

CUTTING EDGE RESEARCH

Gulf War Illness Research Program Overview and Update

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The views expressed in this presentation are those of the author and may not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government



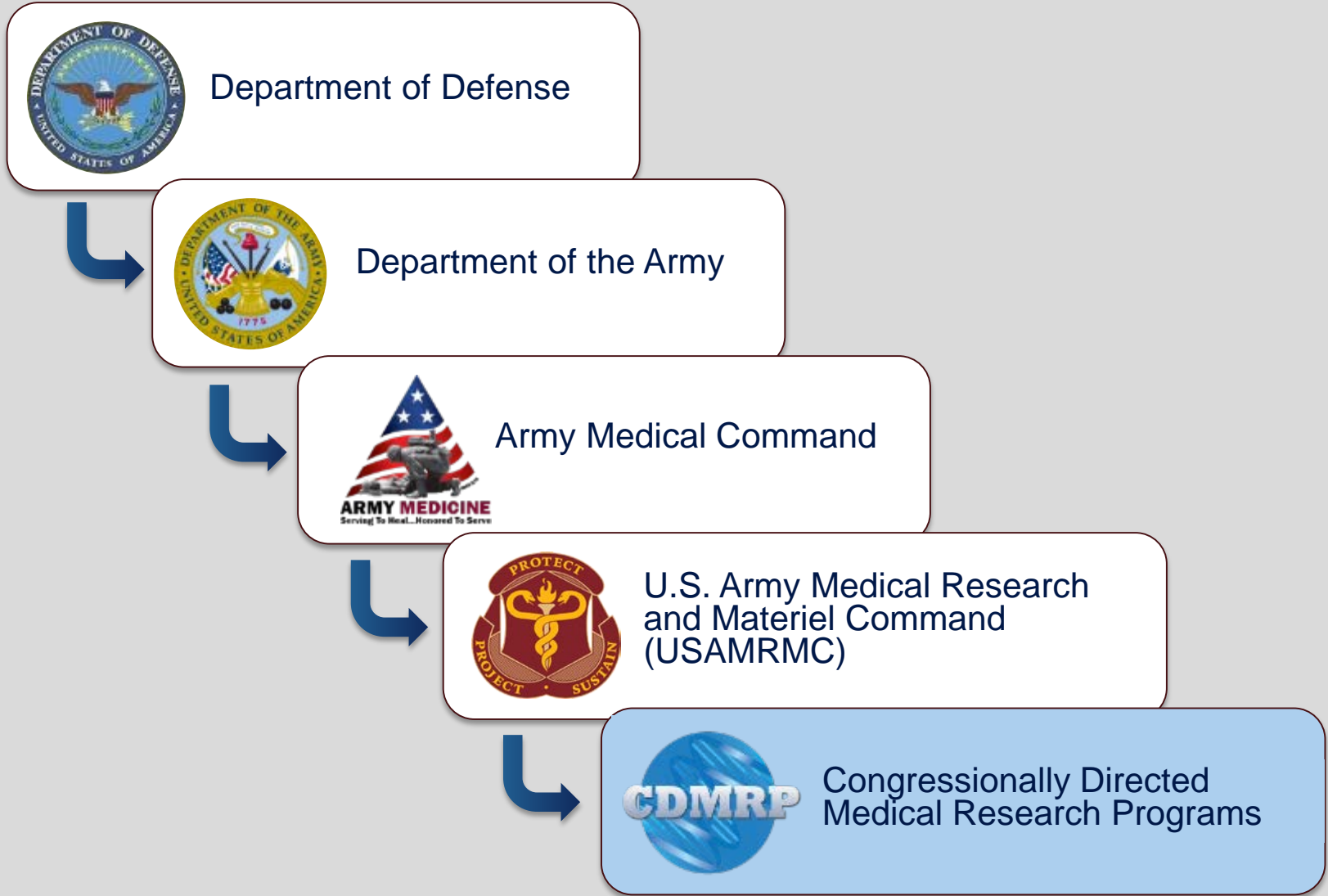
March 21, 2018

Outline

- ◆ **Overview of the Congressionally Directed Medical Research Programs (CDMRP)**

- ◆ **The CDMRP Gulf War Illness Research Program (GWIRP)**
 - ❖ Initiation and Funding History
 - ❖ Program Objectives
 - ❖ Funding Mechanisms and Funded Topics
 - ❖ VA and GWIRP coordination
 - ❖ Near and Longer Term Priorities

WHO is the CDMRP?



CDMRP Vision and Mission

Vision

**Transform healthcare for
Service Members and the
American public
through innovative and
impactful research**

FUNDING GROUNDBREAKING, HIGH-IMPACT RESEARCH

Mission

**Responsibly manage collaborative
research that discovers, develops,
and delivers health care solutions
for Service Members, Veterans and
the American public**

About CDMRP



◆ DoD PROGRAMS

- ❖ Provides support to Program Area Directorates (PADs)/Joint Program Committees (JPCs) for managing extramural and intramural research portfolios to advance their missions

◆ CONGRESSIONAL PROGRAMS

- ❖ Manages extramural research programs directed by Congress
- ❖ Started in 1992 with a focus on breast cancer research; currently includes 31 research programs
- ❖ Congress specifies the focus area; the CDMRP determines research strategy and competitively selects the best projects
- ❖ Unique public/private partnership encompasses the military, scientists, disease survivors, consumers, and policy makers
- ❖ Funds high-impact, innovative medical research to find cures, reduce the incidence of disease and injury, improve survival, and enhance the quality of life for those affected

◆ DIRECTOR

- ❖ Col Wanda Salzer

CURRENT PROGRAMS:

- Alcohol and Substance Abuse Disorders
- Amyotrophic Lateral Sclerosis
- Autism
- Bone Marrow Failure
- Breast Cancer
- Breast Cancer Semipostal
- Duchenne Muscular Dystrophy
- Epilepsy
- Gulf War Illness

