

**U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND (USAMRDC)
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS (CDMRP)
TOXIC EXPOSURES RESEARCH PROGRAM (TERP)
FISCAL YEAR 2022 (FY22) STAKEHOLDERS MEETING
VIRTUAL
15–16 JUNE 2022**

Summary of Stakeholders Meeting Outcomes and Identified Research Gaps

The following is a summary of the main topics discussed during the FY22 TERP Stakeholder's Meeting. Please note that all comments are not captured in this summary report. This summary also does not reflect the opinions or views of the TERP, the CDMRP or the Department of Defense (DOD).

A virtual Stakeholders Meeting of the FY22 TERP was held 15–16 June 2022. Consumers impacted by toxic exposures, advocates, other federal funders, and academic, clinical, and military subject matter experts across various fields of toxic exposures came together to discuss broad perspectives on research and knowledge gaps and patient priorities across the Topic Areas provided in the TERP's FY22 Congressional language, which include:

- Neurotoxin exposure
- Gulf War illness (GWI) and its treatment
- Airborne hazards and burn pits
- Toxic military exposures in general, including prophylactic medications, pesticides, organophosphates, toxic industrial chemicals, materials, metals, and minerals

Specifically, the goals of the TERP Stakeholders Meeting were to: (1) identify knowledge gaps, targeted outcomes, and patient needs related to the four major Topic Areas that align with the TERP's FY22 Congressional language, (2) identify underfunded areas of military-related toxic exposure research and patient care, (3) discuss coordination with other agencies/organizations that fund toxic exposure research, and (4) discuss potential approaches the TERP may use to close some of the identified gaps.

Meeting participants were identified based on responses to the TERP Request for Information (RFI) (results can be found in the TERP Stakeholders Book), and invites were balanced across backgrounds and disciplines. Prior to the meeting, participants were placed into breakout groups based on the area of interest/expertise they identified in their RFI response. Participants were asked to respond to a single pre-meeting question posted on SurveyMonkey © so they could succinctly provide their top three research gaps related to the Topic Area of their assigned breakout groups. The breakout groups were consistent with the four major Topic Areas from the FY22 TERP Congressional language that established the TERP. The four breakout groups were:

- Neurotoxin Exposure
- GWI and Its Treatment
- Exposures to Airborne Hazards and Burn Pits

- Other Military Service-Related Toxic Exposures in General, Including Prophylactic Medications, Pesticides, Organophosphates, and Toxic Industrial Chemicals, Materials, Metals, and Minerals

The meeting opened with plenary presentations from the CDMRP Director and TERP Program Manager, followed by research landscape presentations from TERP-relevant CDMRP programs, including the Gulf War Illness Research Program (GWIRP), Peer Reviewed Medical Research Program (PRMRP), and Neurotoxin Exposure Treatment Parkinson's Research Program (NETP), as well as from external coordinating agencies, including the Department of Veteran's Affairs (VA), National Institute of Neurologic Disorders and Stroke (NINDS), and Military Operational Medical Research Program (MOMRP). A copy of these briefing slides can be found in the attached enclosures.

Following the briefings, TERP Stakeholders Meeting participants were separated out into their breakout groups for discussion of the top research gaps as they pertain to that topic.

A summary of the stakeholders' discussion and input is provided below.

These are not the official programmatic gaps for the FY22 cycle. The stakeholder-defined gaps were used by the TERP Programmatic Panel to determine the program's strategy for funding opportunities. Please refer to future funding opportunities for any final gaps and Focus Areas associated with a specific application receipt cycle.

After the plenary briefings, participants were divided into four breakout groups as described above. The stakeholders were asked to review the breakout group's collective responses to the single pre-meeting SurveyMonkey© question regarding the three most important gaps in that Topic Area/breakout group. Once they reviewed and edited those gaps, they were asked to review the collective list of gaps/themes provided by the broader community in the RFI responses and determine whether any of those gaps should also be added to their list. After the RFI gaps were discussed, the group went through the gaps presented by the invited speakers during the plenary briefings. Towards the end of this breakout session, each breakout group had voted on and had their list of the top five gaps pertaining to their Topic Area. At the start of the second meeting day, a representative from each breakout group presented the top five gaps for their Topic Area to the larger stakeholder group.

A group discussion was held, allowing each breakout group to consider the larger group's input and discuss the identified gaps. The breakout groups then reconvened to review and, if necessary, revise their gaps. Each breakout group then voted to generate their final top five gaps for that Topic Area. The groups also discussed other gaps that were important to their respective Topic Areas, and some groups were able to discuss ideas for how the TERP may be able to close some of the gaps they identified.

A non-prioritized list of the top five gaps identified by each group, followed by a summary of their discussion and some of the other important gaps and research approaches identified, are provided below for each breakout group.

A. Neurotoxin Exposure

For the purpose of this conversation, the following definitions were used:

Neurotoxin- synthetic or naturally occurring substances that damage, destroy, or impair the functioning of the central and/or peripheral nervous system.

(<https://emedicine.medscape.com/article/1743954-overview>)

Toxicant- a poison that is made by humans or that is put into the environment by human activities. (<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/toxicant>)

The “Neurotoxin Exposures” breakout group identified the following topics as the five most important gaps in the neurotoxin exposures field:

- Understanding the relationship between chemical exposure and Parkinson's disease, Alzheimer's disease, and related disorders
- Basic mechanisms of neurotoxicity/neurodegeneration from exposure (from cellular systems through humans)
- Ability to predict and assess exposures
- Innovative treatments for people outside of the acute therapeutic window
- Recognizing the signs and symptoms of chronic low-level neurotoxicant exposures and providing effective therapeutics before permanent damage has been done

During the breakout group discussions of the top five gaps, the stakeholders noted a need to understand the morbidity and mortality in populations exposed to neurotoxins. They added that an understanding of the molecular mechanisms of neurotoxin exposure and disease progression is necessary to identify therapeutic targets. They also emphasized the importance of understanding the mechanistic impact of neurotoxin exposure levels, the need for fundamental studies on the impact of the route of exposure, and the need to understand epigenetics and germline perturbations. The idea of understanding multi-system, complex disorders that can result following neurotoxin exposure was also discussed. The stakeholders noted that data from both historical and future exposures need to be collected to enable an accurate understanding of the exposure dose and duration. They emphasized the importance of identifying and tracking diverse exposures in military operational environments and the lack of tools to monitor and prevent exposures.

In the larger group discussion, it was noted that understanding Mefloquine neurotoxicity should be added to this list as an important gap. It was proposed that consideration be given to identifying/defining/validating what the exposures are, as well as their impacts to military personnel. The stakeholders highlighted the importance of monitoring the effects in real time operational environments and being able to disseminate that information to the medics in the field. They recognized the warning signs, symptoms, and immediate effects of chemical exposures are poorly understood and a better understanding of these outcomes could lead to ways to minimize the impact of the exposure(s). It was also suggested the medications Service Members are already taking or other toxicants they are exposed to also need to be considered.

In addition to the top five gaps identified, stakeholders in the “Neurotoxin Exposure” breakout group discussed a number of other gaps and priorities. They indicated there is a need to identify the biological plausibility of neurotoxins having an effect on GWI. Another gap noted was the need to address environmental exposures from the perspective of the whole exposome. They also highlighted the lack of diagnostic and prognostic biomarkers of GWI caused by neurotoxins and a lack of new treatments for GWI. Stakeholders also identified the need to understand the relationship between neurotoxin exposures and concurrent and/or comorbid neurological and psychological disorders like traumatic brain injury and Post-Traumatic Stress Disorder. They noted the need for developing countermeasures or treatment strategies for severe acute exposures where multiple neurotoxicants are involved and/or neurotoxicant identity may not be known. In addition, they discussed the need to understand the interaction between substance abuse and exposure, the relationship between exposure and neurologic disease phenotype, and the importance of sex, age, and physical fitness as critical biological variables.

Once the top five gaps were identified, the group discussed the following ways the TERP could address these gaps:

- Encourage preclinical studies that can be rapidly translated to humans
- Encourage team science and interdisciplinary research, particularly between academic centers and military research institutes
- Facilitate access to military deployment and health databases
- Facilitate access to existing and/or improved biologic sample collection (e.g., historical samples, dried blood spot repository)
- Release targeted funding mechanisms and high risk-high-reward Topic Areas
- Develop big data sets and perform computational analyses
- Increase the diversity of study approaches
- Encourage collaboration with the VA to conduct large multicenter trials (e.g., the Post Deployment Cardiopulmonary Evaluation Network)
- Encourage better crosstalk between basic and clinical/translational science
- Support models of inhaled toxin exposure using surrogate groups exposed to toxins (e.g., burn, wildfire, house fire)
- Support integrated studies that span different model systems

B. GWI and Its Treatment

The “GWI and Its Treatment” group first identified the following as their top five goals:

- Treatments that are effective and available clinically
- Biomarkers of GWI
- Pathological mechanisms
- Translational research: Translate hypotheses into clinical trials
- Education of VA health care providers regarding GWI research

However, on their second day of discussions, the “GWI and Its Treatment” breakout group further refined their list of gaps to include:

- Treatments and therapeutic strategies that are rapidly deployed to clinical care
- Need for an International Classification of Diseases (ICD) 10 code for GWI and effective clinical care by specifically educated clinicians
- Rapid translation of promising preclinical model findings to clinical research and clinical trials
- Improved definition and diagnosis of GWI
- Understanding of GWI’s pathological mechanisms

During the discussions of these top five gaps, the stakeholders indicated that focusing on existing drugs/treatments or combinations thereof should be prioritized so they can rapidly be used to treat those living with GWI. The notion of individualized treatments was also discussed. The stakeholders identified the need to develop a standard assay that can be used across studies to enable outcomes comparison. They noted that another area that needs to be addressed is the need for feedback to flow from healthcare providers to researchers and from researchers to healthcare providers in order to help reach a consensus regarding which animal model will move the studies closer to clinical trials. The stakeholders in this group discussed the need for animal models that capture the adverse health effects of toxic exposures and how these models could also be used to assess biomarkers. They emphasized the importance of prioritizing the advancement of most promising studies and the need for preclinical and clinical researchers to work together. The stakeholders in this group recommended the continued use of common data elements, biorepositories, and a clinical consortium established by the previous GWIRP. They noted the need for biomarkers to assess treatment efficacy and how some biomarkers may provide information towards an ICD code for GWI.

The stakeholders discussed the importance of the link between genes and exposure outcomes, adding that this link may lead to neurodegeneration. They highlighted the need to research areas including, but not limited to, mechanisms of GWI and their interaction with the aging process, the role of neuroinflammation and mitochondrial function, gut dysfunction, and other comorbidities, such as sleep apnea and gastroesophageal reflux disease. They noted the lack of acknowledgement and communication that Veterans receive from their health care providers and emphasized the impact on their mental health and continuation of care. They also discussed the importance of identifying the interaction of complex exposures and mild traumatic brain injuries and Post-Traumatic Stress Disorder.

Throughout the discussions and refinement of the top five gaps, the stakeholders in this group identified a few other gaps, including the need to develop and/or validate preclinical in silico, in vitro and in vivo models, particularly models of exposure, exposure effects, and illness. They also highlighted the need to understand neurotoxicant-induced illnesses, including GWI, Parkinson’s disease, and brain cancer, noting that this is a critical area that is understudied. Once the five gaps and other priorities were identified, the group discussed the following ideas and approaches regarding how the TERP may fill some of these gaps in the field:

- Encourage team science and interdisciplinary research

- Translate models to clinical trials
- Encourage preclinical and clinical scientists and physicians to work together, possibly through partnered awards
- Improve preclinical trials to be deployable to the Gulf War Veterans
- Support clinical and translational cohort studies focused on epidemiology and etiology
- Ensure continuation of these for GWI research and how they may serve as models for other toxic exposures
 - Common data elements
 - Continued use and ensure that they can be improved upon
 - May apply to other areas of TERP
 - Biorepositories
 - Consider blood samples when leaving the DOD
 - Consider collecting samples from offspring
 - Have been invested in and should be leveraged going forward
 - Identified research cohorts
 - Consortium structure
- VA registries
 - Need better access to researchers for recruitment
- Defense Manpower Data Center data
 - All Service Member data can be useful for human studies
 - Need better access to researchers for recruitment

C. Exposures to Airborne Hazards and Burn Pits

The following are the top five gaps identified by the stakeholders in the exposures to “Airborne Hazards and Burn Pits” breakout group.

- Diagnostics – standard set of tests to rule in certain disease and rule out others (including, but not limited to, small airway disease)
- Identifying and understanding exposures/risks and how that impacts outcome (exposure assessment)
- Mechanisms and specific toxicants related to airborne hazards and health effects
- Longitudinal studies to determine long-term outcomes
- Use of big data and or machine learning for exposure assessment and clinical phenotyping (connecting multiple datasets)

The stakeholders noted the need for standard protocol recommendations for pulmonary disease, not just for small airway disease. They also highlighted the need for better ways to identify the

type of respiratory diseases beyond the standard tests, noting the importance of less invasive, cost-effective biomarkers and the need for highly relevant control populations. They noted the need for a better exposure assessment, including the effects of particulates versus the effects of compounds, the amplified effects of longer exposures, and the effects of simultaneous exposures to multiple compounds. They also indicated the need to prevent exposures by anticipating and controlling them was also important. The stakeholders discussed mechanisms and specific toxicants related to airborne hazards and health effects and the longitudinal studies necessary to determine long-term health outcomes. They highlighted the long-term effects of airborne hazards and specific incidents associated with those deployed during Operation Enduring Freedom and Operation Iraqi Freedom. They noted the correlation between toxins and carcinogens, including clinical manifestations and symptoms and the need to evaluate the immune responses in the lung. There were discussions on the need to understand how the route of exposures can impact the effects and how other organs beyond the lungs may also be effected. The stakeholders then discussed the use of big data and machine learning for exposure assessment, genomics, and clinical phenotyping, noting that big data and machine learning are essential when trying to separate normal and diseased patterns. In addition, they noted that these tools will be able to characterize computed tomography imaging to find patterns and enable the creation of a predictive model.

The stakeholders in this breakout group also discussed other gaps that, while important, did not rise to their top five list. One of these gaps included the need for studies to link specific exposures to phenotypes and studies understanding the complexity of mixed exposures. They also identified a need to identify exposure limits and how there is a current lack of research tying exposures to future exposure mitigation and prevention strategies. The group also discussed the lack of data and research linking exposures to impactful treatment solutions. The discussion for the group eventually came to the topic of deployment-related respiratory disease from exposures to airborne hazards and burn pits. The group agreed there is a need for low-cost treatments for these exposures, as well as low-cost prevention measures. Discussions occurred regarding many topics and gaps within the field; however, these were the main secondary gaps discussed.

After finalizing their top five gaps on the second day, the group discussed the approaches the TERP may use to close these gaps:

- Develop better diagnostic assays
- Develop non-invasive screening methods
- Support models of inhaled toxin exposure using surrogate groups exposed to toxins (e.g., burn, wildfire, house fire)
- Encourage preclinical studies that can be rapidly translated to humans
- Encourage better crosstalk between basic and clinical/translational science
- Support clinical and translational cohort studies focused on epidemiology and etiology
- Understand both short-term outcomes and potential long-term effects of toxic exposures
- Develop big data sets and perform computational analyses

D. Other Military Service-Related Toxic Exposures in General, Including Prophylactic Medications, Pesticides, Organophosphates, and Toxic Industrial Chemicals, Materials, Metals and Minerals

The following are the top five gaps that were identified by the stakeholders in the “Other Military Service-Related Toxic Exposures in General, Including Prophylactic Medications, Pesticides, Organophosphates, and Toxic Industrial Chemicals, Materials, Metals and Minerals” breakout group at the end of the first day.

- Effects/impact/outcomes of human (including acute and chronic multi-pathway) relevant exposures (toxicodynamics and toxicokinetic)
- Toxidrome spanning therapeutics/treatment strategies
- Understanding individual exposures and their links to individual disease outcomes
- Understanding effect modifiers/host factors of toxic exposures (for example pathophysiology, genetics, co-exposures, and sex)
- Advancing exposure assessment methodologies

During their discussion on the second day, the breakout group worked to refine the “toxidrome spanning therapeutics/treatment strategies” gap to the “broad spectrum prevention and treatment strategies that address multiple types of exposures with common symptoms” gap. However, the group was unable to come to a consensus on this gap as there were concerns that fundamental science in this area was insufficient to thoroughly develop this gap.

During the discussion and refinement of these top five gaps, the stakeholders noted that the field needs a better understanding of the kinetics and diagnostics of exposures and the ability to differentiate between occupational and non-occupational exposures. Within this discussion of kinetics and diagnostics, metals and minerals were identified as substances of interest, as were polyfluoroalkyl substances. The group then discussed the difference between plastics and microplastics in terms of exposures. There were differences in opinions on whether this topic should be included within the subgroup. Pesticide exposure was another priority identified by the breakout group. Toxidromes were identified as another gap in the field, as they can be used to understand treatment options, individual exposures, and how the exposures may occur. Repository development was specifically mentioned by the stakeholders as an important gap to be addressed. They discussed the impact of these exposures and how it is important to understand how an individual’s exposures can then be linked to a disease outcome.

The stakeholders noted the importance of understanding both single and combination exposures, as people often are not exposed to just one material/chemical. Stakeholders noted that exposures that occur on military installations should also be of importance, as should the impacts of non-ionizing radiation. The group also discussed non-chemical exposures such as physiological stress and heat stress, noting that these types of exposures can impact the way the body reacts to a chemical exposure.

In addition to the top five gaps that the “Other Military Service-Related Exposures” breakout group voted on, they discussed other important gaps. Mefloquine neurotoxicity and pyridostigmine bromide (PB) were highly discussed exposures in this breakout session, and the

group identified a need to understand the mechanisms behind these and other exposures. The group thought that further evaluation of mechanistic studies surrounding the impact of toxic exposures on oxidative stress, epigenetic changes, and inflammation were also important. In addition, the stakeholders identified that there is a need to understand genetic markers that drive susceptibility to adverse outcomes following toxic exposures. Another discussion was held concerning the effects of direct exposures and irritants and how they compare to the systemic effects of toxic industrial chemicals and materials. The group noted that key exposures need to be identified and information needs to be disseminated to Service Members in order to provide awareness and increase preventative strategies. The stakeholders also identified that repurposing drugs for military Service-related toxic exposures may facilitate new exposure prevention and mitigation strategies. There was also a robust discussion on the molecular and biochemical effects of new generation per- and polyfluoroalkyl substances (PFAS).

