PB], pesticides, sarin) to identify the biological indicators in GWI pathogenesis in a well-established cohort of Gulf War Veterans from the large multi-site Department of Defense-funded Boston Gulf War Illness Consortium (GWIC) (GW120037). Identified epigenetic changes associated with GWI may lead to additional treatment options for Veterans with GWI by targeting these changes.

*DoD-313, “Measurement of Biomarkers in Samples Collected in a Coenzyme Q10 Treatment Trial in Gulf War Illness and Control Subjects” will expand on the promising Phase I/II results tied to Coenzyme Q10 (CoQ10). A Department of Veterans Affairs (VA) clinical trials group headed by Dr. Nancy Klimas was awarded funding to initiate a Phase III placebo control treatment trial of CoQ10. However, this clinical trial does not include studies of biomarkers in the context of baseline and treatment response but does include collection, shipping to the Miami VA, processing and cryopreservation of plasma and peripheral blood mononuclear cells (PBMC) at baseline and during the trial. The current project will examine biomarkers useful as surrogates of severity as well as predictors of response to CoQ10 therapy.

*DoD-314, Partnered award to DoD-313, “Measurement of Biomarkers in Samples Collected in a Coenzyme Q10 Treatment Trial in Gulf War Illness and Control Subjects” will expand on the promising Phase I/II results tied to Coenzyme Q10 (CoQ10). A Department of Veterans Affairs (VA) clinical trials group headed by Dr. Nancy Klimas was awarded funding to initiate a Phase III placebo control treatment trial of CoQ10. However, this clinical trial does not include studies of biomarkers in the context of baseline and treatment response but does include collection, shipping to the Miami VA, processing and

cryopreservation of plasma and peripheral blood mononuclear cells (PBMC) at baseline and during the trial. The current project will examine biomarkers useful as surrogates of severity as well as predictors of response to CoQ10 therapy.

*DoD-315, “Persistent Hormonal Changes in Veterans with Gulf War Illness” will assess the association of GWI with dysregulation of the major pituitary hormonal systems: the growth hormone (GH) axis, gonadotropin axes, thyroid hormone axis, and HPA axis. Hormone measures (including the frequency of hormone deficiencies) between Gulf War Veterans with and without GWI will be compared. The study will also evaluate the relationship between endocrine measures and neurocognitive function through a serious of neuropsychological assessments in Veteran subgroups defined by (a) the presence/absence of comorbid psychiatric conditions (e.g., post-traumatic stress disorder, depression), (b) individual and combined characteristics of deployment (e.g., participation in combat, exposures in theater), and (c) degree of symptomatology in GWI symptom domains.

*DoD-316, “Treatment Strategies in a Mouse Model of Chronic Gulf War Illness” will validate targeting neuroinflammation as a therapeutic by extending pilot studies testing the long term (7-month) effects of treatment with the anti-inflammatory Anatabine in a mouse model of GWI. Investigators will determine whether or not a combined therapeutic approach with Anatabine will mitigate the effects of Gulf War agent exposure more effectively than a single compound approach.

*DoD-317, “Genomic Approach to Find Female-Specific Mechanisms of GWI Pathobiology” will combine the latest state-of-the-art genomics and computational biology methods to identify novel, female-specific mechanisms of transcriptional regulation in GWI, which will facilitate better understanding of GWI pathobiology in women and provide further insights in mechanisms of GWI in men.

*DoD-318, “Glutamate Neuroexcitotoxicity in GWI” will test the effectiveness of a low-glutamate diet in GWI patients, as a way to mediate symptom occurrence by reducing excess glutamatergic neurotransmission.

*DoD-319, “The Use of B-Cell Depletion Therapy (BCDT) in Gulf War Illness: A Phase 1/2 Study” aims to target two different immune pathways, the pro-inflammatory cytokine cascade as well as interfering with autoantibody production. By inhibiting autoantibody production using a B-cell depleting therapy, investigators not only hope to decrease the presence of autoantibodies but decrease pro-inflammatory cytokine expression and reset underlying mechanisms of disease by wiping out B-cell memory cells to prevent future autoantibody production.

*DoD-320, “Role of Vestibular Hypofunction in Exacerbating Autonomic Dysfunction in Gulf War Illness” will examine the role of vestibular dysfunction and its effect on autonomic function. One hundred Veterans with GWI and 50 Gulf War Era Veterans will be screened. Investigators will determine if Veterans with GWI that have impaired vestibular function also demonstrate impaired autonomic function.

*DoD-321, “Gender and Gulf War Illness” will use a GWI female mouse model to study cardiovascular and neuro-inflammatory profiles in response to DFP exposure to test whether reponses correlate with interactions between the gender-specific sex steroids. The study will include examination of responses to drug therapies including Enbrel (ENB), Mifepristone (MIF), or the combination (ENB+MIF) (modulator of TNF-a and adrenocorticoid receptor, respectively).