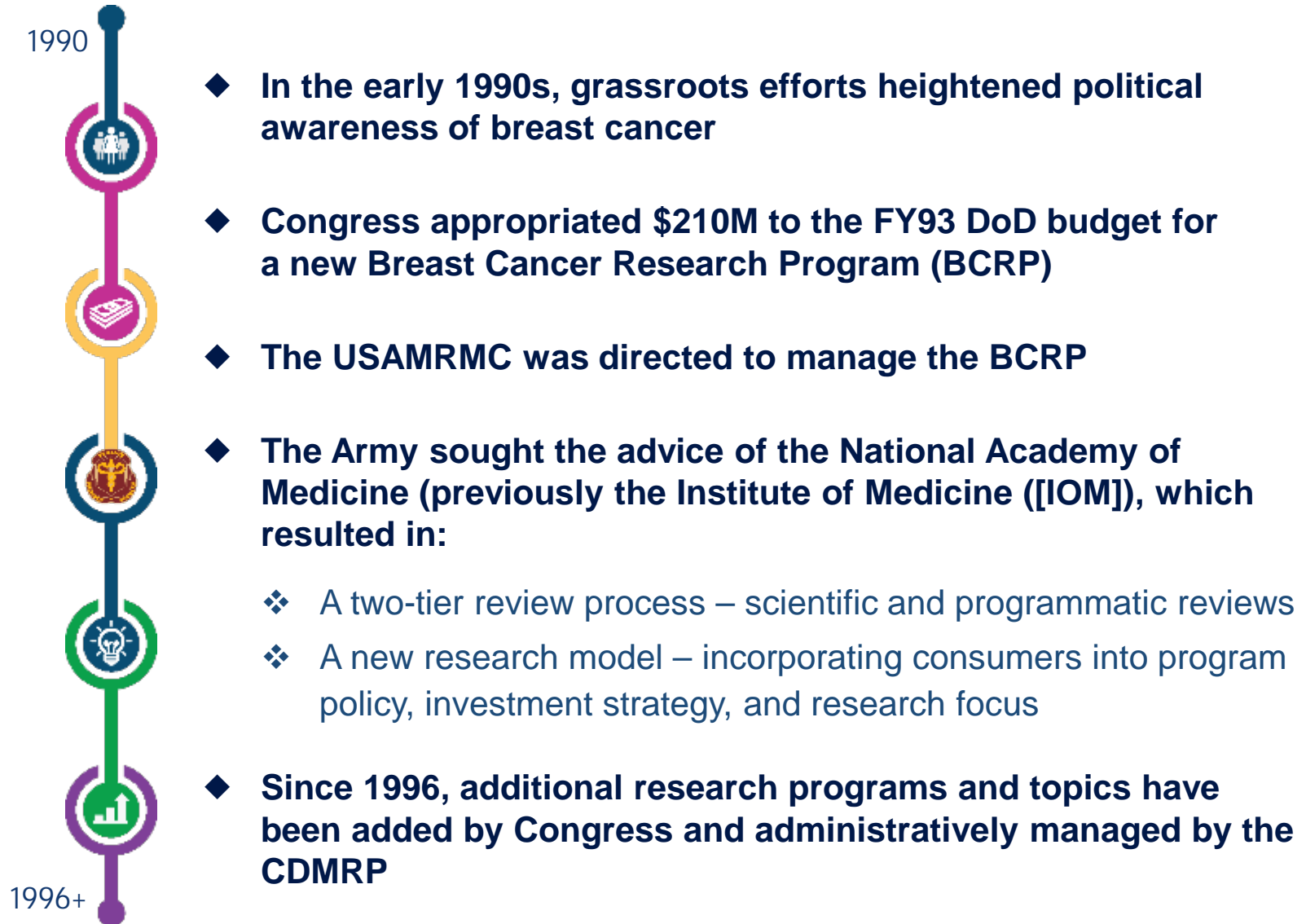
- Hearing Restoration
- Joint Warfighter Medical
- Kidney Cancer
- Lung Cancer
- Lupus
- Military Burn
- Multiple Sclerosis
- Neurofibromatosis
- Orthotics and Prosthetics Outcomes
- Ovarian Cancer

- Parkinson's
- Peer Reviewed Alzheimer's
- Peer Reviewed Cancer
- Peer Reviewed Medical
- Peer Reviewed Orthopaedic
- Prostate Cancer
- Reconstructive Transplant
- Spinal Cord Injury
- Tick-Borne Disease
- Tuberos Sclerosis Complex
- Vision

ADDITIONAL SUPPORTED DoD PROGRAMS:

- Defense Medical R&D
- Defense Medical R&D Restoral
- Psychological Health and Traumatic Brain Injury
- Small Business Innovation/ Small Business Technology Transfer
- Trauma Clinical

History



Two-Tier Review Process

To **find** scientifically meritorious proposals and **fund** those that best fulfill program goals

Peer Review

- Criterion-based: evaluate each application according to the mechanism-specific peer review criteria
- Determination of “absolute” scientific merit
- Outcome: Written critique and scores for individual criteria and overall merit

No standing panels

Peer reviewer panels are recruited *de novo* each year depending on mechanism-specific expertise needs

Partnership

Programmatic Review

- Comparison-based: comparison among proposals of high scientific merit
- Determination of program relevance, adherence to intent and portfolio balance (No “pay line”)
- Outcome: Funding recommendations

Programmatic panel member terms are typically set for 1-3 years

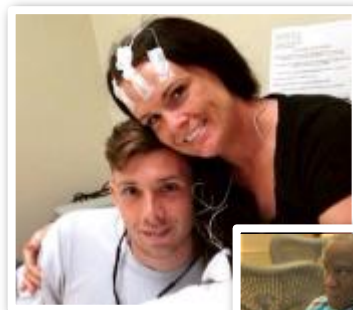
CDMRP may retain expertise for the benefit of the program