The group also discussed a high level list of exposures:

- Toxic/rare earth and heavy metals
- Other metals (Organometallics, metals, minerals, nanoparticles, non- physiologic metals)
- Plastics, plasticizers, microplastics, di(2- ethylhexyl) phthalate (DEHP) in plastics
- Toxic minerals
- Lipophilic toxicants- including legacy persistent organic pollutants and flame retardants
- Polycyclic aromatic hydrocarbons (PAHs)
- PFAS, including new-generation PFAS (e.g., Gen X), legacy PFAS, or a combination of new and legacy PFAS together
- Particulate matter
- Prophylactic medications (PB and Mefloquine)
- Pesticides, insect repellents and organophosphates (e.g., Permethrin and N,N-diethyl-meta-toluamide [DEET])
- Radiation exposures

Due to time constraints and the breadth of topics for discussion by this breakout group, the stakeholders were unable to wrap up with a formal conversation on research approaches the TERP could use to address some of the aforementioned gaps. However, many research approaches were discussed during the context of their discussion on the research, knowledge, and patient need gaps. The following approaches were discussed:

- Understanding the biological mechanisms underlying adverse human health effects
 - Model system development
 - Epidemiology studies
- Integration of human epidemiology, in vitro, in vivo, and in silico data sets
- Organizing and standardizing data to have maximum benefit and availability for future use

- Data sharing

E. Crosscutting Themes

After the breakout discussions, a group discussion of common crosscutting themes was briefly held. Some of these and other crosscutting themes or suggestions that emerged between the breakout groups are provided below.

The conversation about the crosscutting themes began with a discussion on the work that has been done in GWI and a recommendation that the previous work may serve as a model for other toxic exposures. Stakeholders specifically discussed the GWIRP structure for consortia, research cohorts, common data elements, and biorepositories, as these items have worked well in GWI research and the knowledge and structure may be useful for other Topic Areas. The need for the development of biomarkers to aid in diagnosis and determination of an individual's exposure was also identified as a crosscutting theme. Stakeholders identified the need for effective treatments and mechanisms to evaluate treatment efficacy across all of the Topic Areas. The need for preclinical exposure models and mechanisms that can identify long-term effects of acute and chronic exposures were also discussed. Identifying the underlying pathological mechanisms in differently exposed cohorts was another gap identified as a crosscutting theme. The stakeholders agreed that the effects of low-level neurotoxicant exposures and gene exposure interactions need to be explored. Throughout the Topic Areas, there is a need to perform mechanistic studies on specific pathways that are impacted by exposures. Studies aimed at understanding the progression from acute toxicity to long-term illness were also identified as a crosscutting theme. The importance of exposure combinations and mixtures was also a common theme across multiple breakout group conversations.

TERP Next Steps

The lists of gaps from each breakout group were discussed at the TERP FY22 Vision Setting Meeting to inform the discussions of the program's Focus Areas and investment strategy. All outcomes from the Stakeholders Meeting were available to the TERP Programmatic Panel. The outcomes from the Stakeholders Meeting may inform the TERP's Strategic Plan (near- and long-term plans and goals).

Meeting Presentations

Enclosure 1
Moment of Silence Presentation

Moment of Silence

Moment of Silence
Ms. Chelsey Simoni



MRS. CHELSEY SIMONI, RN, MSN, MPH, FP-C

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OUR WHY



SGT Pat Sullivan, 24 years
Acute Respiratory Failure

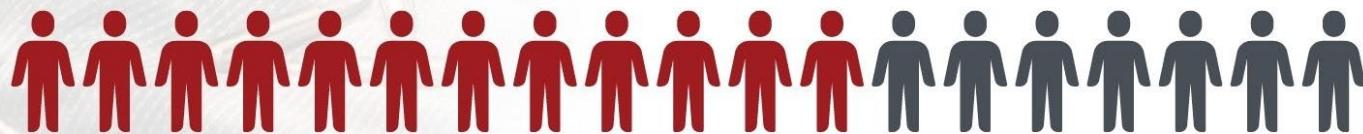
SSG Shawn McCann, 36 years
Acute Myeloid Leukemia

SGM David McDaniel, 48 years
Pancreatic Cancer

COL Rod Coffey, 54 years
Sudden Heart Failure

SSG Eddie Contreras, 45 years
Pancreatic Cancer

SGM Rob Bowman, 44 years
Cholangiocarcinoma



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IRAQ: TOP REPORTED EXPOSURES

Operation Iraqi Freedom (March 2003 - December 2011)



JET FUELS, OILS,
DIESEL AND LEADED
GASOLINE, BURN PITS



UNEXPLODED
ORDNANCE, SHELL
CASINGS



DEPLETED URANIUM,
CHEMICAL
MUNITIONS,
SARIN GAS



IED, VBIED
EXPLOSIONS, ROCKET
ATTACKS



SANDSTORMS, DUST
STORMS, POOR AIR
QUALITY



(Poisson, Boucher, Selby, Ross, Jindal, Efird & Bith-Melander, 2020)

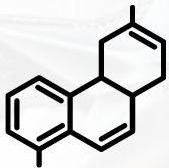
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AFGHANISTAN: TOP REPORTED EXPOSURES

Operation Enduring Freedom (October 2001 to August 2021)



UNEXPLODED
ORDNANCE, SHELL
CASINGS



CHEMICALS, DIOXINS,
FURANS, HEAVY
METALS



MUNITIONS AND
ARMOR MADE WITH
DEPLETED URANIUM



SULFUR GASES,
LOCAL AIR
POLLUTION



TUBERCULOSIS,
VIRAL AND BACTERIAL
INFECTIONS



(Poisson, Boucher, Selby, Ross, Jindal, Efird & Bith-Melander, 2020)

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TOXIC EXPOSURES: GO BEYOND BURN PITS

VIRGINIA



GERMANY



SOUTH KOREA



COLORADO



MISSISSIPPI



AFRICA

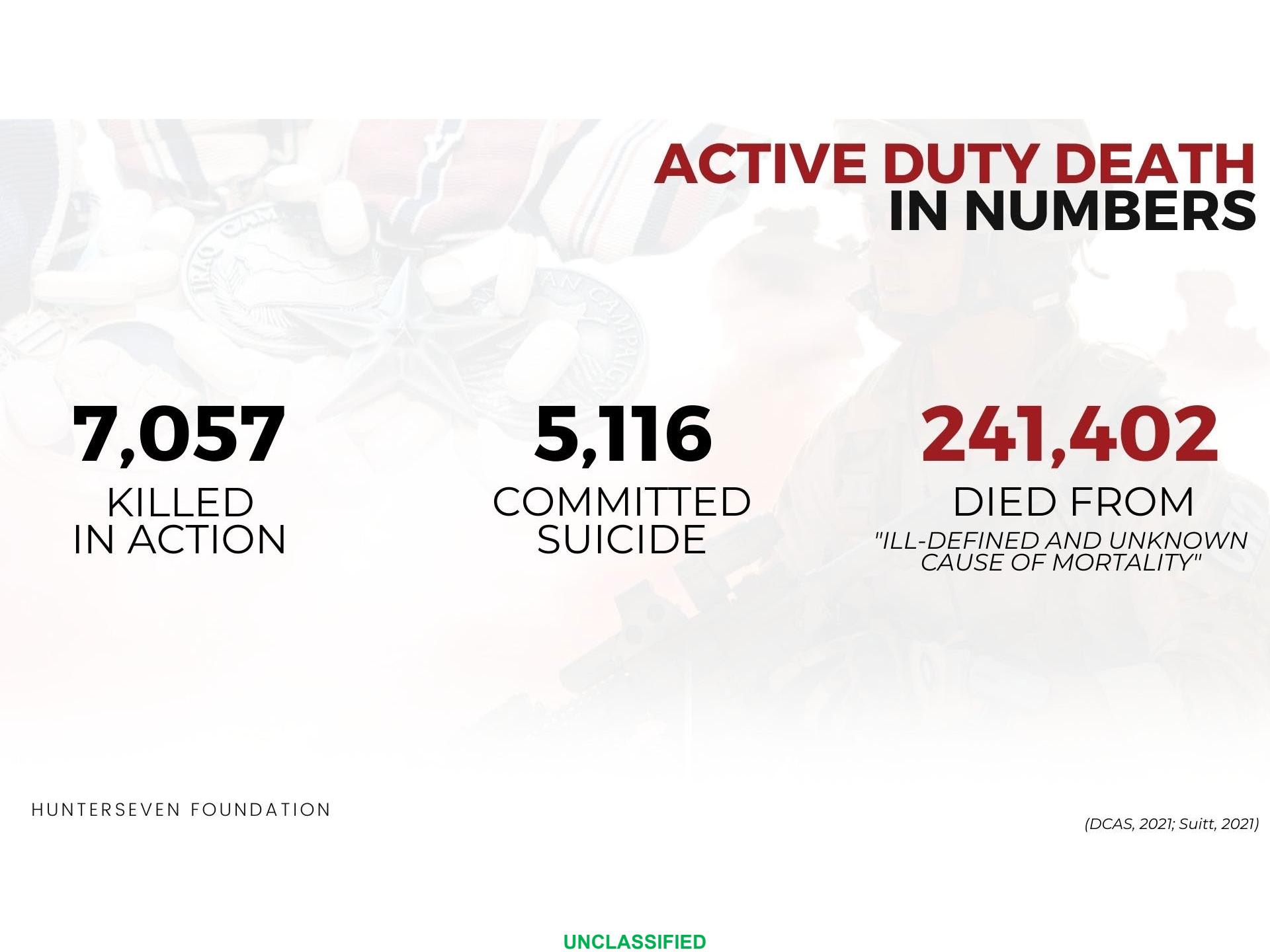


JAPAN



(EPA.gov, Natl. Priorities List, May 2022; EPA.gov, IRIS Advanced Chemical Database, 2022; DOD DENIX Munitions Response Site Inventory, 2022)

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ACTIVE DUTY DEATH IN NUMBERS

7,057

KILLED
IN ACTION

5,116

COMMITTED
SUICIDE

241,402

DIED FROM
"ILL-DEFINED AND UNKNOWN
CAUSE OF MORTALITY"

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(DCAS, 2021; Suitt, 2021)

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WHERE IS THE DISCONNECT

27%

POST-9/11 VETERANS

utilize the Department of Veterans Affairs for medical care. The majority use outpatient, civilian providers.

4%

**OF CIVILIAN
REGISTERED NURSES**

were deemed "*competent*" to provide veteran-centric care in civilian settings.

16%

**OF CIVILIAN CARE
PROVIDERS**

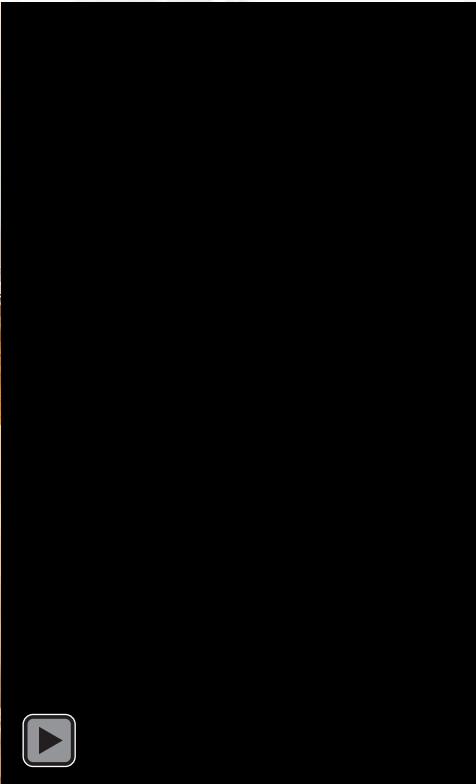
in civilian care centers assessed those who were identified as veterans for exposures to toxins.

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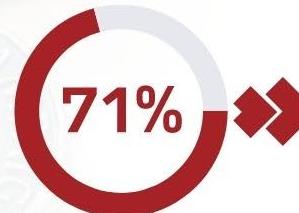
(Bonzanto et al., 2019; Waszak & Holmes, 2017; Gade & Hung, 2021)

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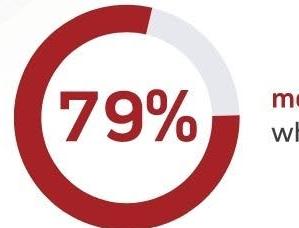
SECONDARY PREVENTION SCREENING SAVES LIVES



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of cancer deaths are caused by cancers not commonly screened for.^{4,5}



mortality rate
when detected late



mortality rate
when detected early

Pending Publication: Simoni, C., Costello, J., Ratliff, J., Blanchette, L., 2022)

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Enclosure 2
CDMRP Overview

The Congressionally Directed Medical Research Programs

HIGH-IMPACT RESEARCH

COL Sarah B. Goldman
Director, CDMRP

15 June 2022



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CDMRP
Department of Defense



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CDMRP Overview



Vision and Mission

Vision

Transforming healthcare through innovative and impactful research



Mission

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

CDMRP - Organizational Structure



Department of Defense



Department of the Army



Army Futures Command



U.S. Army Medical Research
and Development Command
(USAMRDC)



Congressionally Directed
Medical Research Programs

About CDMRP





Hallmarks



- ◆ Congress adds targeted research funds to the DOD budget
- ◆ Funds high-impact innovative research
- ◆ Avoids duplication with other funding agencies and targets unfunded/unmet gaps
- ◆ Funding opportunities publically announced and competed
- ◆ Follows the National Academy of Medicine-recommended model for application review
- ◆ Consumers participate throughout the process and are the “True North” and foundation of the programs
- ◆ Annually adapts each program’s vision and investment strategy allowing rapid response to changing needs
- ◆ Funding flexibility
 - ❖ Funds obligated up-front; limited out-year budget commitments
 - ❖ No continuation funding
 - ❖ No “pay line” – funding recommendations are based on portfolio composition, adherence to mechanism intent, relative impact, and technical merit
- ◆ Transparency and accountability to stakeholders
- ◆ Low management costs maximize research dollars

CDMRP FY22 Appropriations

Research Program	FY22 \$M	Research Program	FY22 \$M
Alcohol and Substance Use Disorders	\$4.0	Orthotics and Prosthetics Outcomes	\$20.0
Amyotrophic Lateral Sclerosis	\$40.0	Ovarian Cancer	\$45.0
Autism	\$15.0	Pancreatic Cancer	\$15.0
Bone Marrow Failure	\$7.5	Parkinson's	\$16.0
Breast Cancer	\$150.0	Peer Reviewed Alzheimer's	\$15.0
Chronic Pain Management	\$15.0	Peer Reviewed Cancer (20 Topics)	\$130.0
Combat Readiness Medical	\$10.0	Peer Reviewed Medical (50 Topics)	\$370.0
Duchenne Muscular Dystrophy	\$10.0	Peer Reviewed Orthopaedic	\$30.0
Epilepsy	\$12.0	Prostate Cancer	\$110.0
Hearing Restoration	\$10.0	Rare Cancers	\$17.5
Joint Warfighter Medical	\$40.0	Reconstructive Transplant	\$12.0
Kidney Cancer	\$50.0	Spinal Cord Injury	\$40.0
Lung Cancer	\$20.0	Tick-Borne Disease	\$7.0
Lupus	\$10.0	Toxic Exposures	\$30.0
Melanoma	\$40.0	Traumatic Brain Injury and Psychological Health	\$175.0
Military Burn	\$10.0	Tuberous Sclerosis Complex	\$8.0
Multiple Sclerosis	\$20.0	Vision	\$20.0
Neurofibromatosis	\$20.0	TOTAL = \$1.54 B	



Understanding CDMRP Funding

- ◆ **Congressional Special Interest (CSI) versus DOD Core funding**
- ❖ CDMRP's CSI funds are directed by Congress and appropriated through the DOD budget – obligated up-front because there is no guarantee of out year funding
- ❖ Core funds are planned through specific budgeting processes and appropriated yearly in response to the President's DOD budget request – projects can be incrementally funded in out-years
- ❖ 2 years to obligate funding, 5 years to disburse funding





Key External Reviews of CDMRP

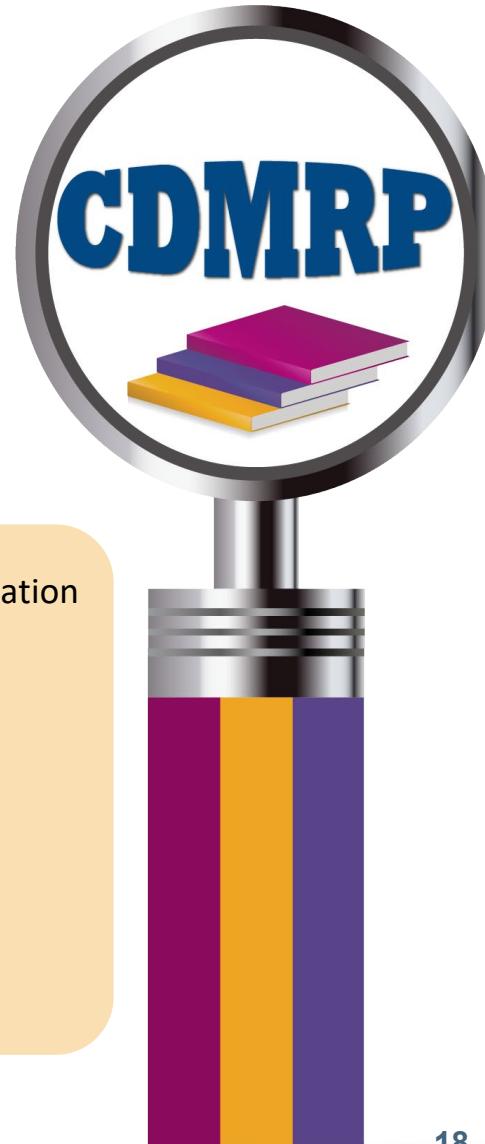
National Academy of Medicine Reviews

- ◆ **1993:** two-tiered review/program cycle recommended
- ◆ **1997:** consumer participation and innovation encouraged
- ◆ **2004:** leveraging non-federal funding sources
- ◆ **2004:** reviewed Prion Diseases Research Program
- ◆ **2016:** lauded inclusion of consumers and overall process, resulted in development of longer-term strategic plans across all programs

