

## GULF WAR ILLNESS RESEARCH PROGRAM (GWIRP): Treatments studied

Type	Intervention	Mechanism of Action	Pre-Clinical	Pilot Trial	Expanded Clinical Trial
<b>Antioxidants</b>	Monosodium Luminol	Antioxidant	yes	-	-
	Sigma-1 Receptor Agonists	Mitochondrial stimulants	yes	-	-
	Methylene blue	Respiratory chain	yes	-	-
	CoQ10 + mitochondrial cocktail	Mitochondrial stimulants/antioxidants	-	yes	-
	Nicotinamide Riboside	-	-	yes	-
	Amino acid carnosine	ROS scavenger	-	yes	-
	Methylphenidate plus a GWI-Specific Nutrient	Mitochondrial stimulant/antioxidants	-	yes	-
	Dietary polyphenol	Antioxidant	-	yes	-
	Phenol resveratrol	Antioxidant	-	yes	-
	Coenzyme Q10	Antioxidant	-	yes	yes

\*Analysis from publicly available award data.

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<i>Anti-Inflammatory</i>	Anakinra; Pentoxifylline, Spironolactone	IL1R antagonist; inhibitors of microglia activation	yes	-	-
	Glycan conjugate immunotherapy	Immune effectors	yes	-	-
	Melatonin	Antioxidant and sleep inducer	yes	-	-
	Montelukast	Modulation of leukotriene	yes	-	-
	Naproxen and Misoprostol	COX inhibition	yes	-	-
	Ganaxolone	Neurosteroid	yes	-	-
	Anatabine	Anti-inflammatory	yes	-	-
	Growth hormone-releasing analogs	Immune effectors	yes	yes	-
	Prednisone	Anti-inflammatory	-	yes	-
	Botanical microglia-modulators	Anti-inflammatory/immune effector	-	yes	-
	Liposomal Glutathione	Anti-inflammatory/immune effector	-	yes	-
	B-Cell Depletion Therapy	Immune effector	-	yes	-
	Intranasal Insulin	Anti-inflammatory	-	yes	-
	Mifepristone alone	Antiglucocorticoid	-	yes	-
	Curcumin	Enzyme inhibitor	yes	yes	-
Entanercept and Mifepristone	Antiglucocorticoid and progesterone blocker	yes	yes	yes	

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<b>CNS Stimulants/ Depressants</b>	Flupirtine	Non-opiate analgesic	yes	-	-
	Dantrolene, Levetiracetam	Blockade of the calcium plateau	yes	-	-
	IGF-1	Neurotrophic factor	yes	-	-
	LDN/OSU-0212320	Brain-penetrant to increase glutamate transport	yes	-	-
	Ketamine	Antidepressant, reversal of elevated Ca <sup>2+</sup> levels	yes	-	-
	Naltrexone and dextromethorphan	CNS Stimulants or Depressants	-	yes	-
	Low-glutamate diet	Neuroexcitability	-	yes	-
<b>Physical CNS Stimulation</b>	Vagus Nerve Stimulation	Physical stimulation of vagus nerve	yes	yes	-
	Portable vestibular stimulator	Vestibular dysfunction	-	yes	-
	Transcranial Direct Cortical Stimulation	Physical CNS stimulation	-	yes	-
	Direct Current Stimulation	Physical CNS stimulation	-	yes	-
	Neuronavigation-guided rTMS	Physical CNS stimulation	-	yes	yes
<b>Micro-biome</b>	Sodium butyrate	Gut microbiome	yes	-	-
	Probiotics and microbiota transfer	Gut microbiome	yes	-	-
	Probiotics	Gut-Brain Axis	-	yes	-
	Low FODMAP diet	Gut-Brain Axis	-	yes	-

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<b>Complementary/ Alternative Medicine</b>	Nutritional supplements, exercise, and sauna	Detoxification	-	yes	-
	Xylitol	Nasal irrigation	-	yes	-
	Sleep-Focused, Mind-Body Bridging	Mind/body	-	yes	-
	Acupressure	Mind/body	-	yes	-
	Yoga	Mind/body	-	yes	-
	Acupuncture	Mind/body	-	yes	-
<b>Antibiotics</b>	Minocycline; Luteolin; Tubacin; Propranolol	Antibiotic; flavonoid; tubulin acetylation inducer; beta-blocker	yes	-	-
	Fingolimod/Gilenya, Naltrexone, Losmapimod, Minocycline	Antibiotic; Inhibitors of neuroinflammatory pathways	yes	-	-
	D-cycloserine	Antibiotic	-	yes	-
<b>Lipid Metabolism</b>	LNA-antimiR-124	Inhibition of microRNA-124	yes	-	-
	HDAC6 Inhibitor	Microtubule-targeting	yes	-	-
	Epicatechin	Microtubule-based	yes	-	-
	Oleoylethanolamide	Lipid metabolism	yes	yes	-

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## GULF WAR ILLNESS RESEARCH PROGRAM (GWIRP): Biomarkers studied