Consumers



The voices and experiences of consumers continue to play a pivotal role in the establishment and growth of CDMRP research programs

Over 2,100 consumers representing over 1,000 organizations have served on CDMRP Peer Review and Programmatic Review panels



FY17 Funding

Program	\$M
Alcohol and Substance Abuse Disorders	\$4.0
Amyotrophic Lateral Sclerosis	\$7.5
Autism	\$7.5
Bone Marrow Failure	\$3.0
Breast Cancer	\$120.0
Breast Cancer Research Semipostal	\$0.6
Duchenne Muscular Dystrophy	\$3.2
Epilepsy	\$7.5
Gulf War Illness	\$20.0
Hearing Restoration	\$10.0
Joint Warfighter Medical	\$50.0
Kidney Cancer	\$10.0
Lung Cancer	\$12.0
Lupus	\$5.0
Military Burn	\$8.0
Multiple Sclerosis	\$6.0
Neurofibromatosis	\$15.0
Orthotics and Prosthetics Outcomes	\$10.0
Ovarian Cancer	\$20.0

Program	\$M
Parkinson's	\$16.0
Peer Reviewed Alzheimer's	\$15.0
Peer Reviewed Cancer (14 Topics)	\$60.0
Peer Reviewed Medical (48 Topics)	\$300.0
Peer Reviewed Orthopaedic	\$30.0
Prostate Cancer	\$90.0
Reconstructive Transplant	\$12.0
Spinal Cord Injury	\$30.0
Tick-Borne Disease	\$5.0
Trauma Clinical	\$10.0
Tuberous Sclerosis Complex	\$6.0
Vision	\$15.0

Additional Supported DoD Programs/Projects ⁽¹⁾

Centers of Excellence	\$2.9
Defense Medical R&D	\$96.0
Defense Medical R&D CSI Restoral	\$35.3
Psychological Health and Traumatic Brain Injury	\$75.0
Small Business Innovation Research/Small Business Technology Transfer	\$0.7

⁽¹⁾ Approximate funding

TOTAL = \$1.1B



Gulf War Illness Research Program

FY08 National Defense Authorization Act

HR 1585 Conferees directed the Secretary of the Army to utilize the authorized funding ... to undertake research on Gulf War Illness. Conferees also directed that activities under the Gulf War Illness program include:

- No studies based on psychiatric illness and psychological stress as the central cause
- Studies of treatments for the complex of symptoms known as “Gulf War Illness”
- Competitive selection and peer review to identify research with the highest technical merit and military value
- Coordinate with similar activities in the VA and the NIH