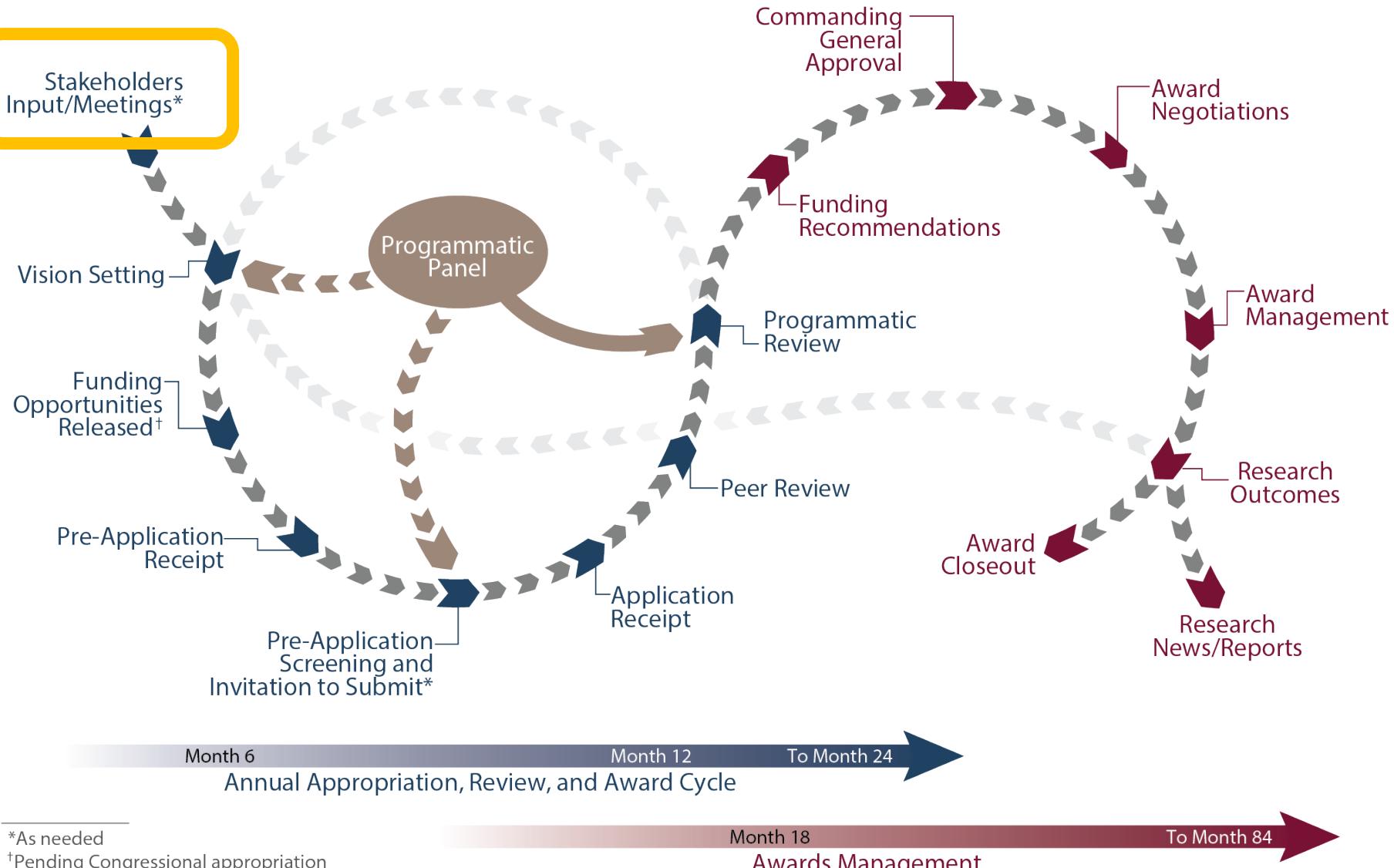
Key Government Accountability Office (GAO) Reviews

- ◆ **2012:** increased coordination and data sharing between DOD and NIH to avoid duplication of effort and maximize Government investments in medical research
- ◆ **2021:** positive assessment of how CDMRP executes annual appropriations, measures return on research investment, coordinates research with the NIH and VA
- ◆ **2021-2022:** Four additional ongoing GAO reviews that involve CDMRP
 - Diversity in Federally Funded Cancer Clinical Trials
 - Federal Funding for U.S.-China Research Collaborations
 - Federal Research Contributions to Drug Development
 - U.S. Support to High-Risk Biological Research in Other Countries

PLUS - 13 additional GAO Reviews involving CDMRP



CDMRP Program Cycle



Stakeholders Meeting

Purpose and Intent

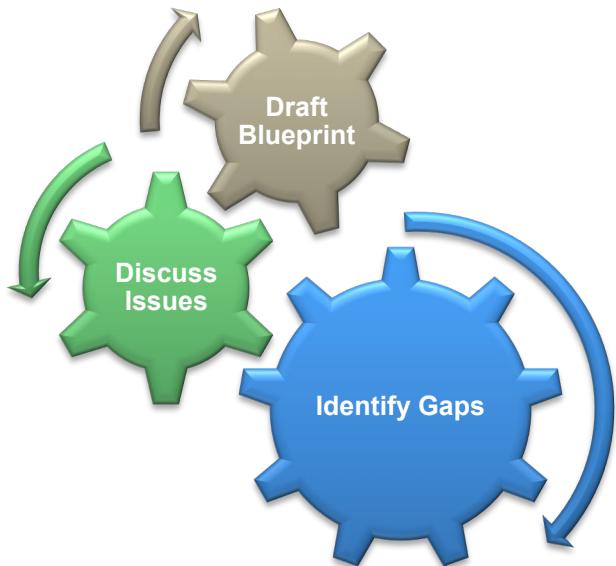
- ◆ CDMRP stakeholders are those with a vested interest (personally or professionally) in one or more research programs and whose support is important to the program(s) success
- ◆ Experts from different subject areas are brought together to pinpoint knowledge gaps, map the landscape of research, identify the outcome and product needs for patient care, and identify the way forward toward an impactful research funding program
- ◆ To build a better program, all voices and opinions are accounted for while focusing on the outcome of preventing, curing, and/or treating the disease or condition



Stakeholders Meeting

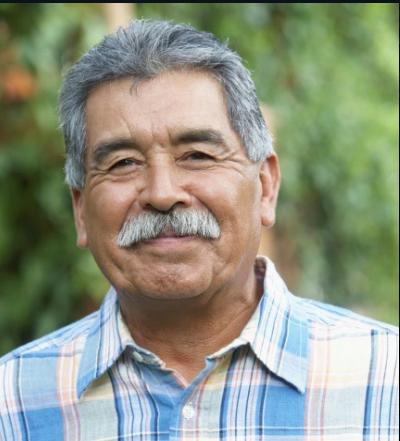
Your input is critical to program success!

- ◆ Consider how your experience, expertise and interests can contribute to an overall strategy for the program
- ◆ Be respectful of others' opinions and take a collaborative approach
- ◆ Provide constructive input that will help support CDMRP in establishing a successful program with the highest impact possible





For your Service and Participation



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Enclosure 3
TERP Overview

Toxic Exposures Research Program (TERP) Stakeholders Meeting

CUTTING EDGE RESEARCH

Melissa (Missy) L. Tursiella, Ph.D.
Program Manager



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Department of Defense



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Outline

- ◆ **Overview of the Toxic Exposures Research Program (TERP)- Congressional Language**
- ◆ **Program Intent**
- ◆ **Stakeholders Meeting Goals**
- ◆ **Request for Information (RFI) Results**

TERP Congressional Language

Consolidated Appropriations Act, 2022

“The agreement notes the number of known and unknown potentially harmful substances that servicemembers are exposed to as part of their military service. Research linked to exposures through various congressionally directed medical research programs, including the Peer-Reviewed **Neurotoxin Exposure Treatment Parkinson's Research Program**, started in 1997 with a focus on dopaminergic neurons that result in Parkinson's disease. Since 2006, the **Peer-Reviewed Gulf War Illness Research Program** has also received congressionally directed funding to study the health impacts caused by deployment of warfighters during the Persian Gulf War. The agreement remains committed to helping veterans affected by **Parkinson's disease, Gulf War illness, and others exposed to potentially toxic substances which result in multiple, diverse symptoms and health abnormalities.**”

TERP Congressional Language

“Transitioning related research to a new, broader program, including **neurotoxin exposure treatment research, research on Gulf War illness, exposures to burn pits, and other service-related exposures to potentially toxic chemicals and materials** will allow the research community to improve scientific understanding and pathobiology from exposure, more efficiently assess comorbidities, and **speed the development of treatments, cures, and preventions**. Therefore, the agreement recommends \$30,000,000 for a peer-reviewed toxic exposures research program. The funds provided in this program are directed to be used to conduct research of clear scientific merit and direct relevance to **neurotoxin exposure; Gulf War illness and its treatment; airborne hazards and burn pits; as well as toxic military exposures in general, including prophylactic medications, pesticides, organophosphates, toxic industrial chemicals, materials, metals, and minerals**.”

Key Points:

- \$30M appropriation
- Support for:
 - Gulf War Illness
 - Burn pits and other airborne hazards
 - Neurotoxin exposures
 - Other toxic exposures in general, including prophylactic medications, pesticides, organophosphates, toxic industrial chemicals, materials, metals and minerals
- Focus on speeding development of treatments, cures, and preventions = maximum benefit to Service Members, Veterans, and the American public

TERP Congressional Language

“The agreement directs the Director of Congressionally Directed Medical Research Programs, to ensure that the program is conducted using **competitive selection and peer-review for the identification of research with the highest technical merit and military benefit**. Further, the agreement directs that this program be **coordinated with similar activities in the Department of Veterans Affairs. Collaborations between researchers at military or veteran institutions and non-military research institutions are encouraged** to leverage the knowledge, infrastructure, and access to military and veteran populations. The inclusion of the toxic exposures research program **shall not prohibit research in any other congressionally directed research program that may be associated with conditions or health abnormalities which may have been the result of toxic exposures.**”

Key Points:

- Two-tier review process to select strong scientific research with maximum benefit to our military
- Coordination with the VA
- Encourages collaborations between researchers at military or veteran institutions with non-military institutions
- Other CDMRP programs may still support efforts focused on diseases/conditions as a result of toxic exposures

The full text for the appropriation supporting the inception of the TERP can be found on pages 150-151 of the Joint Explanatory Statement as Division C, Part 2 of H.R. 2471, the Consolidated Appropriations Act, 2022 (retrieved from https://docs.house.gov/billsthisweek/20220307/BILLS-117RCP35-JES-DIVISION-C_Part2.pdf).

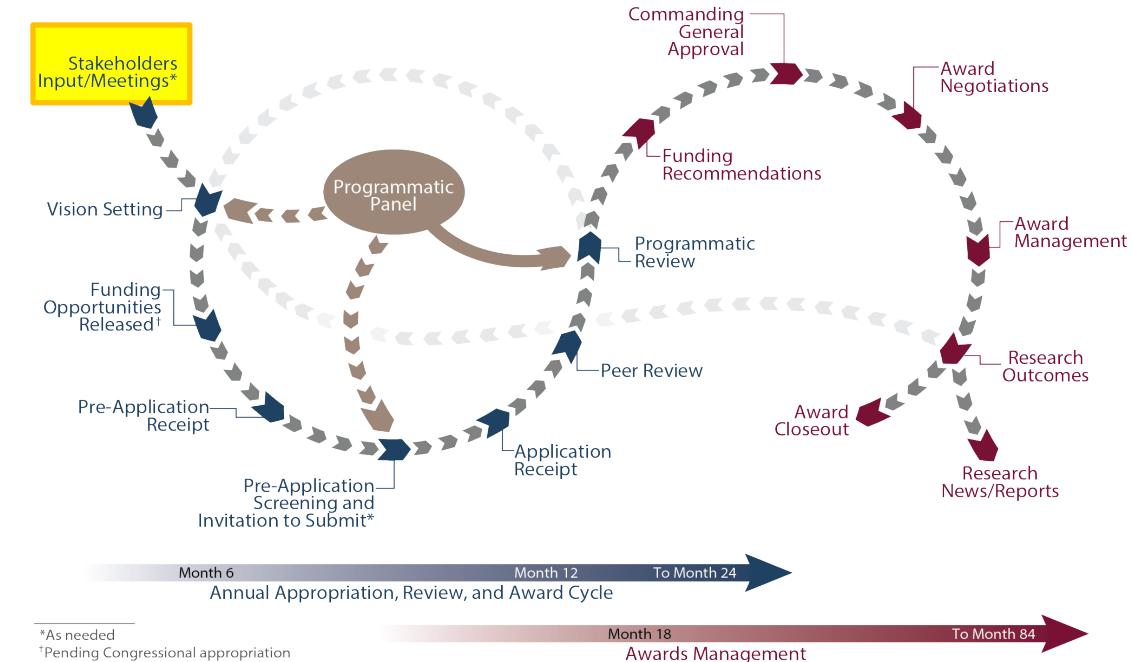
TERP Intent

- ◆ Approaches spanning basic through translational and clinical studies to address the current state of the science for each of the topic areas
- ◆ Adhere closely to Congressional language and intent and to the mission of the CDMRP
 - ❖ “*Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans and the American public*”
 - ❖ Focus on human health!

TERP Program Cycle

Key Events

- TERP website is live
- Stakeholders request for information (RFI) was disseminated
- Meeting/coordinating with other federal offices
- Stakeholders meeting



- Funding opportunity pre-announcement will be released after Vision Setting
- Anticipate funding opportunities will be released in early fall 2022

Expectations: TERP Stakeholders Meeting

Purpose: A forum for an open dialogue among experts, advocates and those affected by toxic exposures to (1) **identify critical issues** relating to neurotoxin exposure, Gulf War illness and its treatment, exposures to air borne hazards and burn pits, and other military service-related exposures in general, including prophylactic medications, pesticides, organophosphates, and toxic chemicals, materials, metals and minerals (2) **acknowledge the underfunded areas of research and patient care** in the field of service-related toxic exposure research and (3) **coordinate with similar activities across other federal agencies**, including the Department of Veteran Affairs.

Expectations: TERP Stakeholders Meeting

Key Meeting Activities

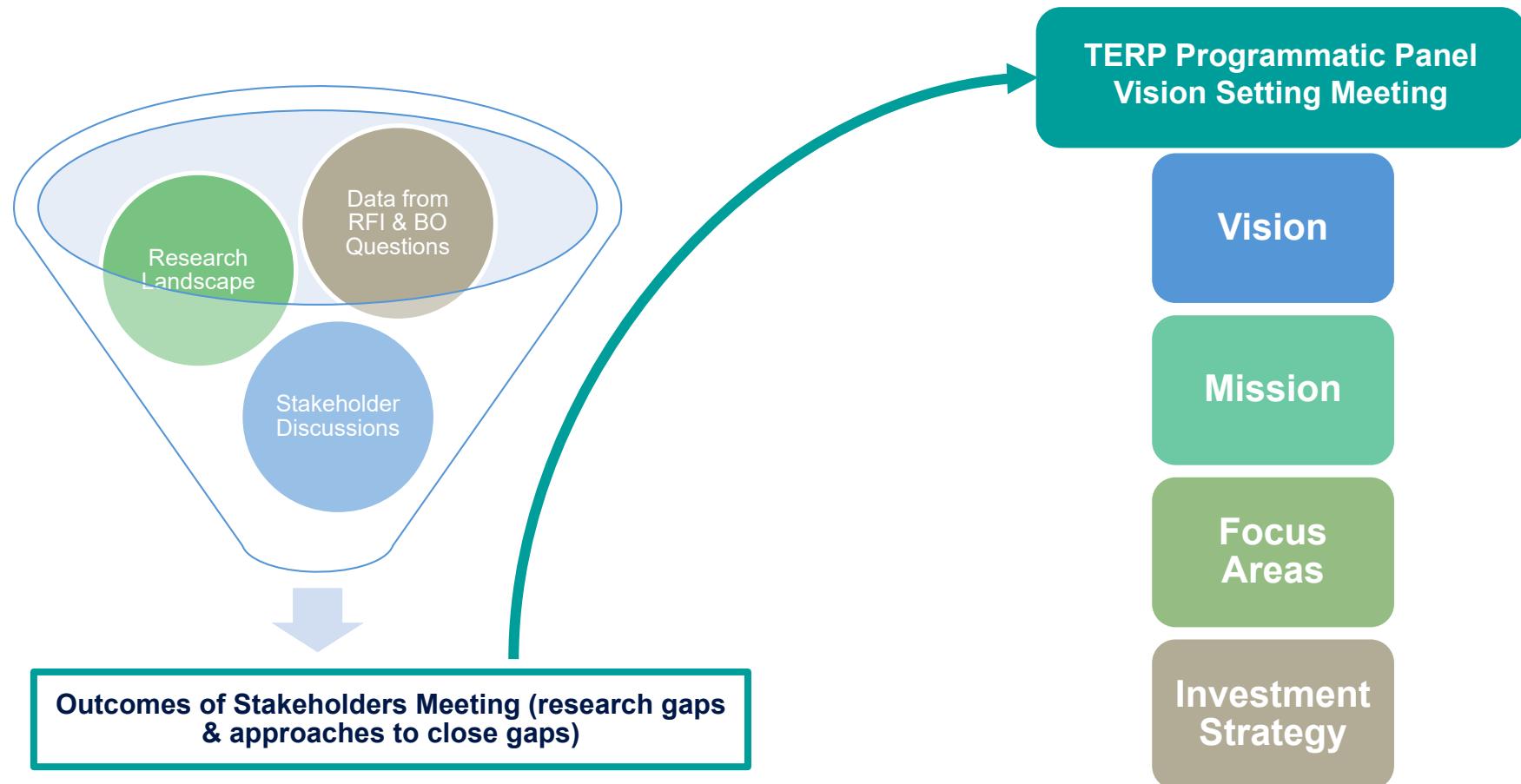
- Presentations from key organizations highlighting the current state of research related to service-related toxic exposures.
- Focused breakout sessions to identify gaps in specific areas of service-related toxic exposure research.
- Identify and prioritize research areas of emphasis to close the gaps in specific areas of service-related toxic exposure research.
- Discussion of concurrent management strategies across Federal agencies for service-related toxic exposure research.

Expectations: TERP Stakeholders Meeting

Outcomes

- ❑ Summary of relevant gaps, refinement of the state of the science in service-related toxic exposures, identification of potential challenges, and opportunities for success.
- ❑ Input from the Stakeholders meeting will be used by the TERP Programmatic Panel at the Vision Setting Meeting to recommend the overall TERP goals, priorities, focus areas, and FY22 investment strategy.
- ❑ The final outcomes of the Stakeholders meeting do not represent the final program strategy of the TERP.

Expectations: TERP Stakeholders Meeting



Vision Setting

TERP Programmatic Panel Vision Setting Meeting

Vision

Mission

Focus
Areas

Investment
Strategy

- ❖ The TERP will hold an annual **Vision Setting** meeting with the Programmatic Panel where the panel recommends the investment strategy, considering factors such as:
 - Congressional language
 - Scientific advancements and emerging technologies
 - Research gaps
 - Portfolio composition
 - Current research landscape
 - Impact
- ❖ After the Vision Setting Meeting the Programmatic Panel's Recommendations are translated into Funding Opportunity Announcements that address the strategy and goals of the program.

TERP Request for Information (RFI)

- ◆ RFI was posted on SAM.gov, disseminated via email and posted on the TERP website.
- ◆ Received 265 responses
- ◆ Respondents were provided with the Congressional language for TERP and asked to use that language as a guide to respond to the questions based on the (4) topic areas listed in the Congressional language:
 - ❖ Neurotoxin Exposure
 - ❖ Gulf War Illness and Its Treatment
 - ❖ Exposures to Airborne Hazards and Burn Pits
 - ❖ Military Service-Related Exposures to Prophylactic Medications, Pesticides, Organophosphates, and Toxic Chemicals, Materials, Metals, and Minerals

TERP Request for Information (RFI)

- ◆ Respondents were also provided with research continuum definitions:



Research Continuum	Definitions
Foundational Science	Elucidate basic research concepts, molecular mechanisms, and pathobiology of the effects of toxic exposure that could lead to new scientific discoveries, including development of biomarkers and treatments.
Epidemiology	Conduct population-level (including at-risk) descriptive studies of the patterns, causes, and effects of health and disease conditions with the overarching aim of identifying risk factors and targets for prevention.
Etiology	Understand the environmental causes of diseases/conditions associated with toxic exposure.
Prevention and Monitors	Develop preventive interventions and screening tools to assess and limit/prevent exposure.
Diagnosis and Treatment	Assessment of diseases, conditions, or other health abnormalities and comorbidities as a result of toxic exposures; biomarkers as a means to diagnose and/or measure progression or therapeutic efficacy; symptom amelioration at different stages of disease, and quantitative evaluations for treatment efficacy.
Survivorship and Quality of Life	Address length and durability of treatment, and long-term consequences of treatment rehabilitation.