*DoD-322, “Tau Pathology as a Contributor to Gulf War Illness and a Basis for Potential Therapy” will differentiate various subtypes of human central nervous system neurons derived from a Gulf War repository bank of human induced pluripotent cells (hiPSCs) and examine tau pathology with and without GWI toxicant exposures. Invesitgators will also screen for potential therapeutic inhibitory compounds and antibodies to alleviate tau phenotypes as well as microtubule stability defects.

*DoD-323, “Identifying Novel Immune and Radiographic CT Imaging Signatures of Chronic Bronchiolitis” will investigate the abnormal pulmonary immune function associated with airway injuries that promote the development of chronic bronchiolitis (CB), a disorder characterized by symptoms of cough, dyspnea, and fatigue resulting from persistent airway inflammation and fibrosis lasting years after exposure. CT scans from Gulf War Veterans with pulmonary symptoms will be used in this study.

*DoD-324, “Next-Generation Biomarkers of Gulf War Illness” will utilize state-of-the-art proteomic and epigenetic technologies to identify unique molecular markers in the blood of ill Gulf War Veterans.

VA Funded Projects

VA initiated funding for eight new projects during FY 2016. These eight projects focused on Brain and Nervous System Function (1) and Symptoms and General Health (7).

VA-198, “Healthcare utilization patterns and associated costs for Gulf War I Era Veterans” is designed to describe the demographics and characteristics of a cohort of Veterans of the 1990-1991 era; to describe healthcare utilization patterns and direct care costs both overall, deployed versus non-deployed Veterans, and for Gulf War illness, cardiovascular conditions, mental health disorders, and complex chronic disease; and to explore patients' decision-making perspectives regarding choice of healthcare location and utilization.

VA-199, “Post-Exertion Malaise in GWI: Brain Autonomic and Behavioral Interactions” will study the mechanisms of symptom maintenance and exacerbation in Veterans suffering with Gulf War illness (GWI). Multiple physiological systems (CNS, autonomic, immune) will be monitored in Veterans with and without GWI. The impact of an exercise challenge (post-exertional malaise) on CNS regulation of pain/fatigue, cardiovascular autonomic function, and immune system activity will be evaluated to determine whether interactions

among multiple systems significantly explain symptoms of GWI. This study could lead to treatments for GWI that are mechanistically based on physiology.

VA-200, “A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy” will attempt to conduct a systematic assessment and characterization of the therapeutic effects of drugs that impact five physiological targets which were selected on the basis of experimental evidence analyzed in a systems biology model. The drug/target pairs can be tested and validated by observing the effects of the therapeutic agents on *in vitro* cultures of peripheral blood mononuclear cells (PBMCs) from GWI patients and controls. The study will to advance the understanding of the underlying mechanisms of GWI using targeted therapies *in vitro* before human clinical trials are conducted.

VA-201, “WRIISC as a Model of Care for Chronic Multisymptom Illness” will look into the reasons why 97% of Veterans with GWI who are referred to VA’s War Related Illness and Injury Study Center are satisfied with the health care they receive. One hundred patients from the WRIISC and 100 patients from other VA medical centers will be followed for 12 months to determine if their degree of satisfaction correlates with their adherence to treatment plans. The most effective components of the WRIISC model of health care would then be integrated into other VA medical centers.

VA-202, “Gulf War Neurotoxicants and Acquired Cognitive and Neuropsychological Dysfunction” will use male and female rats to evaluate the effect of lipopolysaccharide (LPS), alone and with oral pyridostigmine (PB), on the severity and persistence of neuroinflammation and resulting neurofunctional abnormalities. Inflammatory cytokines in CSF and plasma will be measured, tissue neuroinflammation will be examined, and microstructural and metabolic changes will be studied after exposure to LPS and PB. After symptom onset, the effect of treatment with a PPARγ agonist on neuroinflammation will be evaluated.

VA-203, “Novel Interventions for Gulf War Veterans' Illnesses” will compare the effectiveness of Tai Chi with a Stretching and Wellness Education Intervention in two groups of 60 patients each who meet criteria for GWI with significant chronic pain. After a 12-week treatment period, there will be nine months of follow-up to monitor the long-term effects of these non-pharmacologic treatments for pain. Secondary outcome measures that are expected to improve include fatigue, cognition, quality of life, and physical functioning.

VA-204, “Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness” is a two-arm, randomized controlled trial to investigate the efficacy of CBT-I for sleep and non-sleep GWI symptoms in 64 Veterans with GWI. Half of the Veterans will be randomized to CBT-I and half to a treatment-as-usual control group. The primary outcomes will be effect sizes of pre- to-post-treatment changes and maintenance of treatment effects at 6 months in the group randomized to CBT-I. This non-

pharmacologic intervention is also expected to treat some of the non-sleep symptoms associated with GWI.