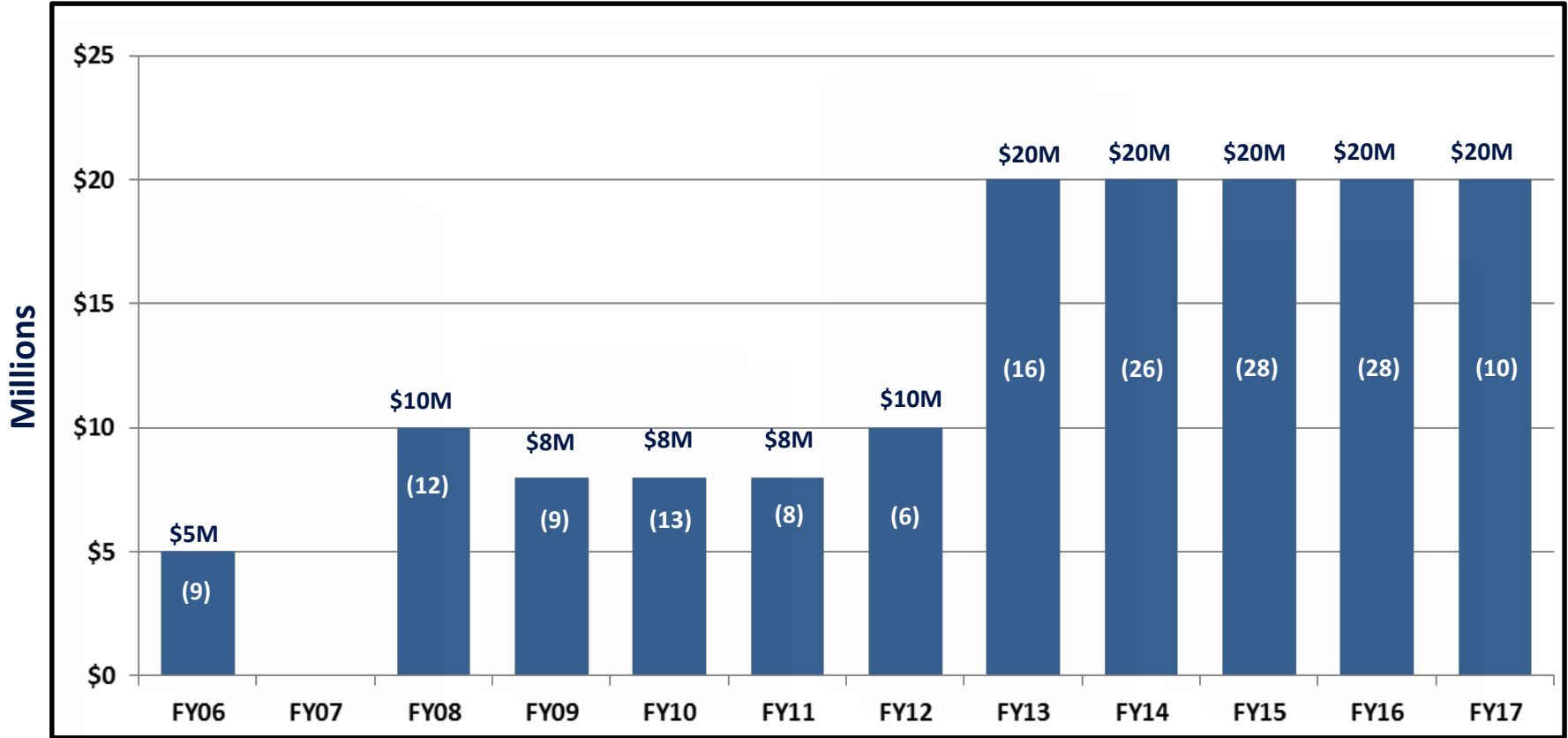
GWIRP Vision and Mission

**Improved health and lives of Veterans who have
Gulf War Illness**

**Fund innovative Gulf War Illness research to identify
effective treatments and accelerate their clinical
application, improve definition and diagnosis, and
better understand pathobiology and symptoms**



GWIRP Funding and Awards



- **Total Congressional appropriations:** \$149M
- **Total full applications received:** 495
- **Total awards:** 165

(# of Awards)

GWIRP Program Webpage

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News & Highlights

Department of Defense Gulf War Illness Research Program Anticipated Funding Opportunities for Fiscal Year 2018 (FY18)

FY17 GWIRP Recommended for Funding List

Resources Initiative by the GWIRP

More...

Vision

Improved health and lives of Veterans who have Gulf War Illness

Mission

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

News & Project Highlights

Gulf War Illness

Vision - Improved health and lives of Veterans who have Gulf War Illness

The Gulf War Illness Research Program (GWIRP) was initiated in 2006 to provide support for research of exceptional scientific merit to study the health effects of deployment on U.S. Warfighters during the 1990-1991 Persian Gulf War. The GWIRP challenges the scientific community to design high-impact research that will improve the health and lives of Veterans who have Gulf War Illness (GWI).



Program Book

GWII is characterized by multiple, diverse symptoms that typically include chronic headache, widespread pain, cognitive difficulties, debilitating fatigue, gastrointestinal problems, respiratory symptoms, sleep problems, and other abnormalities that could not be explained by established medical diagnoses or standard laboratory tests. The population of Veterans affected by GWII is a subset of the nearly 700,000 U.S. Warfighters who served during the 1990-1991 Gulf War. Studies indicate that approximately 25-32% of Gulf War Veterans continue to experience symptoms associated with their deployment.

The GWIRP focuses on funding innovative, competitively peer-reviewed research to (1) provide a better understanding of the pathobiology underlying GWII, (2) identify objective markers (biomarkers) for improved diagnosis, and (3) to develop treatments for the complex of GWII symptoms and their underlying causes. Our Vision is to make a significant impact on GWII and improve the health and lives of affected Veterans and their families.

The Gulf War Illness Landscape (136kb)

The GWIRP has prepared the above Landscape overview of what is currently known about topics consistent with the mission of identifying treatments, improving definition and diagnosis, and understanding pathobiology and symptoms. Applicants are strongly encouraged to read and consider The Gulf War Illness Landscape when preparing applications.

GWII Landscape

<p>Congressional Appropriations</p> <p>\$129.0 million FY06, FY08-16</p> <p>\$20.0 million FY17</p>	<p>Funding Summary</p> <p>155 Awards in FY06, FY08-16</p> <p>Recent Applications Recommended for Funding</p>	<p>Programmatic Panels</p> <p>FY18 Programmatic Panel</p> <p>Previous Years' Programmatic Panels</p>	<p>Peer Review Participants</p> <p>FY17 Peer Review Participants</p> <p>Previous Years' Peer Review Participants</p>
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155 Awards (FY06 – FY16)

\$149M (FY-06-FY17)

GWIRP Supported Initiatives

- Research Resources
- General Guidance for Gulf War Veteran Outreach and Recruitment

Outcomes and Resources

The Gulf War Illness Landscape

- Describes the state of the science and current research gaps
- Covers topics consistent with the GWIRP mission
- Provides context for research priorities
- Reference and link to the landscape are included in each GWIRP Funding Opportunity Announcement
- Applicants are strongly encouraged to read and consider when preparing applications