TERP Request for Information (RFI)

- ◆ **RFI Responses**
 - ❖ reviewed and data were analyzed by TERP staff
 - ❖ open ended questions- analyzed as overarching themes and used to identify a list of gaps for discussion
- ◆ **Breakout Groups – in-depth discussion of knowledge/research gaps and approaches that could potentially be addressed by the TERP**
 - ❖ Responses of participants- top 3 research gaps
 - ❖ More specific gaps as identified in the open-ended RFI
 - ❖ Gaps identified in today's presentations

*Note that the gaps identified in the breakout group question and the RFI are not an exhaustive list and do not represent the opinions the TERP or of all stakeholders; they are meant to serve as a starting point for conversation in each breakout group

Request for Information (RFI) Results

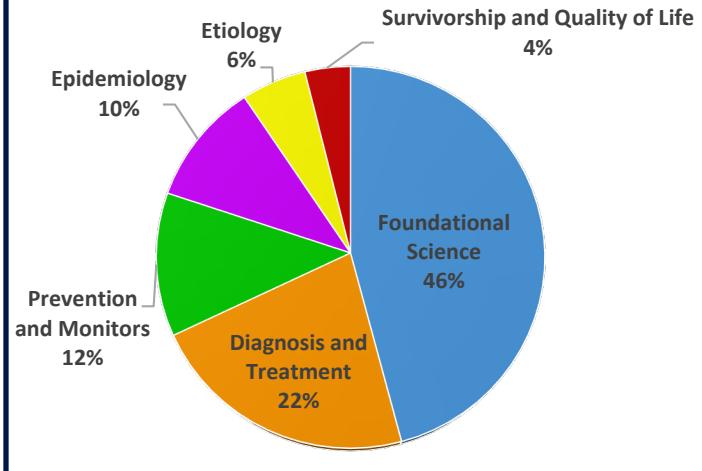
1. For each of the topics listed below, please indicate which of the following areas of the research continuum you believe are the most underfunded. Only one research area on the continuum can be selected per topic.

	I am not experienced in this particular topic area (N/A)	Foundational Science	Epidemiology	Etiology	Prevention and Monitors	Diagnosis and Treatment	Survivorship and Quality of Life
Neurotoxin Exposure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Gulf War Illness and Its Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Exposures to Airborne Hazards and Burn Pits	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Military Service-Related Exposures to Prophylactic Medications, Pesticides, Organophosphates, and Toxic Chemicals, Materials, Metals, and Minerals	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

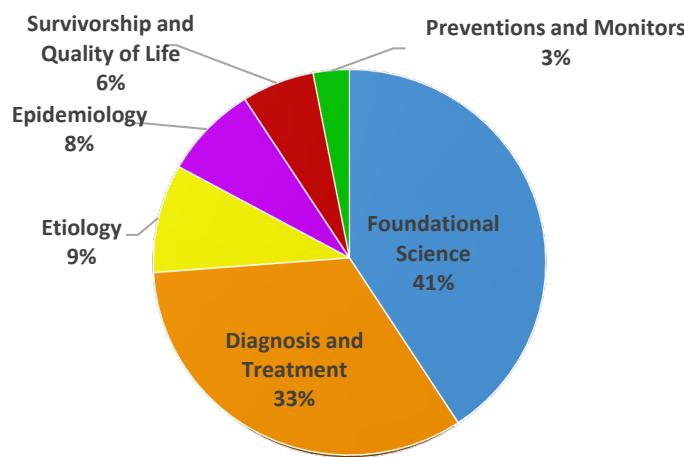
Request for Information (RFI) Results

For all of the topic areas, foundational science and diagnosis and treatment were the top two areas of the research continuum that were identified as being underfunded.

Neurotoxin Exposures



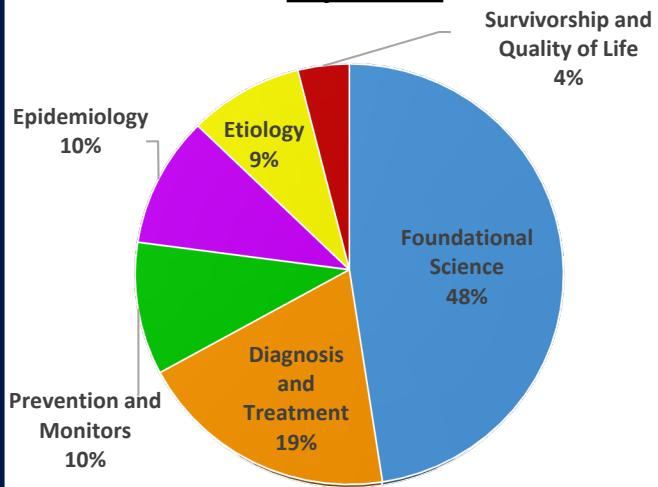
Gulf War Illness and Its Treatment



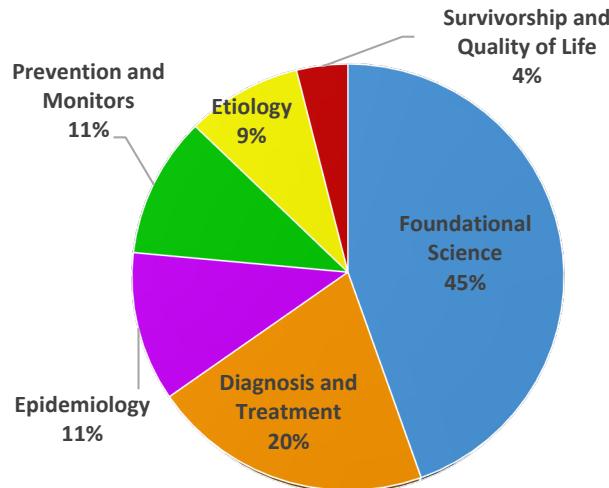
Request for Information (RFI) Results

For all of the topic areas, foundational science and diagnosis and treatment were the top two areas of the research continuum that were identified as being underfunded.

Other Military Service-Related Exposures



Airborne Hazards and Burn Pits



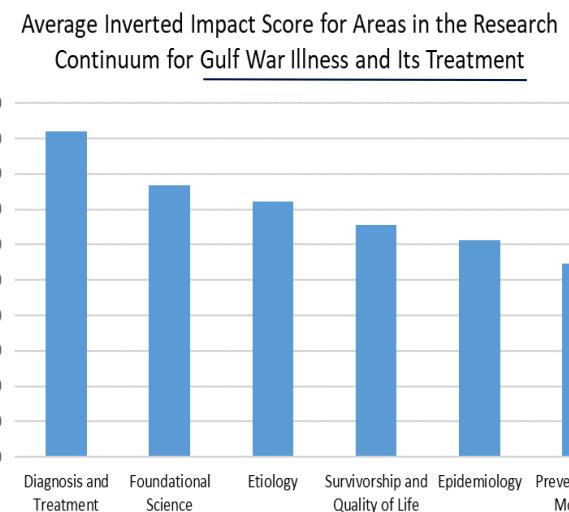
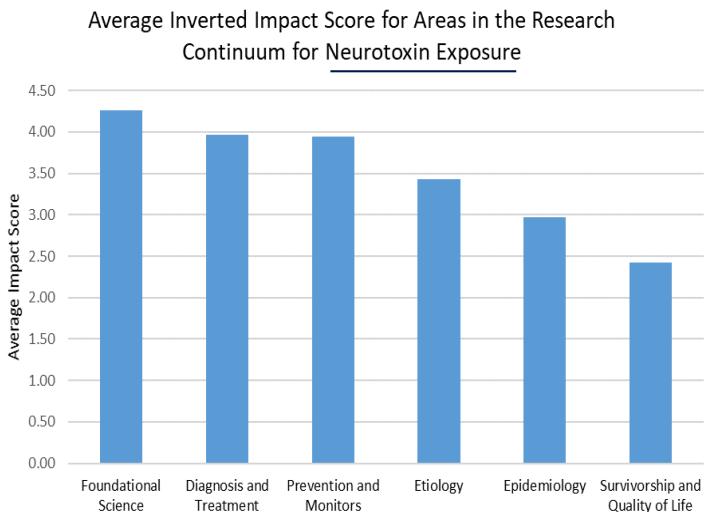
Request for Information (RFI) Results

2. For each topic area, please rank (1-6) the following areas of the research continuum based on which will have the most impact to the least impact. A score of 1 indicates that research area will have the MOST impact on the topic area while a score of 6 indicates that research area will have the LEAST impact.

	I am not experienced in this particular topic area (N/A)	Foundational Science	Epidemiology	Etiology	Prevention and Monitors	Diagnosis and Treatment	Survivorship and Quality of Life
Neurotoxin Exposure	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>
Gulf War Illness and Its Treatment	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>
Exposures to Airborne Hazards and Burn Pits	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>
Military Service-Related Exposures to Prophylactic Medications, Pesticides, Organophosphates, and Toxic Chemicals, Materials, Metals, and Minerals	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>	<input type="button" value="◆"/>

Request for Information (RFI) Results

- **Generally, foundational science and diagnosis and treatment ranked either first or second in terms of being most impactful for each of the four topic areas.**

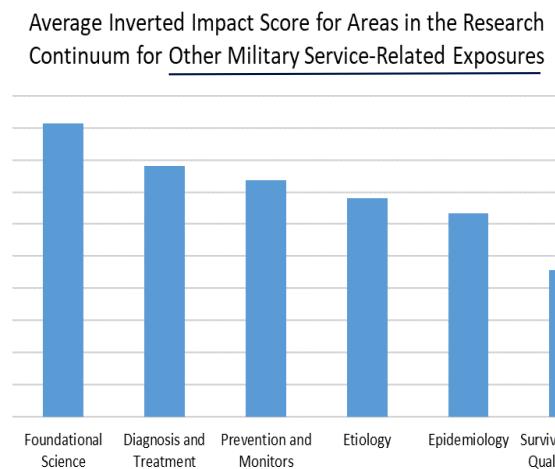
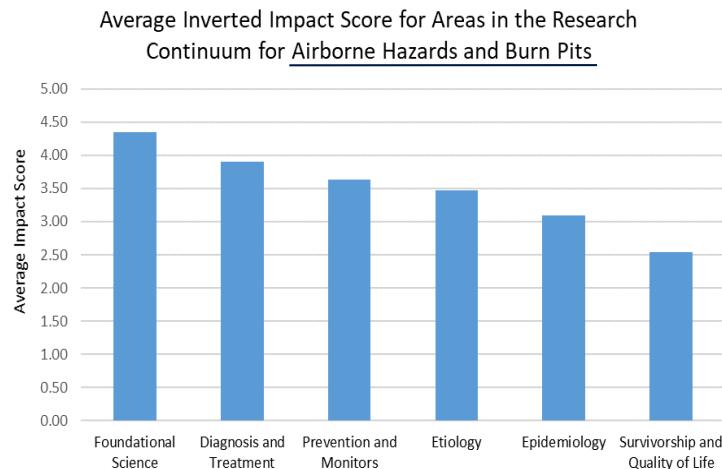


1st	Foundational Science
2nd	Diagnosis and Treatment
3rd	Prevention and Monitors
4th	Etiology
5th	Epidemiology
6th	Survivorship and Quality of Life

1st	Diagnosis and Treatment
2nd	Foundational Science
3rd	Etiology
4th	Survivorship and Quality of Life
5th	Epidemiology
6th	Prevention and Monitors

Request for Information (RFI) Results

- **Generally, foundational science and diagnosis and treatment ranked either first or second in terms of being most impactful for each of the four topic areas.**



1st	Foundational Science
2nd	Diagnosis and Treatment
3rd	Prevention and Monitors
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1st	Foundational Science
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Request for Information (RFI) Results

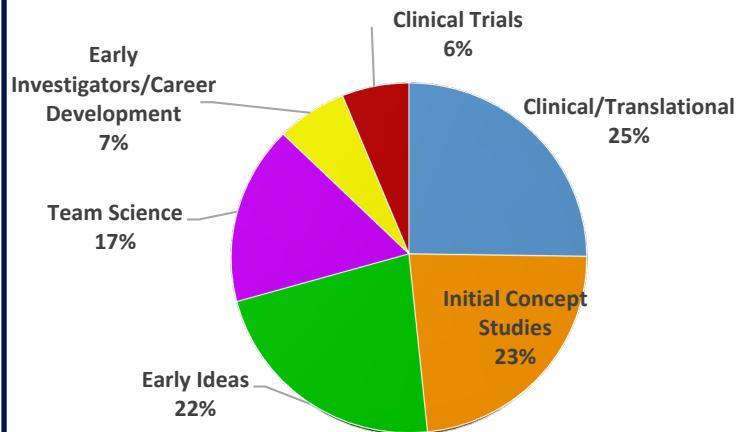
3. Based on the state of the science for each topic listed below, please select up to two types of studies that would be of the greatest benefit to that topic

	I am not experienced in this particular topic area (N/A)	Initial Concept Studies	Early Ideas	Clinical/Translational	Clinical Trials	Team Science	Early Investigator/Career Development
Neurotoxin Exposure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gulf War Illness and Its Treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Exposures to Airborne Hazards and Burn Pits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Military Service-Related Exposures to Prophylactic Medications, Pesticides, Organophosphates, and Toxic Chemicals, Materials, Metals, and Minerals	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

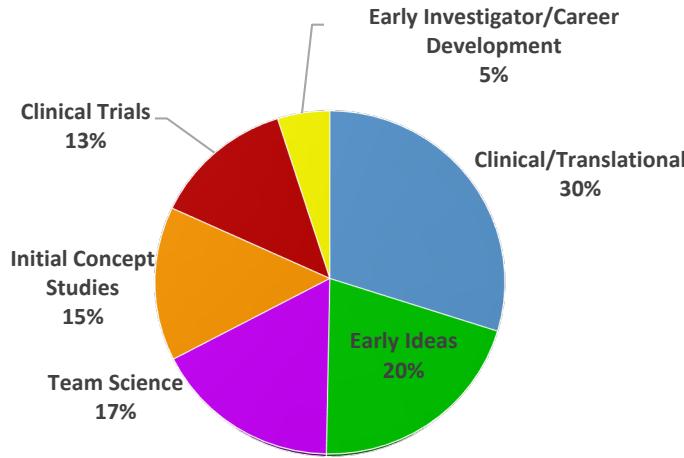
Request for Information (RFI) Results

- Overall, the top study type varied for each of the four topic areas, but early ideas, initial concept, clinical/translational and team science studies were consistently in the top four as being the most beneficial to the topic areas.

Neurotoxin Exposures



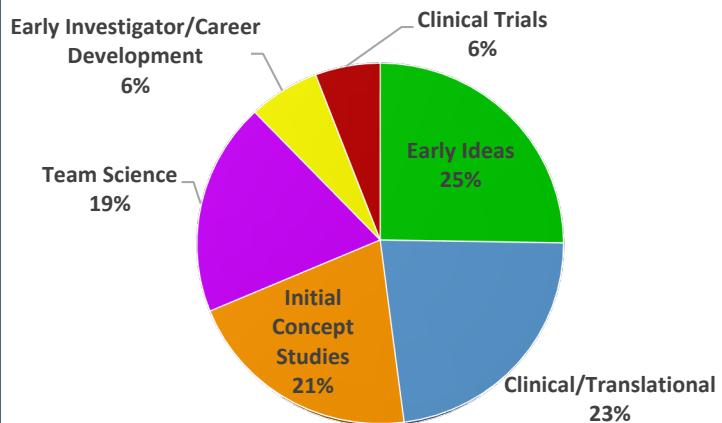
Gulf War Illness and Its Treatment



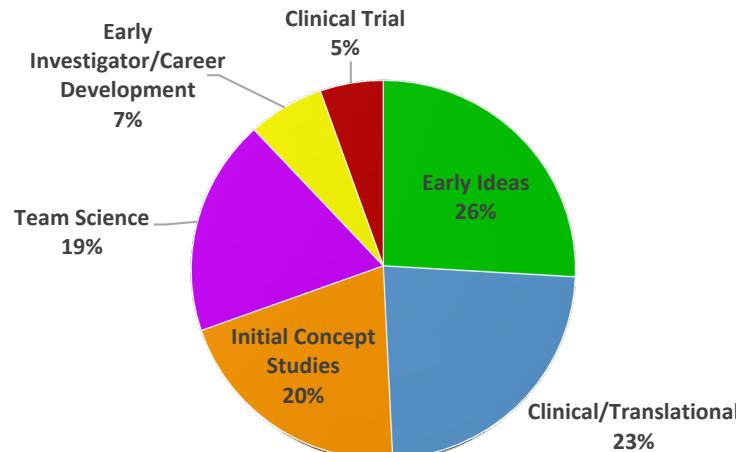
Request for Information (RFI) Results

- Overall, the top study type varied for each of the four topic areas, but early ideas, initial concept, clinical/translational and team science studies were consistently in the top four as being the most beneficial to the topic areas.

Airborne Hazards and Burn Pits



Military Service-Related Exposures

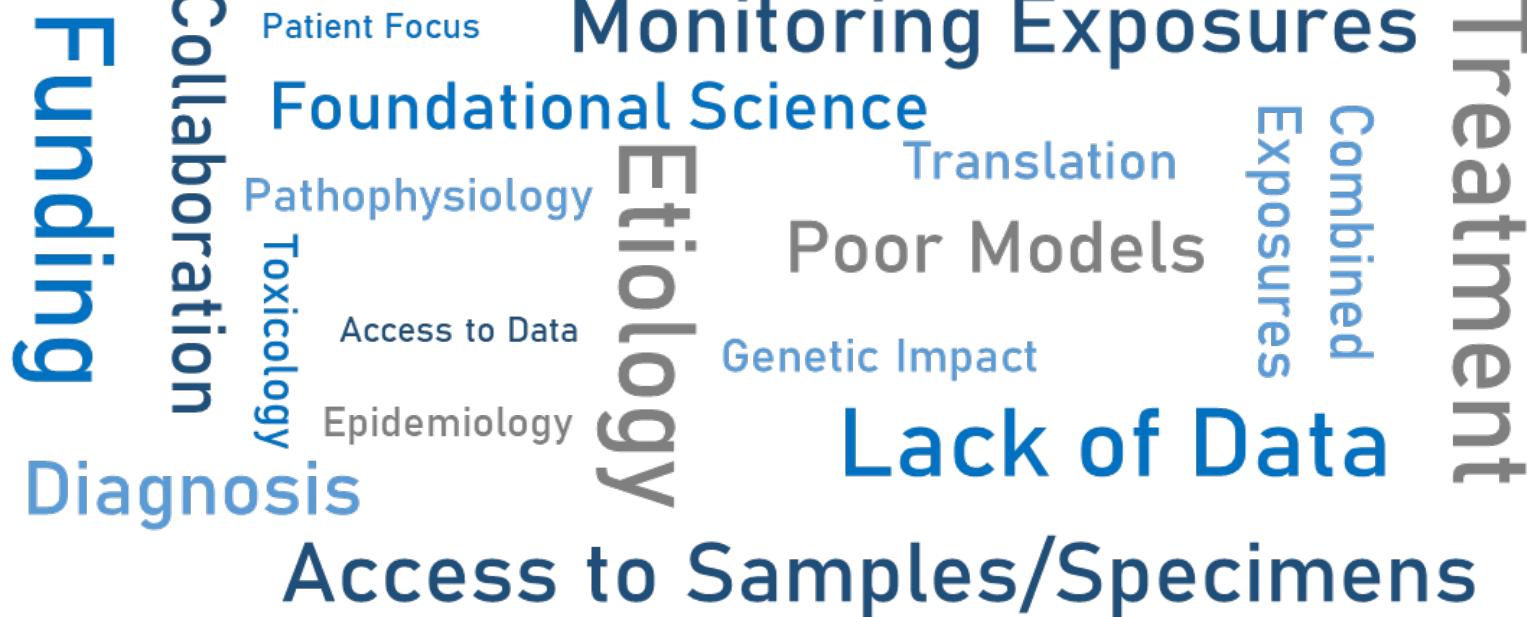


Request for Information (RFI) Results

4. What obstacles are researchers and the patient/consumer community facing that could potentially be addressed by the TERP (100 character limit)?