VA-205, “A Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness” will assess the clinical efficacy and safety of CoQ10 (ubiquinol) in 200 Veterans with GWI, in a double-blind, randomized, placebo-controlled trial, with 100 participants per treatment arm of the study. Subjects will be recruited at four geographically different sites over the course of the 6-month intervention. The primary objective is to assess efficacy, and secondary endpoints will include objective measures of activity and cognitive function as well as an evaluation of putative biomarkers for their ability to predict severity and response to therapy.

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Appendices

Federally Funded Research Projects

Appendix A

Project Index By Department

DEPARTMENT OF DEFENSE PROJECTS

DoD-001	Naval Health Study Program
DoD-001A	Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; A Study of Symptoms Among 1500 Seabees
DoD-001B	Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not
DoD-001C	Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among GW Veterans and other active-duty personnel
DoD-001D	Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in GW Veterans
DoD-001E	Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study
DoD-001F	Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: GWV vs. NDV
DoD-001G	Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian GW Veterans
DoD-002	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET
DoD-004	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey
DoD-007A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling
DoD-007B	Carcinogenicity of Depleted Uranium Fragments
DoD-008A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)
DoD-008B	Development of a Leishmania Skin Test Antigen (LSTA)
DoD-009	Identification of the Genetic Factors Which Control Tropism in Leishmania
DoD-010	Pyridostigmine Synergistic Toxicity Study
DoD-011	Male/Female Differential Tolerances to Pyridostigmine Bromide
DoD-013	Effects of Persian Gulf War Service on Military Working Dogs
DoD-014	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry
DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm

DoD-016	Kuwait Oil Fire Health Risk Assessment
DoD-017	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning
DoD-018	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)
DoD-019	Persian Gulf Veterans Health Tracking System
DoD-021	Study of Variability in Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals with Symptoms Following Participation in Operation Desert Storm
DoD-022	Chronic Organophosphorus Exposure and Cognition
DoD-023	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families
DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study
DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome
DoD-032	Neuropsychological Functioning in Persian Gulf Era Veterans
DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
DoD-034	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents
DoD-035	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War
DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms
DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats
DoD-038	Diagnostic Antigens of Leishmania tropica
DoD-039	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces
DoD-040	Psychological and Neurobiological Consequences of the Gulf War Experience
DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans
DoD-042	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment
DoD-044	Investigation of Seminal Plasma Hypersensitivity Reactions
DoD-045	Air Force Women's Health Surveillance Study
DoD-046	Exploratory Data Analysis with the CCEP Database
DoD-047	Study of Mycoplasmal Infections in GW Veterans

DoD-048	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs. Selected Control Groups
DoD-049	Diagnosis and Dosimetry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts
DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways
DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
DoD-052	Female Gender and Other Potential Predictors of Functional Health Status Among Persian GW Veterans
DoD-053	Long-Term Effects of Subclinical Exposures to Sarin
DoD-054	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure
DoD-055	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects
DoD-056	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine
DoD-057	Physiologic Effects of Stress in GW Veterans
DoD-058	Illness Among Persian GW Veterans: Case Validation Studies
DoD-059	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis
DoD-060	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness
DoD-061	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid
DoD-062	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice
DoD-063	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity
DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine
DoD-065	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment
DoD-066	Testing for mycoplasmal infection replicability of nucleoprotein gene tracking and forensic polymerase chain reaction
DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
DoD-069	Five-Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents
DoD-070	War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes
DoD-071	A Comparison of Post Deployment Hospitalization Between Vietnam and GW Veterans

DoD-072 Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals

DoD-073 Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes

DoD-074 Relationship of Stress Exposures to Health in GW Veterans

DoD-075 Toxic Interactions of Prophylactic Drugs and Pesticides

DoD-076 Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel

DoD-077 Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War

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DoD-081 Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress

DoD-082 Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs

DoD-083 Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism

DoD-084 Psychobiologic Alterations in Persian GW Veterans with and without PTSD

DoD-085 CNS Cytokines and CRH in GW Veterans with Multiple Unexplained Symptoms

DoD-086 Effects of Combat Stress on Structure and Function of the Hippocampus

DoD-087 Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs

DoD-088 Clinical Relevance of Novel Immunological Markers in PTSD

DoD-089 Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder

DoD-090 SPECT Benzodiazepine Receptor and MR Imaging in PTSD

DoD-091 Neurological and Circadian Substrates of PTSD-like Behaviors

DoD-092 Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder

DoD-093 Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up

DoD-094 Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. GW Veterans

DoD-095 Development of Diagnostic tools and alternative treatment drugs for Leishmania

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DoD-097 Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and

	Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis
DoD-098	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans
DoD-099	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations
DoD-100	Antibodies to Squalene
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DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals
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DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala
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DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity
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DoD-109	Disordered Responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms
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DoD-111	Autonomic Dysfunction in GW Veterans
DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?
DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
DoD-114	A Re-examination of Neuropsychological Functioning in Persian GW Veterans
DoD-115	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)
DoD-116	VA/DoD Core Funding of the Medical Follow-Up Agency (See also VA-63; formerly VA-DoD-2D/2V)
DoD-116A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA)
DoD-116B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)
DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
DoD-118	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among GW Veterans (See also VA-61)

DoD-119	Antibiotic Treatment of GW Veterans' Illnesses (ABT) (See also VA-55)
DoD-120	Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents
DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel During Pregnancy and Offspring Development
DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys
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DoD-124	Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin
DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)
DoD-126	Blood-Brain Barrier Transport of Uranium
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DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity
DoD-129	Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness
DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents
DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses
DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness
DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome
DoD-134	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin
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DoD-137	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin
DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses
DoD-140	US DOD Surveillance for Neoplasms in Infancy
DoD-141	Physical, Mental, Social, and Family Health Outcomes of GW Veterans
DoD-142	Illnesses Among Persian GW Veterans: Case Validation Studies (Iowa / Great Britain)

DoD-143 Millennium Cohort Study (See also VA-78)

DoD-144 Psychological Health Screening: Methods and Metrics for Deployed Forces

DoD-145 Early Intervention Research Program to Enhance Soldier Resilience

DoD-146 Assessment of Toxicology Assays Methods & Chemical Exposures Among a Cohort of US Marines

DoD-147 Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications

DoD-148 Predicting operational readiness for deployed Army National Guard and Army Reserve soldiers and families

DoD-149 Longitudinal Health Study of GW Veterans

DoD-150 Validation Study of Gulf War Deployment Files

DoD-151 Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in GW Veterans

DoD-152 Characterization of Intracellular Signaling Pathways Activated by Nerve Agents

DoD-153 Gulf War Illness Research

DoD-154 Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also VA-88)

DoD-155 Neuropsychological Functioning in GW Veterans Exposed to Pesticides and Pyridostigmine Bromide

DoD-156 The Effects of Diesel Exhaust and Stress on the Acute Phase Response and Symptoms in the Chemically Intolerant

DoD-157 Novel Leishmania and Malaria Potassium Channels: Candidate Therapeutic Targets

DoD-158 Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission of Genetic Damage to Offspring

DoD-159 Neurotoxicity from Chronic Exposure to Depleted Uranium

DoD-160 Characterization of the Reproductive Toxicity of Depleted Uranium

DoD-161 Glutamate Receptor Aptamers and ALS

DoD-162 Evaluation of the Effects of Multiple Immunizations Administered in a Stressful Environment on Immunologic Function

DoD-163 Neuroimmune Effects of Inhaling Low Dose Sarin

DoD-164 Efficacy of Adjunct Sleep Interventions for PTSD (EASI-PTSD)

DoD-165 Biomarkers for Amyotrophic Lateral Sclerosis in Active Duty Military – BALSAM