The Gulf War Illness Landscape

Lack of Standard Treatments

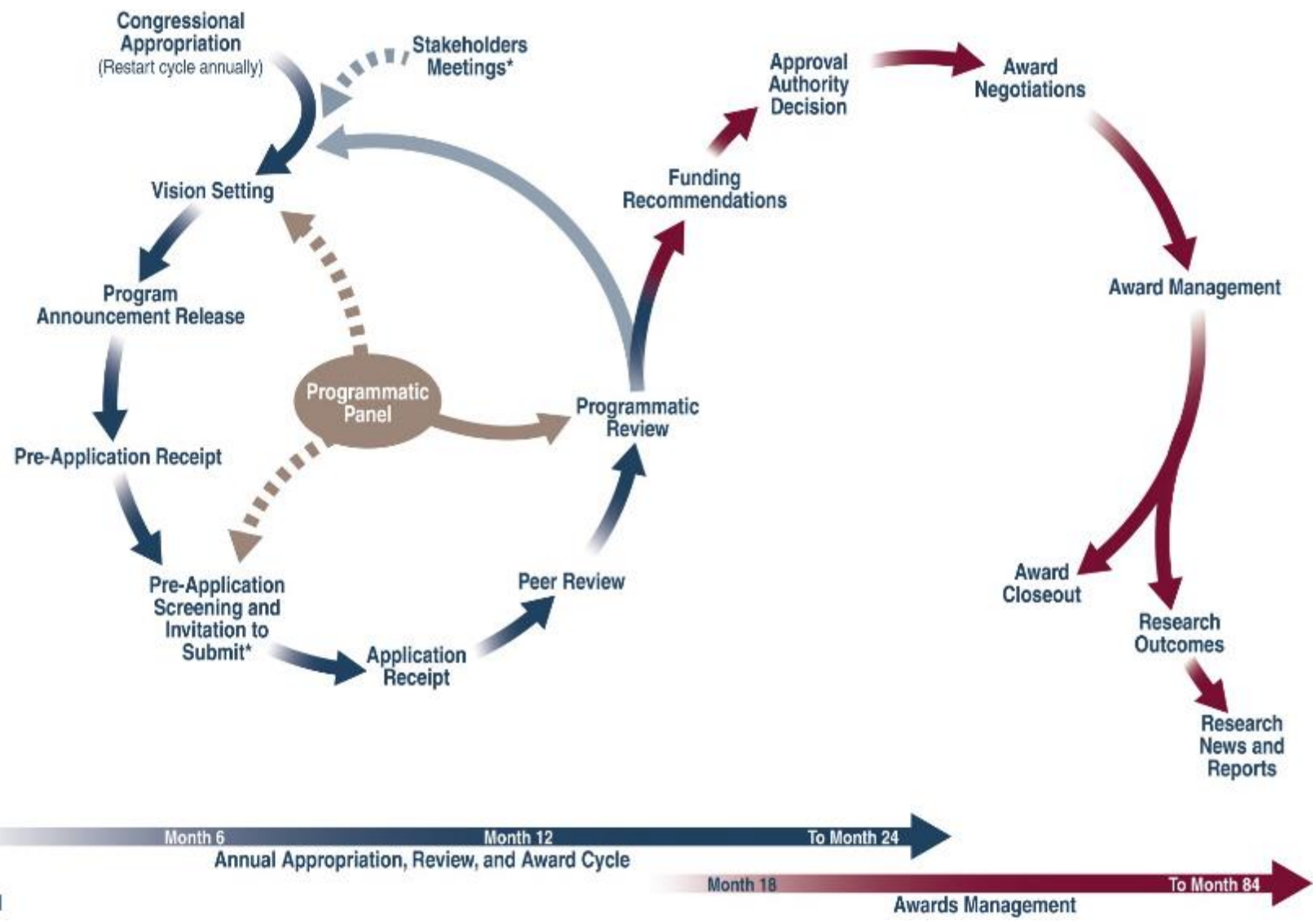
Clinical trials with the potential to have significant impact on the health and lives of Veterans with GWI continue to be an ongoing priority. In the absence of treatments specific for GWI, Veterans have tried a myriad of drugs and therapies to treat their varied symptoms. A primary focus of the GWIRP has been to fund research studies that test treatments for GWI and identify treatment targets. While most of these studies remain in progress, several have already shown varying levels of promise as GWI treatments.

Many Veterans suffering from GWI have sought out complementary/alternative therapies and holistic medicines for relief. Physical modalities (massage, sauna, physical therapy), lifestyle changes (diet change, exercise, avoidance of triggers), herbs, vitamins and nutritional supplements, alternative medicine practices (including but not limited to chiropractic modalities, acupuncture) and unconventional practices (Hubbard detoxification, hyperbaric oxygen therapy, chelation) have all been attempted by GW Veterans trying to ease their pain and other symptoms.

Ongoing trials of pharmaceutical interventions include re-purposing FDA-approved compounds targeting the major symptoms of GWI and/or are based on therapeutic targets identified in model systems. More treatment approaches based on known mechanistic pathways are needed, including a clear definition of clinical targets and defined clinical outcomes. The number of

Department of Defense Gulf War Illness Research Program, October 2016

Program Cycle



*As needed

GWIRP Programmatic Panel

◆ **Anthony Hardie, former Staff Sergeant USA (Chair)**

Florida Veterans for Common Sense

◆ **Roberta F. White, Ph.D.**

Boston University School of Public Health

◆ **Fiona Crawford, Ph.D.**

Roskamp Institute

◆ **Elizabeth Hauser, Ph.D.**

Duke University School of Medicine/
Durham VA Health Care System

◆ **David Jackson, Ph.D.**

U.S. Army Center for Environmental Health
Research

◆ **K. Jeffrey Myers, M.D.**

Department of Veterans Affairs

◆ **Marni Silverman, Ph.D.**

Henry M. Jackson Foundation for the
Uniformed Services University of the Health
Sciences

◆ **Vicky Whittemore, Ph.D.**

National Institute of Neurological Disorders and
Stroke, National Institute of Health

◆ **David K. Winnett, Jr., Captain
USMC Retired**

Veterans for Common Sense

GWIRP Program Objectives

Prioritize treatment and accelerate high-impact research

- Support clinical trials
- Support preclinical screening of therapeutics
- Support mechanistic research that can shed light on optimal treatment
 - Support discovery of therapeutic targets and markers of clinical efficacy
 - Support objective measures to better define GWI and subgroups