Request for Information (RFI) Results

Poorly Defined Exposures



Request for Information (RFI) Results

5. How can the TERP respond to the current obstacles to facilitate progress (100 character limit)?

Request for Information (RFI) Results



Request for Information (RFI) Results

6. Which of the following best describes your role in the toxic exposure research community? (Select all that apply)

- Academia
- Clinician
- Foundation
- Governmental Program Administrator
- Industry
- Consumer/Patient/Caregiver/Advocate

Other (please specify)

➤ Demographics of respondents was diverse; consumers and advocates, healthcare providers, Government scientists and administrators, academic investigators, industry representatives etc.

Request for Information (RFI) Results

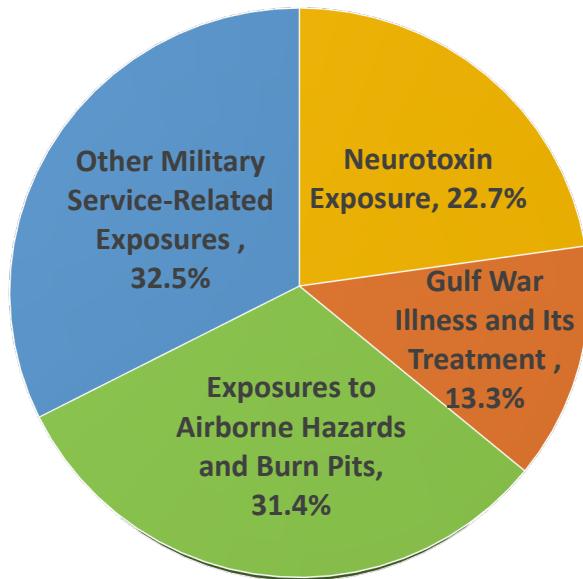
7. From the list of topic areas below, please select the primary topic area that most closely aligns with your area of expertise/interest. A secondary topic area may also be selected, if applicable.

	Neurotoxin Exposure	Gulf War Illness and Its Treatment	Exposures to Airborne Hazards and Burn Pits	Other Military Service-Related Toxic Exposures
Primary Topic Area	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Secondary Topic Area (if applicable)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Request for Information (RFI) Results

- Most invited participants were assigned to their breakout group based on their primary area of interest/expertise; some were placed based on their secondary areas in attempt to balance the breakout groups

Responses by Primary Area of Interest/Expertise



- Invites were balanced across disciplines to facilitate discussion.
- All outcomes and presentations will be made publically available after the meeting

Considerations

- Presentations will provide a general idea of some of the programs supporting efforts in the toxic exposures space; the diseases/conditions and outcomes of toxic exposure also touch other programs across CDMRP and the funding landscape
- Goal: identify a prioritized list of the top 5 research/knowledge gaps for each breakout group; these will inform the FY22 TERP vision setting and investment discussions; program will receive all gaps as part of meeting record
- Keep the breadth and size of the TERP in mind during your discussions
- When generating the prioritized gaps, consider the state of the science and the needs of Service members and Veterans
 - Where are we now ?
 - How do we get to where we want to be ?
 - How can the TERP get us there? What recommendations can we provide to the TERP?
- We recognize the cross talk between these breakout groups. Consider using the group discussions as a time to bring up gaps/ideas that may be applicable to other breakout groups.

For your Service and Participation



Thank you

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Enclosure 4

Gulf War Illness Research Program Overview

Congressionally Directed Medical Research Programs

Gulf War Illness Research Program (GWIRP)

CUTTING EDGE RESEARCH

Mr. Brett Chaney, Science Officer
Toxic Exposures Research Program (TERP)

June 15, 2022



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Table of Contents

- **Introduction**
- **What is Gulf War illness?**
- **GWIRP Overview**
- **GWIRP Award Mechanism Pipeline**
- **GWIRP Accomplishments**
- **Research Gaps for Gulf War illness**

What is Gulf War illness?

Gulf War illness (GWI) refers to a chronic multi-symptom illness that affects veterans of the 1990-1991 Gulf War. It is characterized by multiple diverse symptoms not explained by established medical diagnoses or standard laboratory tests.

Symptoms typically include a combination of widespread pain, headache, debilitating fatigue and memory/concentration/mood problems and can also include chronic digestive difficulties, respiratory symptoms, and skin rashes.

- Symptoms can exist in a spectrum of heterogeneity, making GWI very challenging to diagnose
- Resulted from exposures during the Gulf War, including pesticides, chemical nerve agents (e.g., sarin), prophylactic countermeasures (PB) along with physiological stress from deployment
- Pathophysiology centers around inflammatory response, particularly neuroinflammation, and a persistent proinflammatory metabolic state
- Other contributing factors to pathophysiology include mitochondrial dysfunction, altered lipidomics, gut microbiome dysbiosis and possibly genetic predisposition

GWIRP Vision & Mission

DOD Gulf War Illness Research Program (2006 – 2021)

Vision:

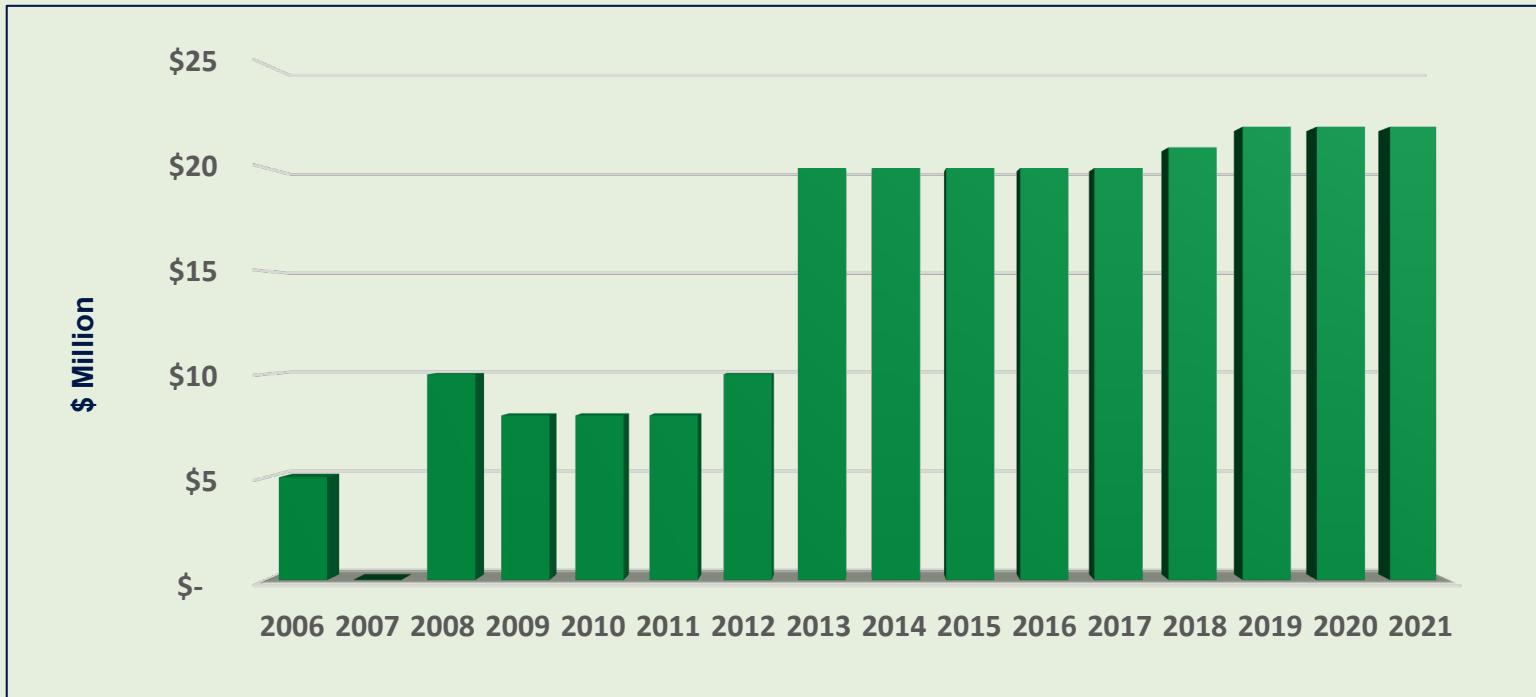
Improved health and lives of Veterans who have Gulf War Illness

Mission:

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

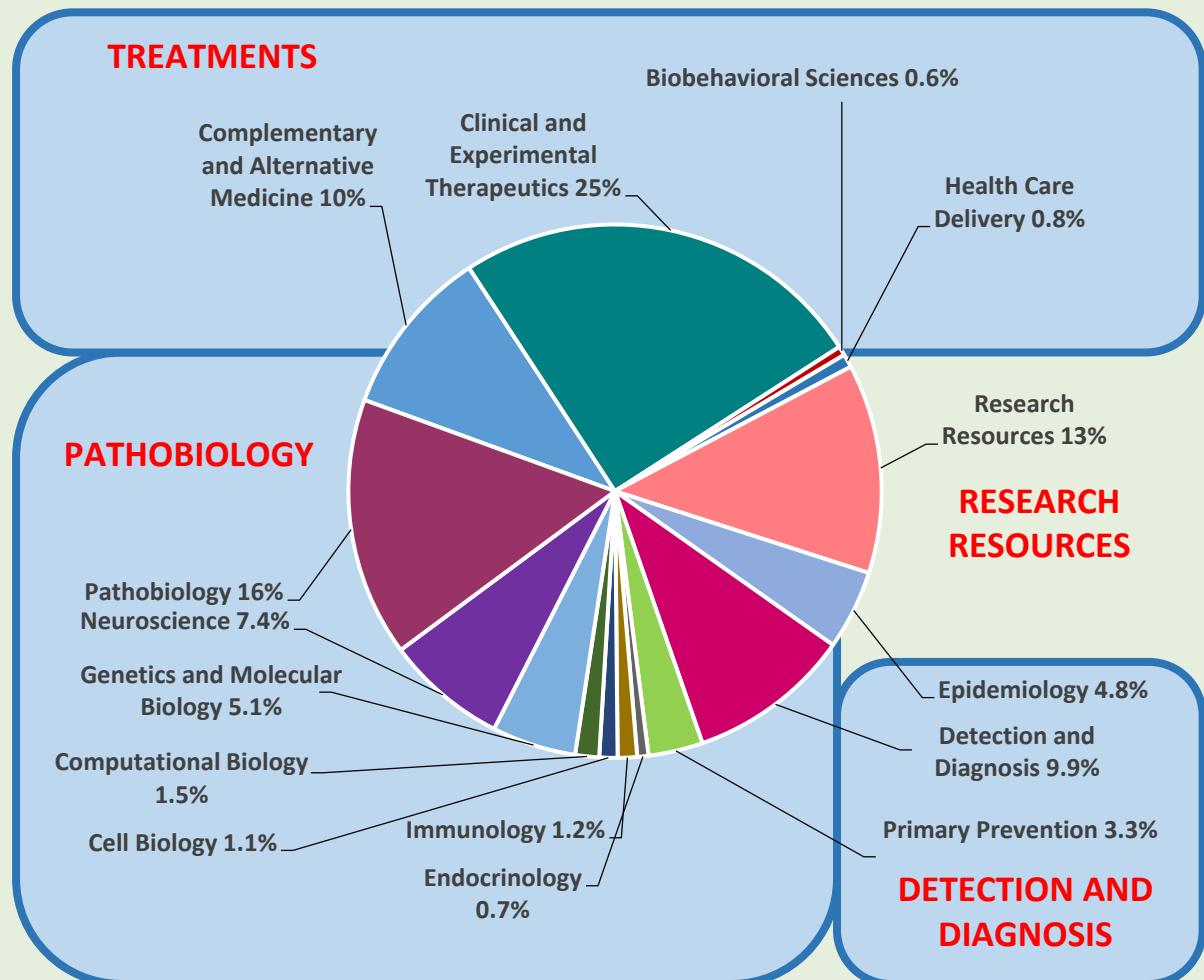
- Three prongs of GWIRP portfolio
 - Identify treatments
 - Improve definition and diagnosis (i.e., biomarkers)
 - Better understand pathobiology

GWIRP Appropriation History



- Total Congressional appropriations: **\$236M**
- **No FY22 appropriation for GWIRP**
- For the past 10 years, the DoD GWIRP has been the leading funder of GWI research

GWIRP Portfolio Overview



- Total awards funded: **239**
 - 37% Treatments
 - 33% Understanding Pathobiology
 - 18% Definition and Diagnosis
 - 13% Research Resources

GWIRP Earlier Funding Opportunities

Understanding Pathobiology

Expanding the field*
Multi-institutional collaboration*

Funding Opportunities

- Investigator-Initiated Research Award
- New Investigator*
- Research Consortium*
- Idea / Hypothesis Development Award

Definition & Diagnosis (Biomarkers)

Treatments for GWI

- Investigator-Initiated Research Award
- New Investigator*
- Epidemiology Research Award
- Research Consortia*

- Innovative Treatment Evaluation Award
- Clinical Trial Award
- Clinical Partnership Award*

- **Funded awards across multiple topic areas and disciplines**

Funding Mechanism Pipeline

Discovery

- Innovative biomarker or treatment research
- Earliest stages of development
- High-risk/High-reward
- No preliminary data required

Qualification

- Preclinical expansion, replication, or comparative studies to validate preliminary or published data in GWI field
- Preliminary data required

Verification

- Proof-of concept clinical translation of validated GWI findings
- Large-scale biomarker research or early phase 1-2a intervention clinical trials
- Strong preliminary data required

Confirmation

- Large-scale confirmatory and pivotal clinical trials to revolutionize GWI clinical care
- Sufficiently-powered phase 2b-3 clinical trials
- Objective biomarkers of effectiveness required

MECHANISM Idea Award

Research Advancement Award

Clinical Evaluation Award

Therapeutic/Biomarker Trial Award

GWIRP Research Outcomes: Mechanistic Evidence

Chronic Inflammation

- Metabolism of organophosphates
- Microglial activation
- Aberrant molecular signaling and homeostasis

Neuro/Immune System Dysregulation

- Distinct molecular responses post-exercise
- Hypothalamic-pituitary-adrenal axis (HPA) feedback
- Neural pain processing

Cellular Energetics

- Mitochondrial damage / apoptosis
- Prolonged phosphocreatine recovery
- Mitochondrial respiratory chain dysfunction

Altered Metabolomics

- Cytokine/chemokine release
- Increased C Reactive Protein
- Lipidomics

Gastrointestinal/ Microbiome Dysfunction

- Altered bacterial phyla composition
- Activated phenotype in enteric glial cells

Genetic Abnormalities

- DNA damage from exposures
- Overall genomic instability
- Epigenetic dysregulation

GWIRP Research Outcomes: Model Development

Animal Models



DFP treatment preceded by corticosterone in mice and rats



Pyridostigmine Bromide (PB) and permethrin in mice



Rats dermally exposed to DEET and permethrin



Low dose Sarin exposure in mice

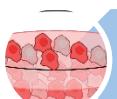


DEET, permethrin, chlorpyrifos, with or without PB



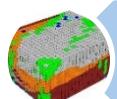
Repeated exposure to chlorpyrifos

Veteran iPSC Models



iPSCs from GWI subjects and controls, advanced to organoid mini-brains

In Silico Models



Computational model of aberrant signaling to screen therapeutics

GWIRP Research Outcomes: Treatment Development

Pre-Clinical Treatment Studies: 39

- Ketamine, Melatonin, Cannabidiol, Propranolol, Minocycline, Anatabine, Curcumin and many more

Pilot Clinical Trials: 29

- CoQ10, yoga, Glutathione, low-carb diet, intranasal insulin, nutraceuticals, resveratrol and many more

Expanded / Validation Phase 2 Clinical Trials: 11

- CoQ10, Low Glutamate diet, Transcranial Magnetic Stimulation, Botanicals, Acupuncture, Growth Hormone, Oleoylethanolamide, Montelukast, Prednisone, Nicotinimide Riboside

GWIRP Research Outcomes: Treatment Development

FY17 Etanercept / Mifepristone Phase I, II (planned), based on in silico and animal model results

- Biomarker: inflammatory profile and autonomic mediators

FY18 Oleoylethanolamide (OEA) Clinical Trial based on in vivo lipidomics analysis

- Biomarker: Lipidomic profile

FY18 Repetitive Transcranial Magnetic Stimulation (rTMS) for Headache in GWI, extends an FY15 pilot study

- Biomarker: Connectomics signatures

FY19 TBTA CoQ10 Phase 2, validation of FY08 trial

- Biomarker: Mitochondrial markers

FY21 TBTA Low Glutamate Diet, validation of FY16 pilot trial

- Biomarker: Antioxidant levels, proinflammatory cytokines

GWI Research Needs

Mechanistic Research Needs

- Extensive genotypic and phenotypic analyses and identification of molecular signatures that underlie symptom clusters (e.g., current VA IN-DEPTH Study)
- Continue to investigate brain-gut interactions and alterations in gut microflora*
- Continue to investigate GWI subgroup differences (e.g., sex, genotype, exposure)
- Why do toxic exposures persist in GWI?
- Parallels of persistent GWI symptoms with long COVID, ME/CFS, etc.
- Continue GWIRP's conceptual research pipeline of development

Infrastructure Research Needs

- Preserving existing GWI research infrastructure like biorepositories and multi-site clinical studies

Clinical Research Needs

- Independent replication and cross validation of currently available findings around inflammatory markers, lipid metabolism, genomic datasets, etc.
- Continue to investigate interventions that have shown promise in early phase studies
- Repurpose existing treatments for faster translation (some of which have shown efficacy in animal models)
- Support clinical trials that target subgroups of Veterans with GWI that have similar symptomology, and include biomarker development*
- Improve GWI clinical trials by encouraging implementation of GWI Common Data Elements, published in August 2021
- Incorporate common comorbidities associated with aging
- Improving Quality of Life (QOL) and managing symptoms, vs. "magic bullet" cure for GWI

* Also cited in a recent review article of biological measures for GWI

Questions?

Enclosure 5

Peer Reviewed Medical Research Program: Overview of Toxic Exposures Research

Peer Reviewed Medical Research Program: Overview for Toxic Exposures Research Program Stakeholders Meeting

Kathryn J. Argue, Ph.D.