Type	Biomarker	Pathway	Pre-Clinical	Clinical	Further Funding
<i>Chronic Inflammation/ Neuro-Immune Responses</i>	9 increased CNS autoantibodies; autoantibody signature	Inflammatory immune response	-	yes	yes
	Lymphocyte and Monocyte populations and C Reactive Protein	Inflammatory immune response	-	yes	-
	Protein-based biomarker signature (26 proteins) that discriminates patients with GWI from healthy controls; lipidomics based signature that can distinguish with high accuracy GWI from healthy controls	Inflammation; lipidomics	-	yes	-
	Neurotropic factors (NTFs), Neuroipoietic cytokines (NPCs), Matrix metalloproteinases (MMPs) and Complement Components (CCs) in CSF and serum	Immune response	-	yes	-

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<b>Chronic Inflammation/ Neuro-Immune responses (Continued)</b>	Phospholipids; IL-1beta, IL-6, IFNgamma, CCR2, CCL2	Immune response	yes	yes	yes
	Inflammatory markers C-reactive protein and erythrocyte sedimentation rate; autoimmune markers	Inflammation	-	yes	-
	Proinflammatory cytokines Eotaxin-1, IL-1beta and IL-15 (fluctuation in daily sampling)	Inflammation	-	yes	-
	Inflammatory cytokines/markers (pro- and anti-)	Inflammation	-	yes	yes
	Depression of prostaglandin F2 alpha (pgf2 $\alpha$ ), prostaglandin D2 (pgd2), leukotriene B4 (lb4)	Fatty Acid Processing	yes	yes	yes
	Omega-6 and omega-3 fatty acids; ethanolamides; lipidomics; autoantibodies against 3-PBA-albumin	Lipid metabolism	yes	yes	yes

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<b>Chronic Inflammation/ Neuro-Immune responses (Continued)</b>	PET imaging neuroinflammation markers in the brain (PK11195 marker)	Neuroinflammation	-	yes	-
	PET imaging using [11C]PBR28 signal binds to translocator protein (TSPO), neuroinflammation marker in brain	Neuroinflammation	-	yes	-
	Positron emission tomography (PET) imaging using [11C]DPA-713 (DPA) of the translocator protein (TSPO), a marker of neuroinflammation	Neuroinflammation	-	yes	-
	Upregulation of genes coding for inflammatory cytokines and chemokines, along with upregulation of genes that code for mechanisms that counteract protection against neuroinflammation	Neuroinflammation	-	yes	yes

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<b>Oxidative Stress &amp; Mitochondrial Dysfunction</b>	Peripheral blood plasma biomarkers of oxidative stress	Oxidative stress	-	yes	-
	Metabolomics (cholesterol products made in mitochondria)	Mitochondrial dysfunction	-	yes	-
	Prolonged muscle phosphocreatine recovery after exercise indicating an association between mitochondrial dysfunction and GWI	Mitochondrial dysfunction	-	yes	-
	Altered levels of citric acid cycle intermediates and correlations between them indicate altered energy metabolism	Energy and Reduction Potential Balance	-	yes	-
	Mitochondrial DNA copy number and DNA repair capacity/mitochondrial respiration in PBMCs	Mitochondrial dysfunction	-	yes	-
	Mitochondrial dysfunction, appearance/morphology	Mitochondrial dysfunction		yes	-

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<b>Genotype / Gene Expression / Epigenetics</b>	Epigenetics/DNA methylation and microRNA signatures	Epigenetics	-	yes	-
	DNA methylation profiles	Epigenetics	-	yes	-
	Elevated somatic mutation frequency; functional DNA repair capacity (nucleotide excision repair genes)	DNA mutation	-	yes	-
	HLA genotype; DRB1*13:02 spared subcortical brain atrophy	Predisposition markers	-	yes	Continued with NIH funding
	PON1 Paraoxonase Genotype	Genotype	-	yes	-
	Gene expression diagnostic classifier (gene expression markers of "exposure" and "protection")	Gene expression	-	yes	-
	Nuclear detoxification genes, BChE and NAT2(g286e)	Gene expression	-	yes	-
	Apolipoprotein E (APOE e4 allele) genotyping	Gene expression	-	yes	yes

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<b>Brain Imaging</b>	Abnormal post-exertional patterns of brain region deactivation during memory tasks can distinguish GWI subgroups and GWI from CFS	CNS Connectivity	-	yes	-
	Brain white matter structural integrity	Brain structure	-	yes	yes
	Functional network connectivity	CNS Connectivity	-	yes	yes
	Neurite density imaging (NDI) + machine learning finding structural changes in the brain to identify GW	Brain structure	-	yes	yes
<b>Respiratory Symptoms</b>	CT-Parametric Response Mapping (PRM) Radiographic Signatures	Lung disease	-	yes	-
<b>Hormone activity</b>	IGF1, cortisol, testosterone, thyroxine levels	Hormone activity	-	yes	-

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