Create a structure that allows the best ideas to emerge from all disciplines

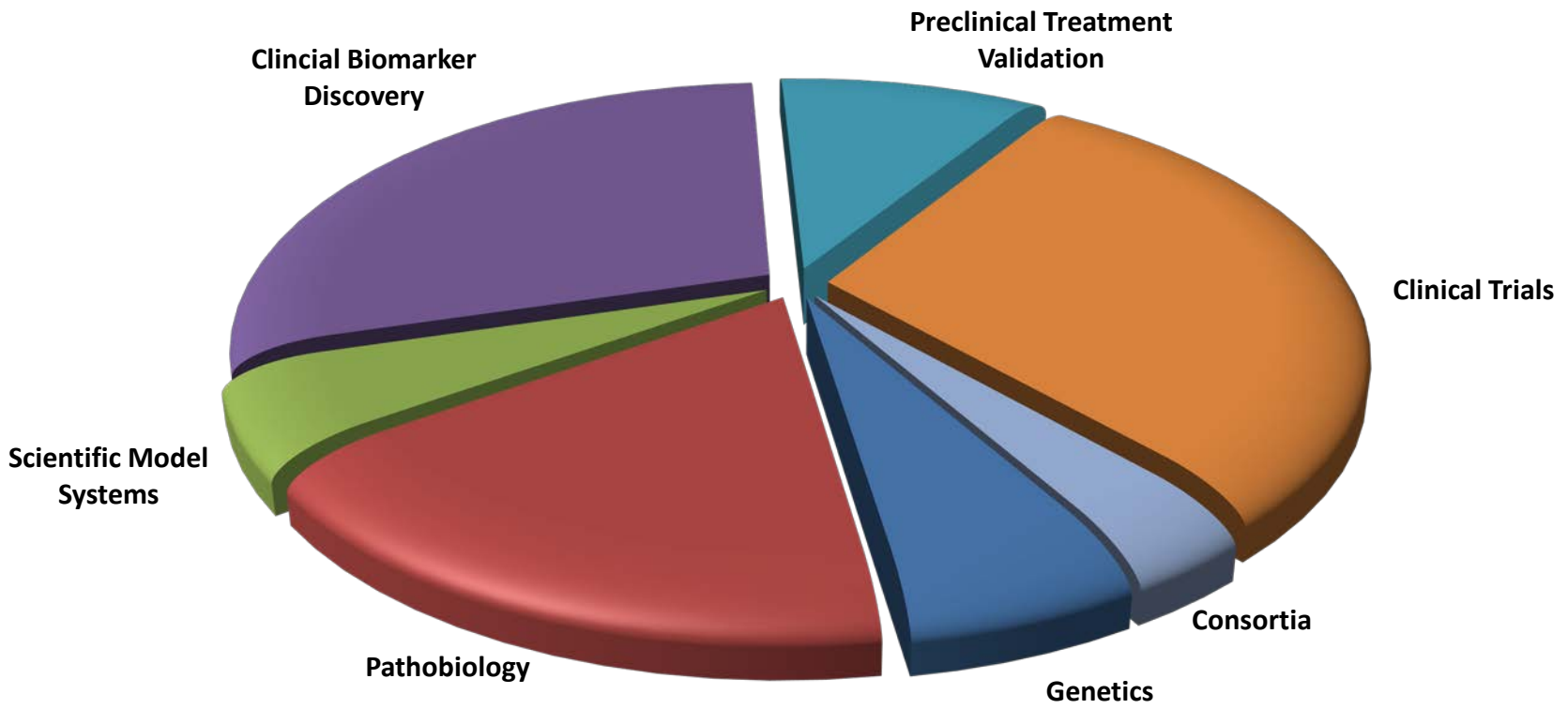
- All organizations and independent investigators at all levels are eligible
- Encourage innovation and stimulate creativity
- Facilitate meaningful collaborations
- Bring new investigators into the GWI field

GWIRP Strategy Through the Years

New funding opportunities developed to fill gaps and address program priorities

	FY06-11	FY12-14	FY15-16	FY17
Gap/Priority	Treatment Basic Research Disease Models Detection	Treatment Preclinical Research Detection Consortia	Treatment Clinical Translation Focused Topics Diagnosis New Investigators	Treatment Quality of Life Research Resources Focused Topics
Funding Opportunities Developed	<ul style="list-style-type: none"> • Clinical Trial • Innovative Treatment Evaluation • Investigator-Initiated 	<ul style="list-style-type: none"> • Clinical Trial • Innovative Treatment Evaluation • Investigator-Initiated • Consortium 	<ul style="list-style-type: none"> • Clinical Trial • Treatment Evaluation • Clinical Partnership • Focused Investigator-Initiated • Epidemiology • New Investigator 	<ul style="list-style-type: none"> • Clinical Consortium • Qualitative Research • Biorepository • Focused Investigator-Initiated
	51 awards	48 awards	56 awards	10 awards

GWIRP Investments FY06-FY16



Completed Clinical Interventions

◆ Coenzyme Q10

- ❖ Golomb BA, Allison M, Koperski S, et al. 2014. Coenzyme Q10 Benefits Symptoms in Gulf War Veterans: Results of a Randomized Double-Blind Study. *Neural Comput* 26(11): 2594-2651.

◆ Mifepristone

- ❖ Golier JA, Caramanica K, Michaelides AC, Makotkine I, Schmeidler J, Harvey PD, Yehuda R. A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War veterans with chronic multisymptom illness. *Psychoneuroendocrinology*. 2016 Feb; 64:22-30.

◆ Carnosine Therapy

- ❖ Baraniuk JN, El-Amin S, and Corey R. 2013. Carnosine treatment for Gulf War Illness: A randomized controlled trial. *Glob J Health Sci* 5(3):69-81.

◆ Acupuncture

- ❖ Conboy L, St. John M, and Schnyer R. 2012. The effectiveness of acupuncture in the treatment of Gulf War Illness. *Contemp Clin Trials* 33(3):557-562.

◆ Mind Body Bridging

- ❖ Nakamura Y, Tuteja AK, et al. Investigating Clinical Benefits of a Novel Sleep-Focused Mind-Body Program on Gulf War Illness Symptoms: A Randomized Controlled Trial. *Psychosomatic Medicine* (79), July/August 2017, pp.706-718.

◆ Nasal Irrigation

- ❖ Hayer S, Rabago D, Amaza I, et al. 2015. Effectiveness of nasal irrigation for chronic rhinosinusitis and fatigue in patients with Gulf War Illness: Protocol for a randomized controlled trial. *Contemp Clin Trials* 41:219-226.