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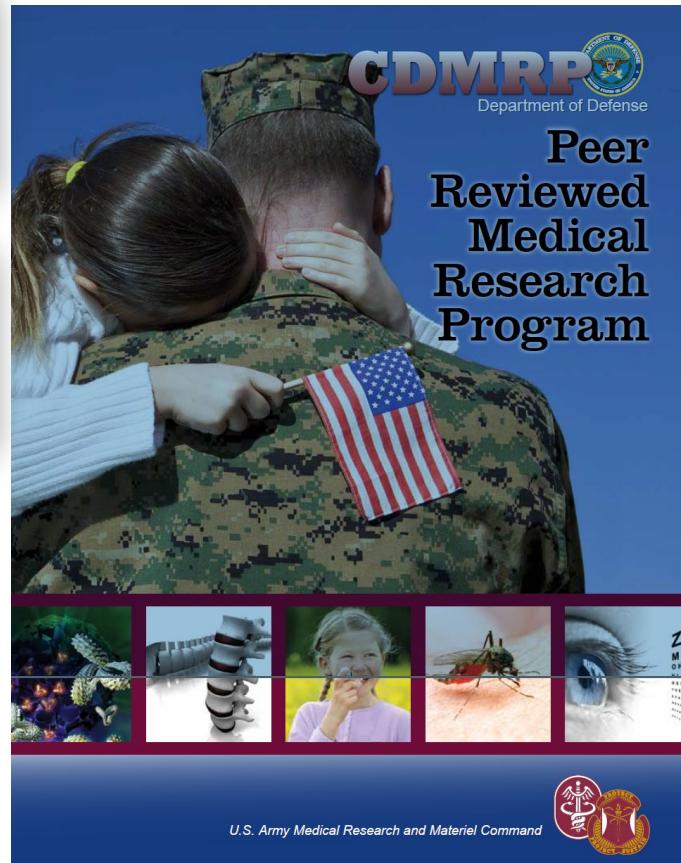
PRMRP Overview

Vision: Improve the health, well-being, and care of all Military Service Members, Veterans, and Beneficiaries

Mission: Encourage, identify, select, and manage medical research projects of clear scientific merit that lead to impactful advances in military health care

◆ History

- ❖ Established in 1999
- ❖ Direction from Congress to support medical research projects of “clear scientific merit” and “direct relevance to military health” in specified Topic Areas
- ❖ FY99-FY22: 224 topic areas
- ❖ FY99-FY21: 1,967 awards totaling \$2.77B



<https://cdmrp.army.mil/prmrp/default>

PRMRP Portfolio-Driven Approach

- Food Allergies
- Guillain-Barre Syndrome
- Inflammatory Bowel Diseases
- Rheumatoid Arthritis
- Cardiomyopathy
- Congenital Heart Disease
- Familial Hypercholesterolemia
- Hypercholesterolemia
- Hypertension
- Vascular Malformations
- Women's Heart Disease
- Hemorrhage Control
- Pathogen-Inactivated Blood Products
- Platelet-like Cell Production
- Trauma
- Viral Diseases
- Hepatitis B
- Malaria
- Plant-Based Vaccines
- Ehlers-Danlos Syndrome
- Endometriosis
- Epidermolysis Bullosa
- Focal Segmental Glomerulosclerosis
- Polycystic Kidney Disease
- Interstitial Cystitis
- Nephrotic Syndrome
- Pancreatitis

- Polycystic Kidney Disease
- Pressure Ulcers
- Dystonia
- Eating Disorders
- Fragile X
- Friederich's Ataxia
- Frontotemporal Degeneration
- Hydrocephalus
- Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
- Myotonic Dystrophy
- Non-Opioid Therapy for Pain Management
- Peripheral Neuropathy
- Rett Syndrome
- Sleep Disorders and Restriction
- Suicide Prevention
- Trauma
- Diabetes
- Mitochondrial Disease
- Nutrition Optimization
- Arthritis
- Fibrous Dysplasia
- Musculoskeletal Disorders (related to acute and bone conditions and injuries)
- Pulmonary Fibrosis
- Respiratory Health
- Trauma

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Auto Immune Diseases
and Immunology

Cardiovascular Health

Hemorrhage Control
and Blood Products

Infectious Diseases

Internal Medicine

Neuroscience

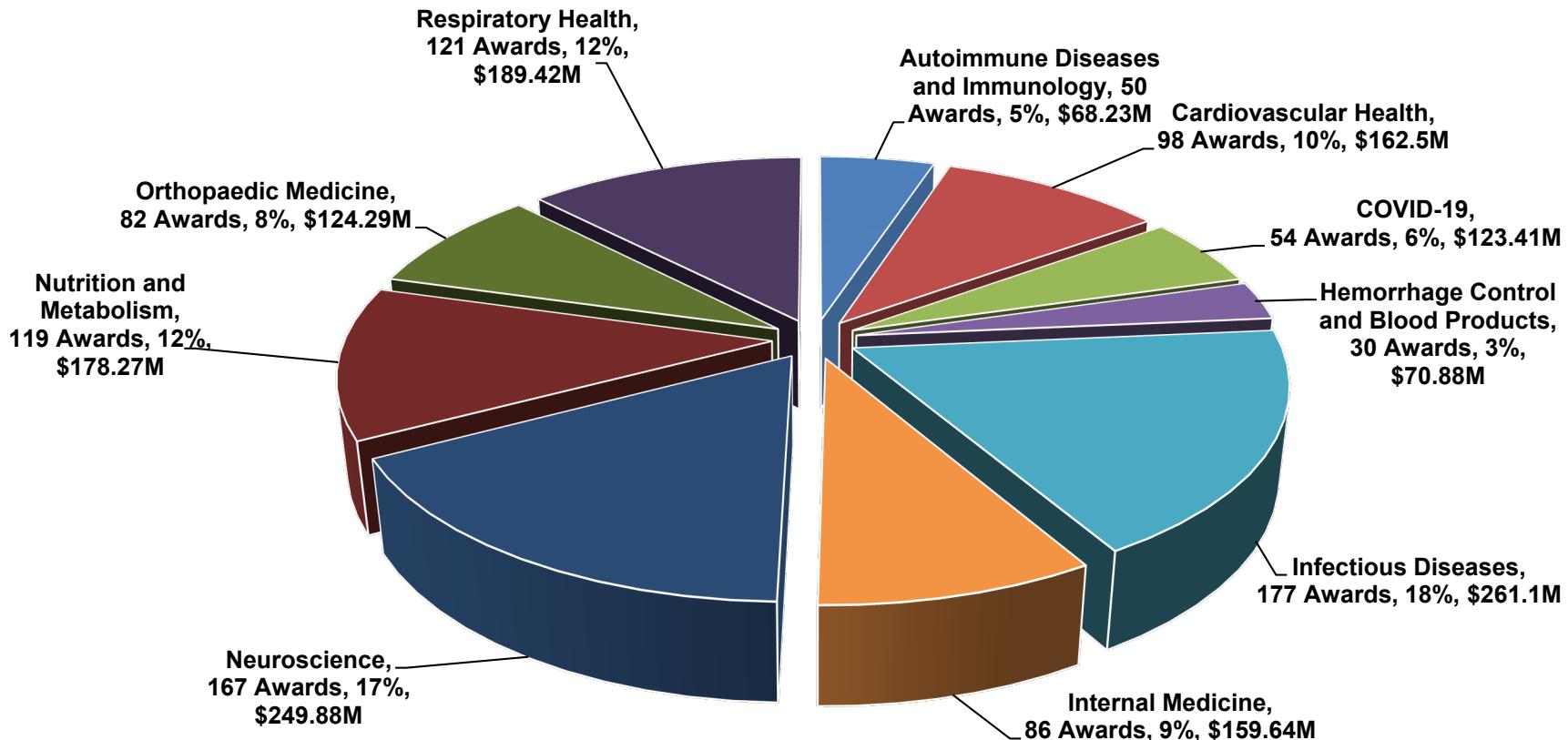
Nutrition and
Metabolism

Orthopaedic Medicine

Respiratory Health

FY17-FY21* PRMRP Portfolios

984 Awards, \$1.589B



Percentages by number of awards

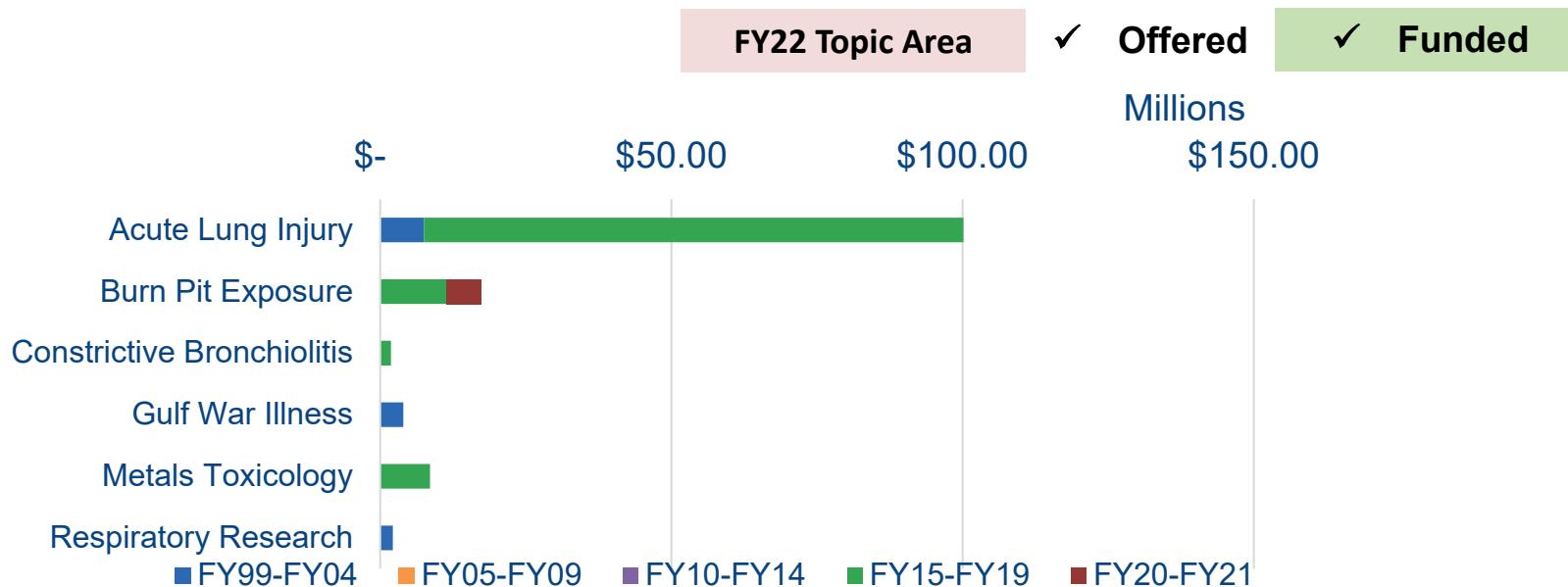
*FY21 not final – awards under negotiation

No preselected allocation of funds per Topic Area/Portfolio

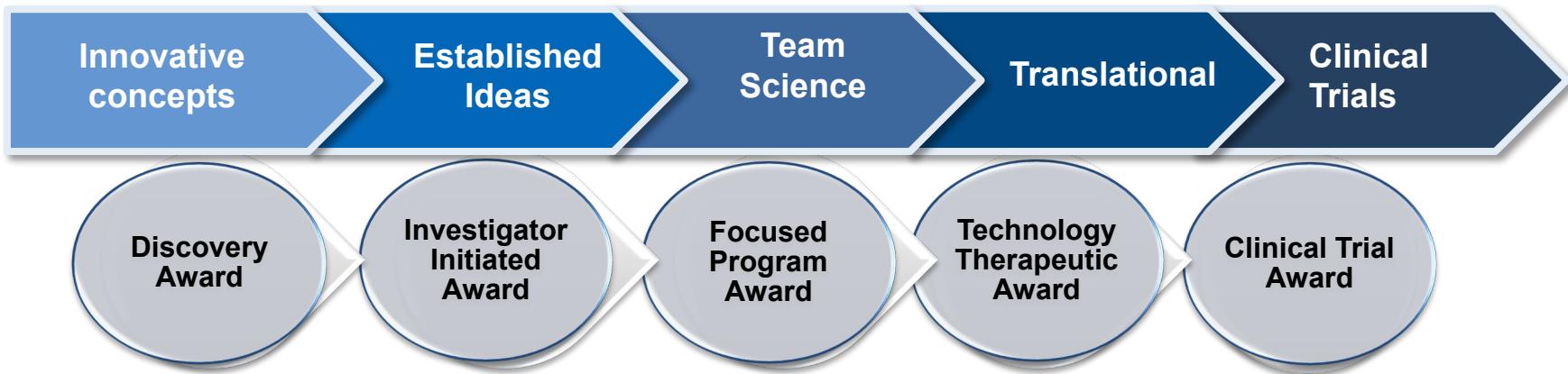
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History of PRMRP Topic Areas Related to Toxic Exposures

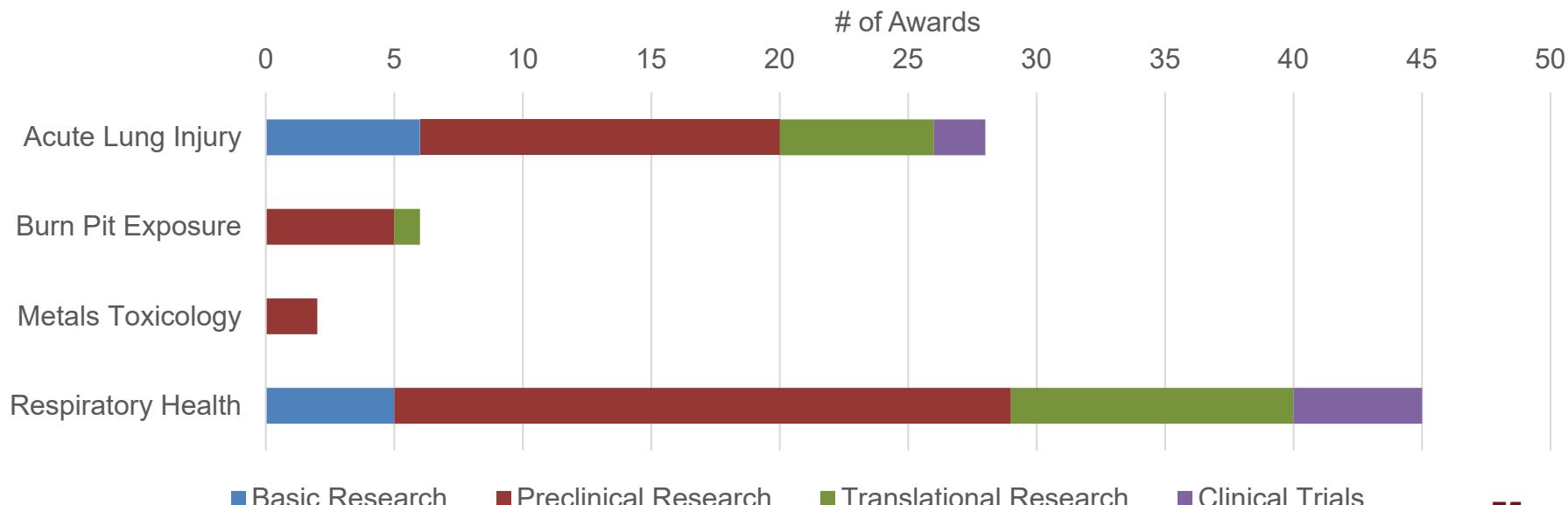
Topic Area	FY99	FY00	FY01	FY02	FY03	FY04	FY05	FY06	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	FY18	FY19	FY20	FY21	FY22	
Acute Lung Injury	✓	✓	✓												✓	✓	✓	✓	✓						
Burn Pit Exposure																✓		✓	✓	✓	✓	✓	✓		
Constrictive Bronchiolitis																	✓	✓	✓	✓	✓				
Gulf War Illness		✓	✓																						
Lung Injury																			✓	✓					
Lung Research	✓																								
Metals Toxicology																✓	✓	✓	✓	✓	✓	✓	✓	✓	
Respiratory Health																✓	✓	✓	✓	✓	✓	✓	✓	✓	



Current Funding Mechanisms Offered



FY17-FY21 Award Maturity



Burn Pit Exposure

- **Six (6) awards totaling \$17,439,581**
- **Research Includes:**
 - **Risk and Treatment:** A Focused Program Award addressing how military airway toxicant exposure increases risk of bronchitis, and whether an therapeutic strategy of improving mucus-mediated toxicant clearance (inhaled hypertonic saline) and suppressing inflammation (prednisone) will mitigate/reverse inhalation-induced bronchitis (clinical trial using wood smoke model)
 - **Mechanism of Disease:** Epithelial repair dysfunction (partnered award)
 - **Risk:** DNA methylation markers associated with adverse health outcomes in Veterans exposed to open burn pits (partnered award)
 - **Epidemiology:** respiratory and cardiovascular health outcomes following burn pit exposure (additional details on next slide)

Impact of Open Burn Pit Exposure on Respiratory and Cardiovascular Health Among Military Veterans

Investigator-Initiated Research Award

PI: Dr. David Savitz at Brown University

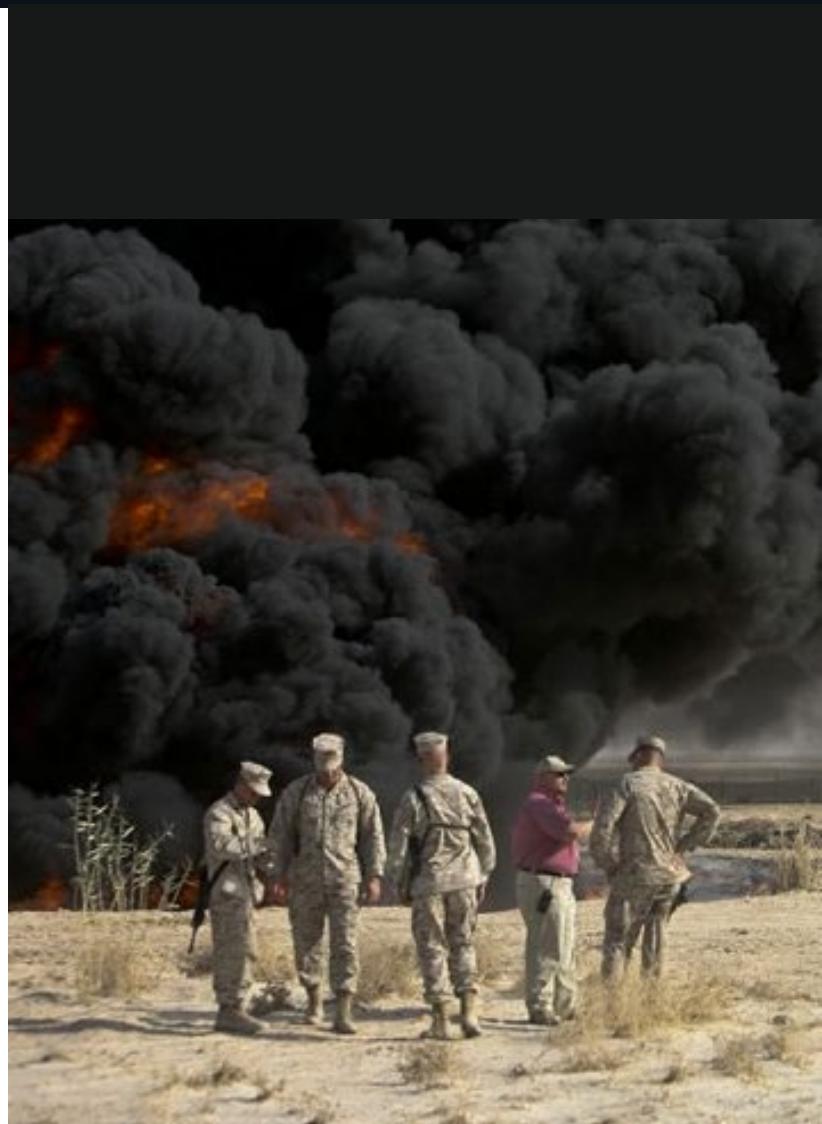
Award Amount: \$1,472,838

Period of Performance: 09/15/2019 - 09/14/2022

Gap: There is a need to address the adverse health events related to exposure to airborne hazards and open pit burning of solid waste and other material.