DoD-166 A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance

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DoD-173	A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in GW Veterans with Chronic Multisymptom Illness
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DoD-175	Novel Pharmacological Approaches for Treatment of Neurotoxicity Induced by Chronic Exposure to Depleted Uranium
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DoD-177	Randomized Trial of an Environmental Medicine Approach to GW Veterans' Illness
DoD-178	Analysis of Paraoxonase Status among US Navy GW Veterans with Increased Postwar Symptoms, Psychological Morbidity and Medical Conditions
DoD-179	Mechanisms of Mitochondrial Defects in Gulf War Syndrome
DoD-180	Exercise-Induced Cerebrospinal Fluid Proteomic Biomarkers of Fatigue
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DoD-182	Trial of Naltrexone and Dextromethorphan for GW Veterans' Illness
DoD-183	Biomarkers of GW Veterans' Illnesses: Tissue Factor, Chronic Coagulopathy, and Inflammation
DoD-184	Treatment of Memory Impairment and Sensorimotor Deficits in an Animal Model for the GW Veterans' Illnesses
DoD-185	Neuroinflammatory Pathobiology in Gulf War Illness: Characterization with an Animal Model
DoD-186	Small Intestinal Microbial Community in Gulf War Illness
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DoD-188	Epithelial Cell TRPV1-Mediated Airway Sensitivity as a Mechanism for Respiratory Symptoms Associated with Gulf War Illness
DoD-189	Discovery of AMPA Receptor Potentiating Aptamers as Cognitive Enhancers
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DoD-191	Neuroimmune Interactions, Low-Dose Sarin Inhalation, and Gulf War Syndrome
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DoD-193	Genome Instability: A Common Link in Gulf War Illness Patients
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DoD-198	Oxidative Stress
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DoD-202	Brain-Immune Interactions as Basis of Gulf War Illness: Consortium Development
DoD-203	Redefining Gulf War Illness Using Longitudinal Health Data: The Devens Cohort
DoD-204	Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Syndrome
DoD-205	The HPA Axis and Metabolic Outcomes in GW Veterans
DoD-206	Investigating Clinical Benefits of a Novel Sleep-Focused, Mind-Body Program on Gulf War Illness Symptoms: An Exploratory Randomized Controlled Trial
DoD-207	Gulf War Illness Research Development Consortium (GWIC)
DoD-208	Genome-Wide Association Study of a Validated Case Definition of Gulf War Illness in a Population-Representative Sample
DoD-209	Proteomic Immune Profiling for the Therapeutic Modulation of Cognitive Impairment in a Novel GWI Mouse Model
DoD-210	Assessment of Diverse Biological Indicators in Gulf War Illness: Are They Replicable? Are They Related?
DoD-211	Detection of Xenotropic Murine Leukemia Virus-Related Virus (XMRV) in Gulf War Illness: Role in Pathogenesis or Biomarker?
DoD-212	Integrative Physiology of Gulf War Illness: Role of Autonomic Function, Central Neural Processing, and Sleep
DoD-213	Effectiveness of Acupressure Treatment for Pain Management and Fatigue Relief in GW Veterans
DoD-214	Abnormalities in Human Brain Creatine Metabolism in Gulf War Illness Probed with MRS
DoD-215	Identifying Immune Drivers of Gulf War Illness Using a Novel Daily Sampling Approach

DoD-216	Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness
DoD-217	Efficacy of Treatments Tried: A Survey of GW Veterans
DoD-218	Establishing a 1991 Veterans Research Network to ImproveCharacterization of Gulf War Illness and Provide a National Resource for Veterans and Investigators
DoD-219	Organophosphate-Related Alterations in Myelin and Axonal Transport in the Living Mammalian Brain
DoD-220	Biomarker Discovery in GW Veterans: Development of a War Illness Diagnostic Panel
DoD-221	Role of microRNAs in the Pathobiology of Gulf War Illness: Identification of Potential Novel Therapeutic Targets
DoD-222	Brain Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC)
DoD-223	Persistent Neural Membrane Protein Misregulation Following Neurotoxicant Exposure
DoD-224	Understanding Gulf War Illness: An Integrative Modeling Approach
DoD-225	The Role of Protein Radicals in Chronic Neuroimmune Dysfunction and Neuropathology in Response to a Multiple-Hit Model of Gulf War Exposures
DoD-226	Gulf War Illness: Assessment of Bioenergetics in Brain and Muscle
DoD-227	Monosodium Luminol for Improving Brain Function in Gulf War Illness
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DoD-231	Use of a Portable Stimulator to Treat GWI
DoD-232	Characterizing Treatable Causes of Small Fiber Polyneuropathy in Gulf War Veterans
DoD-233	Assessment of MRI-Based Markers of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness
DoD-234	A Prospective Open-Label Clinical Trial of Methylphenidate plus a GWI-Specific Nutrient Formula in Patients with Gulf War Illness and Concentration Disturbances
DoD-235	Treating Gulf War Illness with Novel Anti-Inflammatories: A Screening of Botanical Microglia Modulators
DoD-236	Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness
DoD-237	Direct Test for Neuroinflammation with [11C]DAP713-PET Scanning
DoD-238	Restoring the Brain's Lipid Homeostasis as a Therapeutic Avenue for Treating the CNS Symptoms of Gulf War Illness
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DoD-240	Novel Therapeutic Approaches for the Treatment of Depression and Cognitive Deficits in a Rodent Model of Gulf War Veterans' Illness
DoD-241	Gulf War Illness Inflammation Reduction Trial
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DoD-244	Muscle Mitochondrial Assessments in Gulf War Illness
DoD-245	Gulf War Illness as a Brain Autoimmune Disorder
DoD-246	START and STOPP in GWI
DoD-247	Neurovascular and Autonomic Dysfunction Associated with Gulf War Illness Pain
DoD-248	D-cycloserine: A Novel Treatment for Gulf War Illness
DoD-249	Effect of Diet on Gulf War Illness: A Pilot Study
DoD-250	An Integrated Genomics and Cell Biology Approach to Correlate Novel GWI Indicators of Infections and Neuroinflammatory Mechanisms with Targeted Drug
DoD-251	Microtubule Abnormalities Underlying Gulf War Illness in Neurons from Human-Induced Pluripotent Cells
DoD-252	Preclinical Treatment of an Organophosphate Model of Gulf War Illness
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DoD-256	Novel Autoantibody Serum and Cerebrospinal Fluid Biomarkers in Veterans with Gulf War Illness
DoD-257	Novel Autoantibody Serum and Cerebrospinal Fluid Biomarkers in Veterans with Gulf War Illness
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DoD-262	Testing the Model: A Phase I/II Randomized Double Blind Placebo Control Trial of Therapeutics: Liposomal Glutathione and Curcumin
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DoD-264	An Objective Blood Test from Stimulated Gene Expression for Classification and Outcome Assessment in Clinical Trials of Gulf War Illness