◆ Naltrexone and Dextromethorphan

Ongoing Clinical Interventions

◆ Active Trials

- ❖ Probiotic (VSL#3)
- ❖ Intranasal insulin
- ❖ Botanical Microglia Modulators
- ❖ Yoga*
- ❖ Prednisone
- ❖ Methylphenidate plus a GWI-Specific Nutrient Formula*
- ❖ Flavonoid-rich dietary supplementation
- ❖ Portable vestibular stimulator
- ❖ D-cycloserine
- ❖ Low FODMAP diet
- ❖ Mitochondrial cocktail
- ❖ Liposomal Glutathione and Curcumin
- ❖ Vagus nerve stimulation
- ❖ Repetitive Transcranial Magnetic Stimulation (rTMS)
- ❖ Transcranial Direct Cortical Stimulation (tDCS)

- ❖ B-Cell depletion therapy
- ❖ Low-glutamate diet
- ❖ Resveratrol
- ❖ tDCS by targeting the occipital nerve field

◆ Newly Recommended

- ❖ Entanercept and mifepristone (through phase II)
- ❖ Antioxidant (CoQ10 or glutathione) + intranasal insulin
- ❖ Nutraceutical, Bacopa

Pre-Clinical Treatment Pipeline

Therapeutic	Mode of Action
Monosodium Luminol	Antioxidant
Dantrolene, Levetiracetam	Pharmacological blockade of the calcium plateau
Oleoylethanolamine	Ethanolamide to inhibit NFkB phosphorylation
IGF-1	Neurotrophic factor
Curcumin	Enzyme inhibitor
LNA-antimiR-124	Inhibition of microRNA-124
LDN/OSU-0212320	Brain-penetrant small molecule that increases glutamate transport
Naltrexone, Losmapimod, Minocycline	Inhibitors of neuroinflammatory pathways
Anatabine	Anti-inflammatory
Melatonin	Antioxidant and sleep inducer
Ketamine	Antidepressant, reversal of elevated Ca ²⁺ levels
Growth Hormone-Releasing Hormone (GHRH) Analogs	Inhibit the activation of signaling mediators common to the innate immune system
Sigma-1 Receptor Agonists	Restore mitochondrial energy metabolism in neurons and enhance neuroplasticity
Glycan conjugate immunotherapy	Restore the immune system balance
Glial and cytokine inhibitors (TNFα, IL-1)	Interfere with glial activation, inhibition of two major components of inflammatory signaling

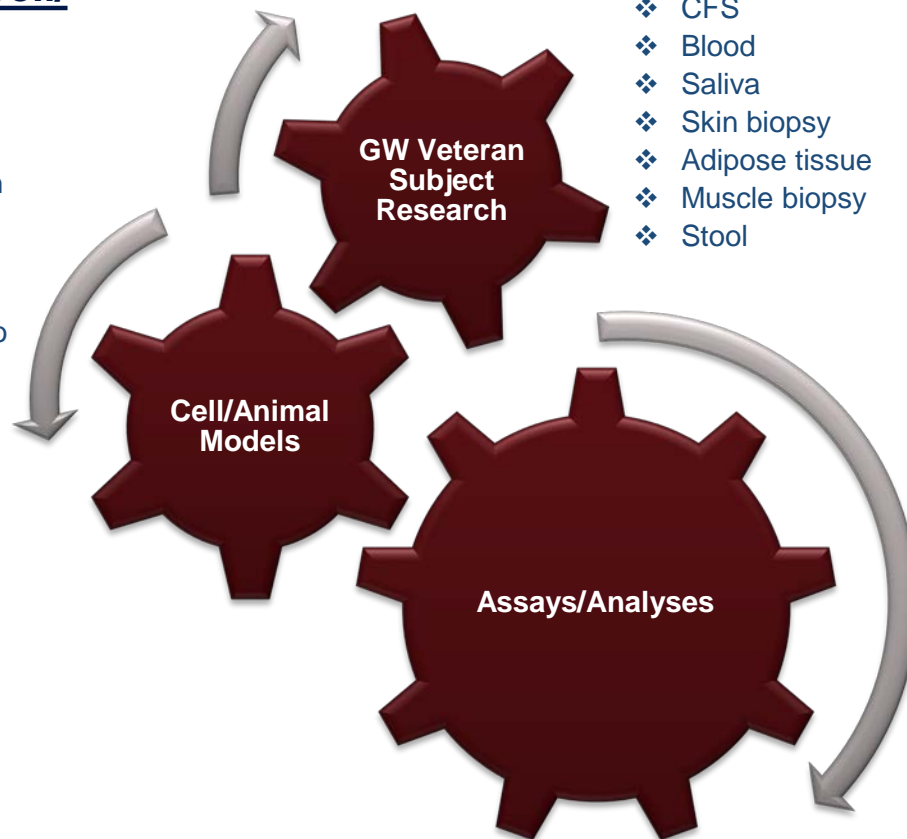
Mechanistic Research

GWIRP-Supported Cell/ Animal Models:

- ❖ iPSCs
- ❖ Low dose sarin
- ❖ DEET and permethrin
- ❖ PB and permethrin
- ❖ DFP preceded by corticosterone
- ❖ Repeated exposure to chlorpyrifos
- ❖ DEET, permethrin, chlorpyrifos, +/- PB
- ❖ Inhalation model

Limitations:

- Need to model long term sensitization as a consequence of initial exposure



GWIRP-Supported Clinical Sampling:

- ❖ CFS
- ❖ Blood
- ❖ Saliva
- ❖ Skin biopsy
- ❖ Adipose tissue
- ❖ Muscle biopsy
- ❖ Stool

Limitations:

- Length of time elapsed
- Lack of earlier data points
- Confounding effects of aging
- Repeated/lifetime exposures matter