Study Design: Correlate deployment history with incidence of respiratory or cardiovascular disease in a cohort of Veterans.

Outcomes to Date: Dr. Savitz and his team have acquired deployment histories for ~600,000 Veterans deployed to Afghanistan or Iraq, developed base-exposure matrix with assigned burn pit exposure potential, linked to healthcare data from the VA. Analysis will be conducted in the next year.



Burn Pit Research Under other Topic Areas

- **Five (5) awards totaling \$18,936,364 have been funded under other Topic Areas:**
 - **Diagnosis (Acute Lung Injury):** 2p-SpectraFLIM, a portable noninvasive imaging-based diagnostic to track lung metabolic health using a seek and focus approach; validated in rodent toxin exposure model
 - **Mechanism of Disease (Constrictive Bronchiolitis):** Test the hypothesis that inhalation exposure results in loss of p73 (a factor required for maintenance of multi-ciliated cell phenotype), leading to a defective mucosal immune barrier
 - **Treatment (Respiratory Health):** Clinical trial to test efficacy of L-Citrulline Supplementation for deployment-related asthma
 - **Mechanism of Disease and Epidemiology (Respiratory Health) :** Focused Program Award addressing the hypothesis that exposure to airborne particulate matter primes the respiratory epithelium for enhanced injury through investigation of patient samples at the Center for Deployment Lung Disease at National Jewish Hospital; Will look for metal content in lung tissue samples, investigate gene expression profiles, and look for correlations in medical history data
 - **Mechanism of Disease (Respiratory Health) :** Expansion of above-mentioned study to further findings on pathogenesis of deployment related lung disease through patient immune cell profiling

Metals Toxicology

- Three (3) awards totaling \$8,544,827
- Research Includes:
 - **Diagnosis and Epidemiology:** Focused Program Award detailed on the following slide
 - **Diagnosis:** Early preclinical development of a microscale sensor for toxic metals in biologically or environmental samples
 - **Diagnosis:** Early preclinical development of a portable device to detect heavy metals in whole blood sample; Results were published last year: Zhang X, Chia E, Fan X, Ping J. Flow-sensory contact electrification of graphene. *Nat Commun.* 2021 Mar 19;12(1):1755. doi: 10.1038/s41467-021-21974-y. PMID: 33741935; PMCID: PMC7979811.

Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments

Focused Program Award

PI: Melissa McDiarmid at University of Maryland, Baltimore

Award Amount: \$7,967,578

Period of Performance: 09/22/2016 – 09/29/2022

Gap: This award addresses the overarching challenge of establishing an evidence based to refine the decision-making and clinical management of the Veteran or Service Member with retained embedded metal fragments

Study Design: Preclinical animal studies to better understand the health effects of embedded fragments, identification of novel biomarkers to improve early detection of toxicity and resulting tissue injury and assess return-to-duty potential, and epidemiological studies to correlate respiratory health parameters in a cohort of Veterans (VA-TEF Registry cohort) with metal inhalation and blast exposure

Outcomes to Date: Preclinical studies are mostly completed and final analysis is underway for the human subjects research projects. Found reduced levels of some synaptic proteins in a rodent model. Also identified that most metals solubilize and are then excreted through the urine, suggesting the importance of tracking renal function in patients. Identified genes involved in oxidative stress and altered cell function in kidney as potential biomarkers.

FY22 Respiratory Health Strategic Goals

Topic Areas:

- Pulmonary Fibrosis
- Respiratory Health

- Sustained Release Drug Delivery
- Trauma

Foundational Studies

- Determine how airborne hazards, toxins, or nanomaterial exposure cause respiratory injury/disease

Prevention

- Prevent lung injury caused by trauma, transfusion, mechanical ventilation, infection, or hemorrhagic shock

Diagnosis

- Develop and validate sensors to assess environmental and/or physiological levels of exposure to airborne hazards or toxins
- Develop a fieldable toolset to monitor lung dysfunction/failure
- Improve early detection for interstitial lung disease

Treatment

- Develop and test novel treatments, including precision medicine approaches, to slow progression or reverse lung injury/disease
- Develop improved fieldable devices to treat traumatic/acute lung injury in far forward settings, including toolsets to enable correct airway placement, oxygenation in austere settings, or miniature and/or semi-automated ventilator
- Develop novel delivery mechanisms and/or improved pharmaceuticals to prevent/treat high-altitude pulmonary edema (HAPE)

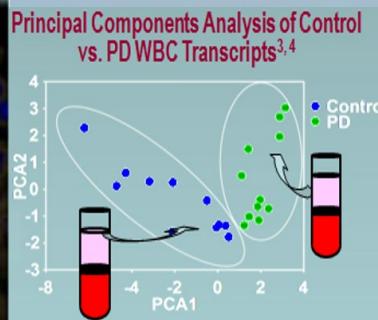
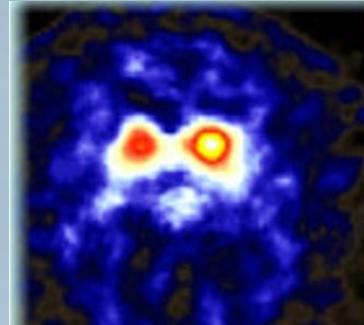
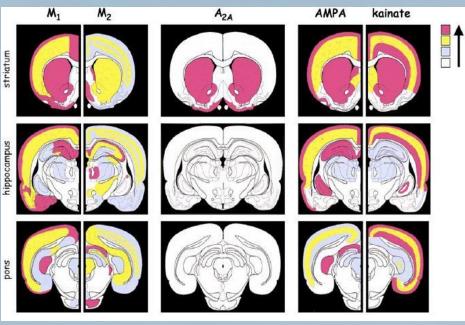
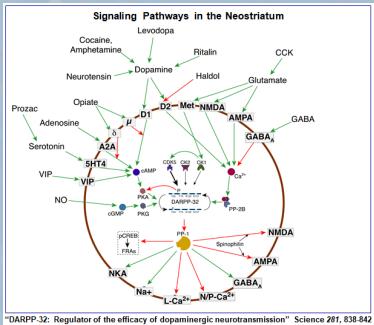
Enclosure 6

Neurotoxin Exposure Treatment Parkinson's Research Overview

Neurotoxin Exposure Treatment Parkinson's Research (NETPR)

15 June 2022

CUTTING EDGE RESEARCH



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NETPR Overview

Vision: Eliminate Parkinson's disease through neurotoxin exposure and treatment related research in partnership with scientists and consumers

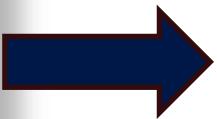
Mission: Support Parkinson's research by investigating the underlying biologic mechanisms and therapeutic interventions of neuro-degenerative effects caused by deployment, environmental, and occupational exposures in Service members and Veterans.

Congressional Appropriation: \$486.75 Million FY97-20
FY21 Appropriation \$16M
271 Awards FY97-20

NETPR Overview

Strategy:

- Identify environmental risks for Parkinson's disease (PD)
- Identify biological mechanisms linking environmental risk to motor and non-motor signs and symptoms of PD
- Develop therapeutic interventions to ameliorate and/or cure PD



Focus Areas:

- Mechanisms in Early PD
- PD Progression
- Environmental Factors
- Gene Environment Interactions
- Neurovascular Unit
- Tau Protein
- Neuroplasticity
- Non-Motor Symptoms
- Cognitive and Psychiatric
- Sleep Dysfunction
- Digital Health Technology
- Exercise as Therapy

Research Continuum

Number of awards aligned under each TERP Research Continuum category that are currently either open or closed

	Foundational	Epidemiology	Etiology	Prevention and Monitoring	Diagnosis and Treatment
Closed TERP aligned Awards	25	9	18	14	21
Open TERP aligned Awards	11	5	4	0	2

FOUNDATIONAL SCIENCE

Disruption of Dopaminergic and Cholinergic Function in Military Deployment: Implications to Parkinson's disease

PI: Gary W. Miller, Ph.D.
Emory University

Examined the potential risks of the carbamate Permethrin on the dopaminergic system. Determined that permethrin upregulated dopamine transporters and increases motor activity in a rodent model. Results were independently verified in two other studies.

Results from USARIEM determined that permethrin treated uniforms were correlated with blood levels twice that of normal use. Instructions were provided for waiver of pregnant service members wearing permethrin treated uniforms until additional safety tests were conducted. (ALARACT 289/2012).

Airborne Pollutants as Triggers of Parkinson's disease via the Olfactory System

PI: Patrik Brundin, M.D.,
Van Andel Research Institute in Partnership with Univ of Southern California and Michigan State University

Examined whether ambient air pollutants, particularly nanosized particulate matter, initiates or exacerbates neuro-inflammation in olfactory structures and results in molecular events that increase risk of development of Parkinson's disease.

Results: Although COVID related restrictions slowed work on the project, there were two publications associated with the partnered project.

EPIDEMIOLOGY

Neurotoxins and Neurodegenerative Disorders in Japanese-American Men Living in Hawaii

PI: George Webster Ross, M.D.

Pacific Health Research Institute

Examined bio-accumulated organophosphates in approximately 300 brains of agricultural workers who worked in cane and pineapple fields in Hawaii during the early 20th century. All samples were from individuals with full clinical evaluations and full neuro-pathologic evaluations.

Results: Identified a significant and positive relationship of bioaccumulated Heptachlor epoxide in the subset of individuals with clinical and molecular markers of Parkinson's disease. Also identified a correlation of increased Lewy body formation and bioaccumulated Heptachlor epoxide isomer b, methoxychlor, and benzene hexachloride b.

California Parkinson's Disease Registry Pilot Project - Coordination Center and Northern California Ascertainment

PI: Carolyn Tanner, M.D.

The Parkinson's Institute in Partnership with University of California Los Angeles

Conducted a pilot study to establish the structure for a "Parkinson's disease registry". Exploratory investigations were conducted on the association between Parkinson's disease and linked toxicant chemical exposures identified from the California Department of Public health application data.

Results: Formed the basis for more extensive studies in California, three of which were funded by CDMRP.

Etiology

Characterization of Intracellular Signaling Pathways Activated by Nerve Agents

PI: Allen Fienberg, Ph.D.

Intracellular Therapies Incorporated in partnership with USAMRICD

Characterized the effects of an organophosphate on intracellular signaling pathways altered *in vivo* to explore how the toxic agent alters neurotransmitter signaling pathways in the brain. Sarin was used as the test organophosphate,. The project examined signaling pathways for all 12 cholinergic receptors, determined those most active during organophosphate presence, identified two intervention points and appropriate candidate compounds to prevent deleterious physiological effects. Injection studies were done in collaboration with USAMRICD and inhalation studies with the Netherland's military.

Outcomes included four peer reviewed publications and two military technical reports:

Genetic and Epigenetic Mechanisms Underlying Acute and Delayed Neurodegenerative Consequences of Stress and Anticholinesterase Exposure

PI: Hermona Soreq, Ph.D.

Hebrew University, Jerusalem, Israel

Examined the hypothesis that acute psychological stresses and exposure to anticholinesterases induce long-term perturbations in the structure/function of neurological tissues associated with an increase in acetylcholinesterase (AChE) levels which, over a prolonger period, result in neurodegeneration.

Prevention and Monitoring

Jet fuel Exposure and Neurological Health in Military Personnel: A Feasibility Study

PI: Susan Proctor, D.Sc.,
USARIEM

Jet propulsion fuel 8 (JP-8) was recognized by the Department of Defense as the single largest chemical exposure for its personnel. The project conducted an epidemiological field study to examine the relationship between JP-8 fuel exposure and adverse neurological outcomes in military personnel working in a cold climate environment. During the study the PI developed unique means of monitoring exposures, identified biomarkers which were later incorporated as recommendations in National Research Council publication: "Toxicologic Assessment of Jet-Propulsion Fuel 8", and measured whether cumulative JP-8 exposure was associated with neurocognitive and neurophysiologic performance outcomes. The studies were carried out in collaboration with the U.S. Air Force.

Diagnosis and Treatment

Establishing an `At Risk` Cohort for Parkinson`s Disease Neuroprevention Using Olfactory Testing and DAT Imaging

PI: Kenneth Marek, M.D.

Institute for Neurodegenerative Disorders

Determine if screening for hyposmia followed by screening for dopamine transporter deficit can identify individuals at risk for conversion to clinical PD, and to evaluate disease progression markers in the prodromal (pre-motor) period. The project developed a strategy to detect individuals at increased risk for PD by sequentially testing two biomarkers of Parkinsonism, olfaction deficits and DAT imaging.

Results of the project suggest that both baseline dopamine transporter imaging (DAT) and DAT trajectory are predictors of future conversion of an individual to clinical diagnosis of Parkinson's disease. Results also suggest that DAT imaging is a precise and usable biomarker for risk of PD development and for following progression of the condition from the prodromal to clinical stages of the condition.

Heterogeneity of Parkinson's disease Patients: Identification and characterization of neuroprotective factors of early dopaminergic neuron degeneration.

PI: Marc Flajolet, Ph.D.

The Rockefeller University

Based on the 19 previously identified master regulators of dopaminergic neuron functioning, the project is assessing several of the proteins in iPSC lines in order to determine their neuroprotective function and develop small candidate compounds capable of being used as therapeutic interventions in Parkinson's disease.

The project determined that SATB1 is a genetic risk factor for Parkinson's disease, and that loss of SATB1 induces cellular senescence in a mouse model of Parkinson's disease with a loss of dopaminergic, but not cortical neurons. The senescent neurons secrete inflammatory factors that induce an immune response in the tested mice that is associated with the dopaminergic neuron loss. The project is examining potential candidate compounds as a therapeutic intervention.

Challenges

- ◆ Failure to follow-up on genetic projects at the National Institute of Aging.
- ◆ Co-morbid issues complicating toxin exposure disease risk.
- ◆ Need for increased collaboration with researchers outside the field of Parkinson's research.
- ◆ Difficulties in recruitment:
 - ❖ Disinclination of patients to enroll in clinical trials
 - ❖ Disinclination of patients to have Cerebral Spinal Fluid Harvested
 - ❖ Frailty of affected population

NETPR OVERVIEW

QUESTIONS?

Enclosure 7
Veterans Health Administration
Health Outcomes Military Exposures

VETERANS HEALTH ADMINISTRATION

HEALTH OUTCOMES MILITARY EXPOSURES (HOME)

William J Culpepper II, PhD, MA
Deputy Director, Epidemiology Program, HOME
Co-Director, MERP Taskforce



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Health Outcomes Military Exposures

VA has an office specifically devoted to possible health effects of military environmental exposures called Health Outcomes Military Exposures (HOME)

Mission Statement

HOME serves Veterans and their families as the leader and authority on health outcomes of military exposures through science, policy, education and communication.

Vision Statement

HOME is a trusted team that Veterans and stakeholders rely on as a definitive source of information on military exposures.

We have a comprehensive website that covers many exposure topics:

<https://www.publichealth.va.gov/exposures/topics/index.asp>

We also have an app!

<https://mobile.va.gov/app/exposure-ed>



HOME consists of **four interrelated programs**:

- **Environmental Health**
 - Pre-911 Programs / Post-911 Programs
 - Radiation dose evaluations
 - Environmental Health Field Support
- **Epidemiology:**
<https://www.publichealth.va.gov/exposures/research-studies.asp>
- **War Related Illness and Injury Study Center (WRIISC):** 3 sites – California; Washington, DC; New Jersey
- **Toxic Embedded Fragment/Depleted Uranium (TEF/DU) Center:** Maryland

Whole of Government Partners: DoD, DHHS, CDC, ATSDR, NIH, FDA and EPA



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Health Outcomes Military exposures

What we do:

Six Congressionally-mandated exposure registries

- Agent Orange
- Gulf War
- Ionizing Radiation
- Airborne Hazards and Burn Pit Registry
- Toxic Embedded Fragments
- Depleted Uranium

Tracking Exposures better:

- **Individual Longitudinal Exposure Record/Registry (ILER) and the electronic health record**

Current Actions:

- Gulf War Illness Definition
- Airborne Hazards / Burn Pits
 - VA Review for SecVA and determination of 3 new presumptive conditions (asthma, sinusitis, rhinitis)
- Research / Surveillance/ Epidemiology
- Karshi-Khanabad (K2)
- Garrison Environmental Concerns
 - Camp Lejeune contaminated water
 - PFOS/PFOA contaminated water (national sites and military bases)
- Other concerns: Emerging Issues, Liver Flukes, Antimalarials, Palomares and Enewetak (nuclear clean-up)



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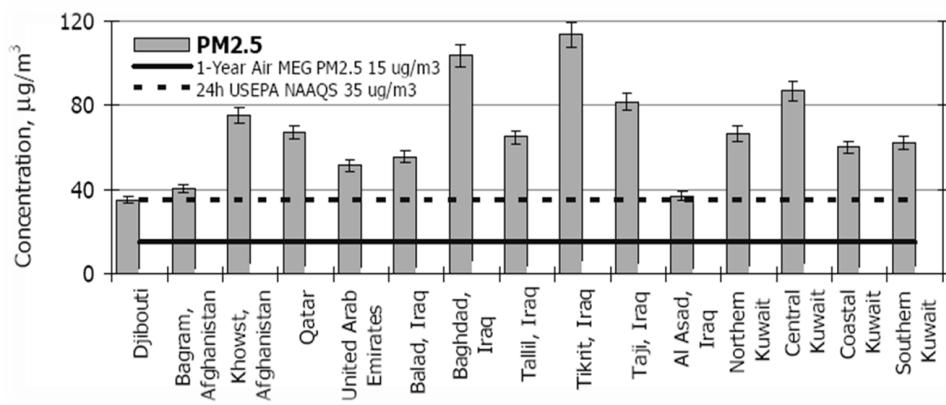
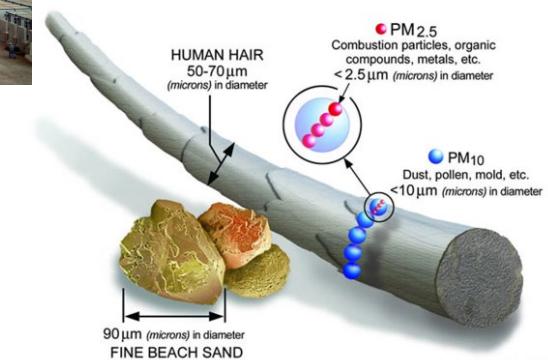
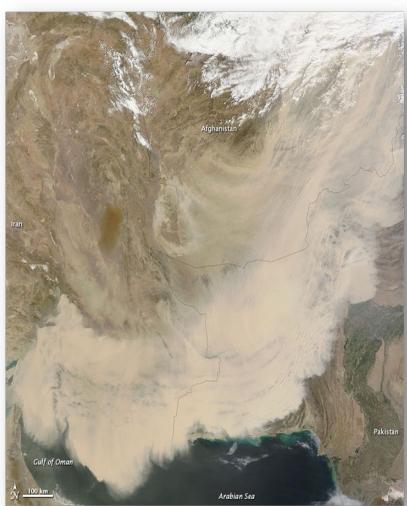
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Many environmental and occupational exposures due to Military Service



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Epidemiology & Exposure Science

Epidemiology: The study of the occurrence and distribution of health-related states or events in populations and application of this knowledge to control health problems. Epidemiology studies identify association not cause.