DoD-265	An Objective Blood Test from Stimulated Gene Expression for Classification and Outcome Assessment in Clinical Trials of Gulf War Illness
DoD-266	A Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Anti-Inflammatory Compound Anatabine to Treat Pain in GWI Patients
DoD-267	Diagnosis of Late-Stage, Early-Onset, Small-Fiber Polyneuropathy
DoD-268	Diagnosis of Late-Stage, Early-Onset, Small-Fiber Polyneuropathy
DoD-269	The Role of Desert-Dust Metals in the Pathobiology of Gulf War Illness
DoD-270	Examination of Plasma PON1 Paraoxonase Activity and Genotype in Gulf War Veterans
DoD-271	Neuroepidemiologic Case Definition of Gulf War Illness from Neuroimaging and EEG in a Population-Representative Nested Case-Control Sample of Gulf War Veterans
DoD-272	Examination of Neuroimaging, Cognitive Functioning, and Plasma Biomarkers in a Longitudinal Cohort: Fort Devens, Part 1
DoD-273	Examination of Neuroimaging, Cognitive Functioning, and Plasma Markers in a Longitudinal Cohort of Gulf War Deployed Veterans: The Fort Devens Cohort, Part 2
DoD-274	Stress Hormone Enhancement of OP-Induced Neuroinflammation as an Animal Model of GWI: The Role of Toll-Like Receptors and Plasticity
DoD-275	Stress Hormone Enhancement of OP-Induced Neuroinflammation as an Animal Model of GWI: The Role of Toll-Like Receptors and Plasticity
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DoD-278	Metabolomics Distinguish Veterans with Gulf War Illness: Replicating and Expanding Promising Results
DoD-279	Neurodegenerative Changes after Exposure to Gulf War Insults
DoD-280	Curcumin Nanoparticle Therapy for Gulf War Illness
DoD-281	Exploring Mechanisms Underlying Impaired Brain Function in Gulf War Illness through Advanced Network Analysis
DoD-282	Gulf War Women's Health Cohort
DoD-283	Therapeutic Inhibition of microRNA-124 for the Treatment of Gulf War Illness
DoD-284	Alleviating Headache and Pain in GWI with Neuronavigation-Guided rTMS
DoD-285	Disentangling the Effects of PTSD from GWI for Improved Diagnostics and Treatments
DoD-286	Persistently Elevated Somatic Mutation as a Biomarker for Clinically Relevant Exposures in GWI
DoD-287	Improving Cognitive Function in Veterans with Gulf War Illness by Improving Cerebral Vascular Function

DoD-288	Pyridostigmine Bromide, the Enteric Nervous System, and Functional Gastrointestinal Disorders in Gulf War Illness
DoD-289	Investigating Increased Glutamate Transporter EAAT2 Function as a Potential Therapeutic Approach for Gulf War Illness
DoD-290	Mitochondrial Dysfunction and Gulf War Illness
DoD-291	Identification of Causes and Treatments for Chronic Pain in a Model of Gulf War Illness
DoD-292	Therapeutic Intervention of Glial-Mediated Enhancement of Neuroinflammation in an Established Model of GWI
DoD-293	Evaluation of Treatment Efficacy with a Potent Novel Immunomodulatory Glycan Conjugate in Gulf War Illness
DoD-294	Improving Diagnostics and Treatments for GWI Females by Accounting for the Effects of PTSD
DoD-295	GWI: Molecular Analysis of Disease Endophenotypes and Response to Acupuncture Treatment
DoD-296	Susceptibility of Cathepsin A to Organophosphate Pesticides and Nerve Agents
DoD-297	Quantitative Acute and Chronic Assessments of Gulf War Chemical Toxicity in Rats Using Neuroelectrophysiological Measurements and PBPK Models
DoD-298	Computer-Aided Decoding of Brain-Immune Interactions in Gulf War Illness (GWI): A Joint Embedding on Brain Connectomic and Immunogenomic Markers
DoD-299	Sigma-1 Receptor Agonists as a Novel Therapeutic for Brain Mitochondrial Dysfunction in Gulf War Syndrome
DoD-300	A Pilot RCT on the Effect of Resveratrol on Mood, Memory Deficits, Hippocampal Inflammation, and Neurogenesis in Veterans with Gulf War Illness (GWI)
DoD-301	Growth Hormone-Releasing Hormone (GHRH) Antagonist: Evaluation of Beneficial Effects for Gulf War Illness
DoD-302	Investigating Gene-Environment Interactions in Multiple Cohorts of 1990-1991 Gulf War Veterans
DoD-303	Direct Current Stimulation for Pain Treatment of Gulf War Illness
DoD-304	Human Leukocyte Antigen in Gulf War Veterans: Association with Symptoms and Inflammatory Markers
DoD-305	Glutamate Receptor and Kynurenine Pathway Functioning in the Pathobiology of Gulf War Illness
DoD-306	Mitochondrial Dysfunction and Aberrant Immune Activation in the Pathobiology of Gulf War Illness
DoD-307	Identification of Causes and Treatment for Chronic Depression in a Rodent Model of Gulf War Illness
DoD-308	Genetic Basis of Individual Differences in Susceptibility to Gulf War Illness
DoD-309	Gene Expression to Advance Understanding, Aid Diagnosis, and Define Treatment Targets in Gulf War Illness
DoD-310	Melatonin for Reversing Brain Dysfunction in Gulf War Illness