GWIRP-Supported Assessments:

- ❖ Cytokine panels
 - ❖ Mitochondrial assays
 - ❖ Genetic analysis
 - ❖ Genomics/Proteomics/
Lipodomics
 - ❖ Genome-wide association
 - ❖ RNA-Seq
 - ❖ Neuroimaging
 - ❖ Neuronal cultures
 - ❖ Histology
 - ❖ Physiological testing
 - ❖ Cognitive testing
-
- ❖ Computational Modeling

Mechanistic Outcomes

Progress

Evidence of:

- Mitochondrial dysfunction
- Neuro/Immune system dysregulation
- Autonomic imbalance
- Altered brain structure and function
- Microvascular injury
- Evidence of SFPN
- Alterations in gut microflora
- Microtubule dysfunction
- Na⁺ and K⁺ channel dysfunctions
- Alterations in axonal transport
- Altered lipid homeostasis
- Altered calcium homeostasis
- Toll-like receptor priming
- Tau pathology
- Epigenetic alterations
- DNA breakage
- Detoxification pathways
- SNPs
- Gender differences

Challenges

- Availability of negative or neutral study outcomes to enable prioritization
- Different biological systems rarely evaluated in the same Veteran
- Few individual findings have been replicated/validated by multiple investigators

Opportunities

- Greater transparency
- DoD/VA coordination
- Multi-scale investigations
- Replication/validation studies
- Integrated approaches – combining computational modeling with animal models and clinical data

Potential Outcomes:

- Targeted and effective treatments
- Objective measures to define GWI and subgroups
- Markers of clinical efficacy

DoD GWIRP / VA Coordination

- **VA Gulf War Veterans' Illnesses Program Manger (PM) attends annual GWIRP Programmatic Review and Vision Setting meetings**
- **GWIRP contributes funding data and project information to the VA GWVI Report to Congress**
- **GWIRP PM attends RACGWVI meetings**
- **GWIRP PM participation on VA convened working groups**
- **Participation in GWI Workshops and VA field-based meetings**
- **GWIRP funds many VA Investigators**
- **VA has funded GWIRP spin-off proposals**
- **Regular briefings/updates between Gulf War PMs and electronic coordination (FedRePORTER)**

Fiscal Year 2018 Priorities

Treatment and Step-Wise Research Mechanisms

➤ Clinical Trial Initiatives

- Clinical trial award to move preclinical candidates into trial; projects may range from small proof-of-concept trials through expansion to large-scale, definitive trials
- Launch of the first set of trials under the newly established Clinical Consortium leveraging existing consortia organizations and collaborations

➤ Investigator-Initiated Focused Research

- Backbone of the program for discovery and preclinical development
- Two Tiers:
 - 1 - Discovery and proof of concept; no preliminary data
 - 2 - Validation and development; preliminary data in GWI field required
- Replication/validation of previous observations, including multiple model systems, replicating preliminary data with more time points, additional doses, etc. is encouraged

➤ Qualitative Research

- Fills gaps in treatment and care knowledge
- Development of materials aimed at clinicians or for Veterans/caregivers
- Explores not only care and treatment but barriers to knowledge and two-way communication

➤ Contributions to the Biorepository Resource Network

- Encourage submission of samples and data to the GWIRP supported Biorepository Resource Network
- Community research resource
- Establish common data elements and sample standardization

Resource-Generating Mechanisms

Longer Term Strategic Plan

- The GWIRP undertook a planning project in early 2018 to develop a more strategic, longer-term approach for the research under its management
- 3- to 5- Year Strategic Plan to be posted on the CDMRP Website Spring 2018

Plan Outline:

- Program Overview
- Current GWI Research Landscape
- GWI Funding – GWIRP and VA
- Strategic Objectives for the GWIRP
 - Strategic Direction
 - Strategic Goals
 - Short-Term Investment Strategy
- Measurable Outcomes – Tracking and Informing Future Initiatives

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- Bone Marrow Failure
- Breast Cancer
- NEW** Gulf War Illness
- NEW** Lung Cancer
- Multiple Sclerosis
- Ovarian Cancer
- NEW** Parkinson's
- NEW** Peer Reviewed Cancer
- Peer Reviewed Medical
- NEW** Peer Reviewed Orthopaedic
- NEW** Tick-Borne Disease

Anticipated FY18 Funding Opportunities →

Latest News

- VRP** Wireless, Web-Based Interactive Control of Optical Coherence Tomography with Mobile Devices [↗](#)
TVST, February 28, 2018
- VRP** Study finds genetic link between thinner corneas and increased risk of glaucoma [↗](#)
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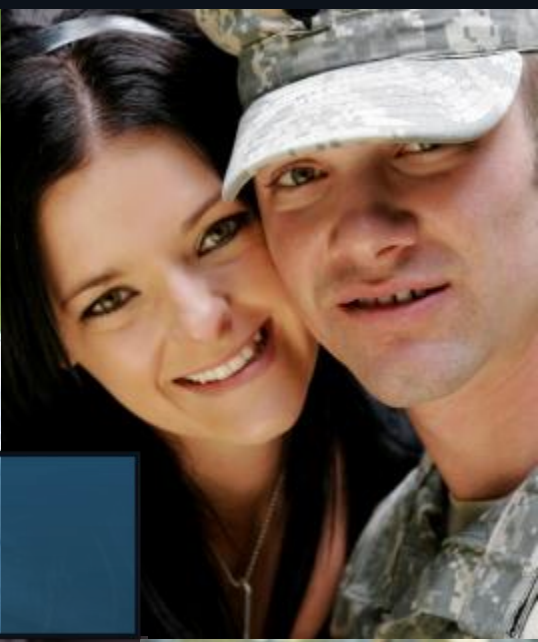
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