DoD-311	The Role of Oxidative Stress and Mitochondrial Dysfunction in Cognitive Impairments in Gulf War Illness
DoD-312	Identification of Epigenetic Signatures as Biomarkers of Gulf War Illness
DoD-313	Measurement of Biomarkers in Samples Collected in a Coenzyme Q10 Treatment Trial in Gulf War Illness and Control Subjects
DoD-314	Measurement of Biomarkers in Samples Collected in a Coenzyme Q10 Treatment Trial in Gulf War Illness and Control Subjects
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DoD-316	Treatment Strategies in a Mouse Model of Chronic Gulf War Illness
DoD-317	Genomic Approach to Find Female-Specific Mechanisms of GWI Pathobiology
DoD-318	Glutamate Neuroexcitotoxicity in GWI
DoD-319	The Use of B-Cell Depletion Therapy (BCDT) in Gulf War Illness: A Phase 1/2 Study
DoD-320	Role of Vestibular Hypofunction in Exacerbating Autonomic Dysfunction in Gulf War Illness
DoD-321	Gender and Gulf War Illness
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HHS-001	Health Assessment of Persian GW Veterans from Iowa
HHS-002	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18
HHS-003	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and Blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires
HHS-004	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian GW Veterans in Mississippi
HHS-005	Cognitive Function and Symptom Patterns in Persian Gulf Veterans
HHS-006	Defining Gulf War Illness
HHS-007	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
HHS-008	Strategy to Identify Non-Additive Response to Chemical Mixtures
HHS-009	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
HHS-010	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer
HHS-012	Genetic Epidemiology of ALS in Veterans

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VA-002	National Health Survey of Persian Gulf Veterans
VA-002A	VA National Survey of Persian Gulf Veterans - Phase I
VA-002B	VA National Survey of Persian Gulf Veterans - Phase II
VA-002C	VA National Survey of Persian Gulf Veterans - Phase III
VA-003	Use of Roster of Veterans Who Served in Persian Gulf Area
VA-004	Boston Environmental Hazards Research Center Program
VA-004A	Evaluation of Cognitive Functioning of Persian Gulf Veterans
VA-004B	Evaluation of Neurological Functioning in Persian Gulf Veterans
VA-004C	Gulf War and Vietnam Veterans Cancer Incidence Surveillance
VA-004D	Evaluation of Respiratory Dysfunction Among GW Veterans
VA-004E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility
VA-004F	Validity of Computerized Tests
VA-005	East Orange Environmental Hazards Research Center Program
VA-005A	Health and Exposure Survey of Persian Gulf Veterans
VA-005B	Physiological and Psychological Assessments of Persian Gulf Veterans
VA-005C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans
VA-005D	Effects of Genetics and Stress on Responses to Environmental Toxins
VA-006	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research
VA-006A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)
VA-006B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
VA-006C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)
VA-006D	DNA Damage from Chemical Agents and Its Repair (Project IV)
VA-006E	Clinical and Epidemiology Leishmania Research
VA-007	Desert Storm Reunion Survey
VA-008	Psychological Test Data of GW Veterans Over Time

VA-009 Evaluation of Cognitive Functioning in Persian GW Veterans Reporting War-related Health Problems

VA-010 Memory and Attention in PTSD

VA-011 Neuropsychological Functioning in Veterans

VA-012 Psychological Assessment of Operation Desert Storm Returnees

VA-013 Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study

VA-015 Vaccine-Mediated Immunity Against Leishmaniasis

VA-016 Protective Immunity in Experimental Visceral Leishmaniasis

VA-017 Immunological Evaluation of Persian Gulf Veterans

VA-018 Chronic Gastrointestinal Illness in Persian Gulf Veterans

VA-020 Psychological Adjustment in Operation Desert Shield/Storm Veterans

VA-021 A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS

VA-036 Stress Symptoms and Their Causal Attribution in Desert Storm Veterans

VA-040 Musculoskeletal Symptoms in Gulf War Syndrome

VA-046 Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder

VA-047 Retrospective Verification of Mustard Gas Exposure

VA-048 Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance

VA-049 Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction

VA-050 Neuropsychological findings in a sample of Operation Desert Storm Veterans

VA-051 Psychobiological Assessment of Desert Storm Veterans

VA-053 Spouses and Children Program

VA-054 Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress

VA-055 Antibiotic Treatment of GW Veterans' Illnesses (ABT) (See also DoD-119)

VA-056 Birmingham's GW Veterans' Illness Demonstration Clinic (13)

VA-057 Case Management and Residential Rehabilitation for Persian GW Veterans (13)

VA-058 Implementation and Evaluation of GW Veterans' Demonstration Project (13)

VA-059 Demonstration Treatment Program for GW Veterans with Unexplained Physical Symptoms (13)

VA-060 Identification and Management of Sleep Disorders in GW Veterans

VA-061	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among GW Veterans (See also DoD-118)
VA-062	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
VA-063	VA/DoD Core Funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)
VA-063A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)
VA-063B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)
VA-064	Boston Environmental Hazards Research Center
VA-064A	Functional Neuroimaging in Lead Exposed Adults
VA-064B	Quantification and Validation of Structure-Function Relationships Through Visuospatial Test Performance
VA-064C	Development of a Structured Neurotoxicant Assessment Checklist (SNAC) for Clinical use in Veteran Populations
VA-065	San Antonio Environmental Hazards Research Center
VA-065A	Does a Variant of the Human SOD2 Gene Increase Sensitivity to Hazards?
VA-065B	The Contribution of FEN-1 to Genetic Integrity Subsequent to Oxidative Stress
VA-065C	The Importance of Hydrogen Peroxide Detoxification in Cellular Protection
VA-065D	Do Defective Gpx1 and ALDH2 Genes Increase Sensitivity to Environmental Hazards?
VA-066	Physiological Responding in Posttraumatic Stress Disorder
VA-067	Olfactory Functioning in GW Veterans
VA-068	Family Study of Fibromyalgia
VA-069	Cardiovascular Hyporeactivity and Fatiguing Illness in GW Veterans
VA-070	A Clinical Evaluation of the Health Status of Persian GW Veterans in VISN 8
VA-071	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
VA-073	Pain Sensitivity in GW Veterans with Medically Unexplained Musculoskeletal Pain
VA-074	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
VA-075	ALS and Veterans: Are Veterans at Increased Risk?
VA-076	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD

VA-077	HPA Axis Reactivity in Men and Women with Chronic PTSD
VA-078	Millennium Cohort Study (See also DoD-143)
VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior
VA-082	Pituitary Adrenal Function in People with Fatiguing Illness
VA-083	Neuropsychological Assessment of a Population-Based Sample of Persian GW Veterans and Controls
VA-084	Neurobiology of Severe Psychological Trauma in Women
VA-085	Associative Learning in Veterans with and without Combat Experience
VA-086	A Clinical Trial of Magnetic Stimulation in Depression
VA-087	Improving Outcomes of Depression in Primary Care
VA-088	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also DoD-154)
VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis
VA-090	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness
VA-090A	Neuronal Hyperexcitability and Motor Neuron Regeneration
VA-090B	Gene Expression and Proteomic Strategies in Severe Psychiatric Disorders
VA-090C	Developmental Differences in Alcohol Withdrawal Sensitivity
VA-090D	Seizures and Neuroplasticity: Physiology and Biochemistry
VA-091	The Role of Dietary Choline in Neuroprotection
VA-092	Acetylcholinesterase Activity in GW Veterans
VA-093	HPA Axis Alterations in PTSD: A Comparison of Gulf War and Vietnam Veterans
VA-094	The Immunology of Chronic Cutaneous Leishmaniasis
VA-095	The Role of Signal Regulatory Proteins in Astrocytomas
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VA-097	Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas
VA-098	Post-Transcriptional Gene Regulation of VEGF in Malignant Gliomas
VA-099	Vaccination Against Visceral Leishmaniasis with a Multi-Epitope Vaccine
VA-100	Studies of the Blood-Brain Barrier and it's Manipulation

VA-101	Biomarkers Discovery in ALS
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VA-168 Sleep Neurobiology and Circuitry

VA-169 Prevention of Hippocampal Neurodegeneration Due to Age and Apnea

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