Exposure status often limited to comparing deployed to non-deployed or veterans to non-veterans. Better and more quantitative exposure assessments are needed.

Post 9/11: Airborne Hazards, CHAI, K2 Surveillance Program, PFAS, MWD

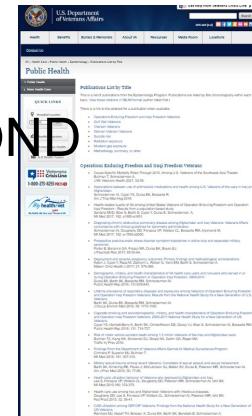
Pre 9/11: Gulf War Follow-up Study, GW Illness Case Definition

Vietnam Era: VE-HEROeS, Army Chemical Corps

Mortality Studies: Vietnam, 1990-91 Gulf War (ODS/S), OEF/OIF/OND

Occupational Exposures / Military Working Dogs

<https://www.publichealth.va.gov/epidemiology/publications.asp>



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Epidemiology Program

- Brief overview of the program history
 - Agent Orange Research Office
 - Environmental Epidemiology Service (EES)
 - Focused on health effects of military experiences
 - POWs
 - Radiation exposures
 - Mustard and other chemical weapons testing (SHAD)
 - Mortality studies (suicide, injury, PTSD)
 - Environmental Agents Service/ Office of Public Health and Environmental Hazards/ OPH/ PDHS
- Population based studies/healthcare utilization



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Epidemiology Program

- Primary data sources for PDHS epidemiology studies
 - Surveys (web, paper, telephone)
 - Health care utilization data
 - Mortality data
 - From VA/ DoD Suicide Data Repository
 - Sourced from the National Death Index, National Center for Health Statistics, CDC
- Our focus is on population level inquiry
 - We also learn about the health of non-VHA using population
- Epidemiology studies identify association not cause
- **Military Exposures Research Program (MERP)**
 - ORD and HOME collaboration
 - Emphasis on advancing exposure assessment beyond deployment status



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of Veterans Affairs

Karshi-Khanabad (K2) 2001-2005

- All K2 Veterans eligible for VA healthcare per priority score
 - Any Veteran with K2-related health concerns encouraged to seek environmental health examination and to file claim with Veteran Benefit Administration (VBA)
 - [Health Care for Veterans - Public Health \(va.gov\)](https://www.veterans.gov/public-health)
 - All K2 Veterans eligible for DU testing (at no cost)
 - To date 97 tests completed with 0 instances of DU isotopic signature
 - [Depleted Uranium - Public Health \(va.gov\)](https://www.veterans.gov/public-health)
- Most (\approx 70%) of K2 Veterans eligible for enrollment in the AHOBPR based on other deployments to SW Asia in support of OEF/OIF
- Adding K2 as eligible location for enrollment in AHOBPR
- K-2 Veterans covered under new respiratory disease presumptions

NEXT STEPS

- 15,035 deployed to K2
- Assemble data from MHS, CHAMPUS/TriCare, VHA, and MDR
- Build longitudinal database
- Working with ATSDR, convene the first of several K2 community engagement panels
- Conduct morbidity & mortality analyses



Army troops follow an airman at Karshi-Khanabad Air Base
United States Air Force, photo by Tech. Sgt. Scott T. Sturkol



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Epidemiology Program – Recent Publications

Publications March and April

- Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy
 - The Lancet [<https://www.thelancet.com/action/showPdf?pii=S1470-2045%2822%2900219-4>]
 - Melissa A. McDiarmid, MD, MPH, DABT, Medical Director, VA Depleted Uranium and Toxic Embedded Fragment Surveillance Centers
- The mental health of Vietnam theater veterans – the lasting effects of the war: 2016–2017 Vietnam Era Health Retrospective Observational Study
 - Journal of Traumatic Stress [<http://dx.doi.org/10.1002/jts.22775>]
 - Dr. Yasmin Cypel, Senior Epidemiologist, HOME
- A Burning Question (Constrictive Bronchiolitis)
 - New England Journal of Medicine [<https://www.nejm.org/doi/full/10.1056/NEJMcps2119930>]
 - Dr. A. Rabin, VA Ann Arbor, Airborne Hazards Burn Pit Center of Excellence, University of Michigan and Rutgers University
- The Power of Prevention: Prevention and Preparedness in Public Health
 - American Journal of Preventive Medicine
 - Dr. Michael Brumage, Deputy Chief Consultant, HOME



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Epidemiology Program

The Epidemiology Program designs and conducts studies of Veteran populations to understand how to prevent and treat health effects of military service.

William.Culpepper@va.gov (Joel)

<https://www.publichealth.va.gov/epidemiology/index.asp>

<https://www.publichealth.va.gov/epidemiology/studies/index.asp>

<https://www.publichealth.va.gov/epidemiology/publications.asp>



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Presumption

- Presumption determination
 - Secretary, Veterans Affairs
 - Legislation
- Why presumption vs Direct Service Connection?
- Recent presumptions for:
 - Airborne Hazards
 - Methodology
 - Agent Orange
- Developing a new Model
 - Use of VBA data
 - National Academy of Sciences Engineering and Medicine consensus reports
 - Other scientific review panels



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Home Website



The screenshot shows the official website of the U.S. Department of Veterans Affairs. At the top, there is a navigation bar with links to 'Post Deployment Health S...', 'VA Identity and Access M...', 'VA Publications List by Title ...', 'AOL - News, Weather, Ent...', and 'Google'. Below the navigation bar is the Department of Veterans Affairs logo. The main header features the text 'U.S. Department of Veterans Affairs'. On the right side of the header is a 'Get help' button with a star and a phone icon. Below the header, there is a search bar and a 'SITE MAP' link. The main content area has a dark blue background with the text 'VA » Health Care » Public Health » Military Exposures'. Below this, the page title 'Public Health' is displayed in a large, bold, blue font. A sidebar on the left is titled 'Public Health' and includes links for 'Public Health Home', 'Military Exposures', 'Military Exposures Home', '4 Ways to Find Exposures', 'Agent Orange', 'Gulf War Veterans' Illnesses', 'Radiation', and 'Benefits'.

WARS & OPERATIONS



[Operation Enduring Freedom \(Afghanistan\)](#)

[Iraq War \(OIF/OND\)](#)

[Gulf War](#)

[Vietnam War](#)

[More Wars & Operations »](#)

EXPOSURE CATEGORIES



[Chemicals \(Agent Orange, contaminated water...\)](#)

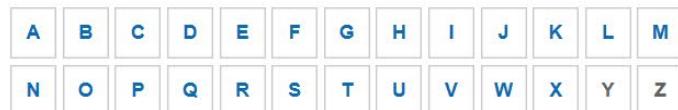
[Radiation \(nuclear weapons, X-rays...\)](#)

[Air Pollutants \(burn pit smoke, dust...\)](#)

[Occupational Hazards \(asbestos, lead...\)](#)

[Warfare Agents \(chemical and biological weapons\)](#)

EXPOSURE TOPICS A-Z



Registry Evaluation

A free [medical assessment](#) for possible health problems related to specific environmental hazards

Health Care

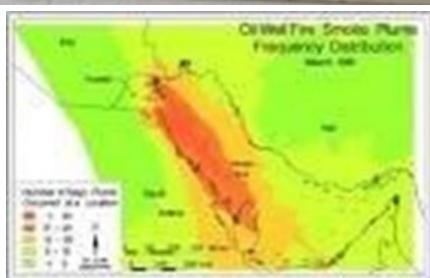
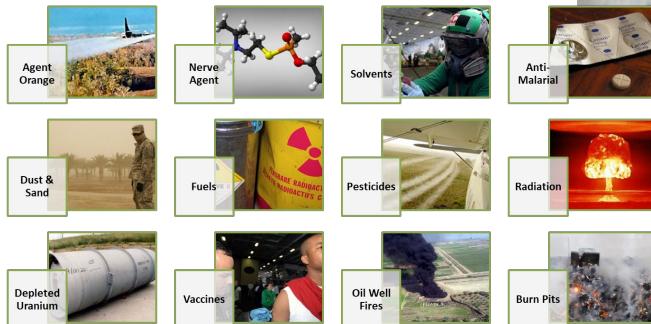
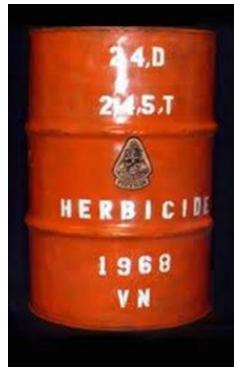
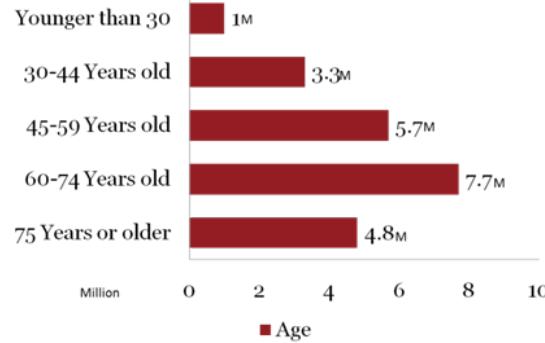
[Health care services](#) for eligible Veterans, how to qualify and apply

Research Studies

Publications & Reports

<https://www.publichealth.va.gov/exposures/index.asp>

Health Outcomes Military exposures



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Enclosure 8
Veterans Health Administration
Gulf War and Military Exposures Research Program

VETERANS HEALTH ADMINISTRATION

1990-91 Gulf War & Military Exposures Research Programs Office of Research and Development

Presentation for: DOD CDMRP TERP

Presented by: Karen Block, PhD – Senior Program Manager

Date of Briefing: JUNE 15-16, 2022



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BOTTOM LINE UP FRONT: BLUF

- Military exposures research is a high visibility, high priority topic for VA and ORD.
- ORD FY22-23 focus is to build and strengthen 1990-91 Gulf War Illness research investments and initiate a Military Exposures Research Program (MERP).



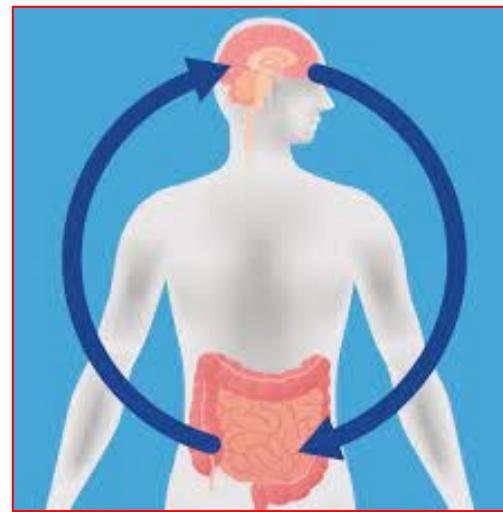
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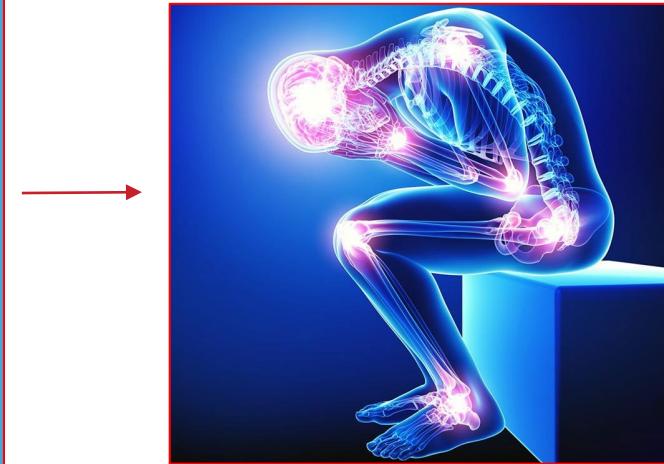


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of Veterans Affairs

Military Exposures and Chronic Multi-symptom Illness



Brain/Gut Axis



Systemic Inflammation

Cognitive Dysfunction

Joint Pain/Fibromyalgia

Irritable Bowel Syndrome

Migraine Headaches

- ❖ Gulf War Service members were exposed to single/combination toxicants of unknown quantities.
- ❖ Exposure assessment is a challenge.
- ❖ Basic understanding of toxic effects under military conditions is limited.



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VA-ORD Funding (2011-2022)

1990-91 Gulf War Research (SPLD)

FY	Applications Rec'd	Projects Funded	% Funded	Funds Approved
2011	26	3	12%	\$4M
2012	32	7	22%	\$11.4M
2013	35	7	20%	\$12.6M
2014	40	5	13%	\$7.5M
2015	33	8	24%	\$13.2M
2016	26	4	15%	\$2.5M
2017	29	5	17%	\$5.3M
2018	27	5	19%	\$2.6M
2019	21	5	24%	\$5M
2020	12	4	33%	\$3.4M
2021	16	3	18%	\$4.6M
2022 (S22)	7	2	29%	\$1.5M

- Budget \$16M/year
- Funding rate: 25%
- 224 VA Funded Projects (1997-2022)



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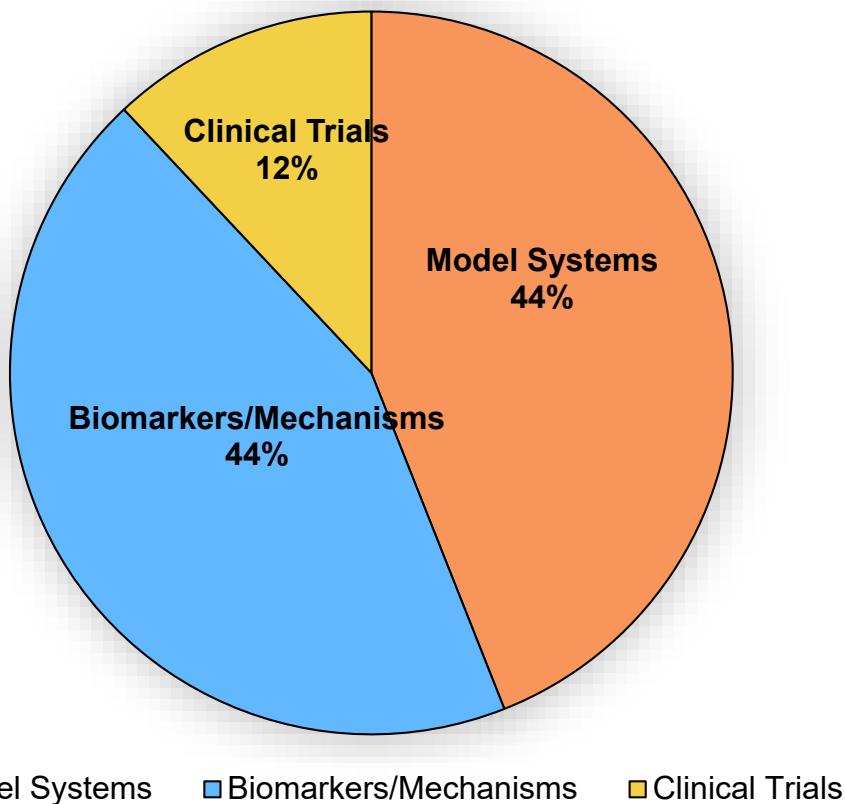
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VA Active Gulf War Research Projects

GULF WAR PORTFOLIO BALANCE, 2022



Model Systems

Biomarkers/Mechanisms

Clinical Trials

Microbiome and Brain/Gut axis

Lipid Metabolism

Oxidative Stress

Mitochondrial Dysfunction



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Active Gulf War Research Projects, 2022 (1 of 3)

Treatments/Clinical Trials

- rTMS in alleviating Pain and Co-morbid symptoms in GWVI.
PI: Leung I01 CX001986 NCT04182659
- Microbiome targeted oral butyrate therapy in Gulf War multi-symptom illness.
PI: Chatterjee I01 CX002372 NCT05367245



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Active Gulf War Research Projects, 2022 (2 of 3)

Biomarkers/Mechanisms/Preclinical

- An investigation of the relationship between toxicant exposures during Gulf War deployment and prodromal Parkinson's disease.
PI: Chao, Linda *I01 CX000798*
- Biomarker Candidates in Gulf War Veterans: A 10-year Follow-up Investigation.
PI: Marx, Christine E *I01 CX001569*
- Post Exertional Malaise in GWI: Brain Autonomic and Behavioral Interactions.
PI: Cook, Dane *I01 CX001329*
- Toxicant Exposure Impacts Host-pathogen interactions within the Reproductive Tract.
PI: Gaddy, Jennifer A *I01 BX005352*
- Advancing Non-Invasive Diagnostics and Treatments of Deployment-Related Chronic Lung Disease in Gulf War Veterans.
PI: Osterholzer, John *I01 BX004740*
- Toxicology study of emissions from a burn pit simulator.
PI: Ravi, Nathan *I21 BX005178*
- VA: NIH Project IN-DEPTH.
PI's: Reinhard, Klimas, Ashford
- Alveolar macrophage dysregulation in the pathogenesis of Gulf War respiratory illness.
PI: Berenson, Charles *I01 CX002521-01*



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Active Gulf War Research Projects, 2022 (3 of 3)

Model Systems/Preclinical

- Immune Basis for Hippocampal Cholinergic Deficits in Pyridostigmine-treated Rats.
PI: Reagan, Lawrence I01 BX002664
- Acute exercise tolerance among Veterans with Gulf War Illness.
PI: Lindheimer, Jacob IK2 CX001679
- Gulf War Veterans' Illness: Symptom Chronicity via Interactions of Diet and Lifestyle Risk Factors with the Gut Microbiome.
PI: Kuhn, Donald I01 BX004757
- CMA: Immune/Inflammatory Priming in Exacerbating Responses to GWVI.
PI: Chatterjee, Saurabh I01 CX001923
- VA Biorepository: Gulf War Veterans' Illnesses Biorepository.
PI's: Huber, Bertrand; Brady, Christopher; Renner, Stephen I01 BX003063
- The role of the brain stem in GWVI pathology.
PI: Furst, Ansgar I01 CX002182
- Dopamine neurotransmission in Gulf War Veteran's Illness.
PI: Badgaiyan, Rajendra I01 CX002099
- Integrating genomics and metabolomics data to identify molecular characteristics of Gulf War Veterans' illnesses
PI: Hauser, Elizabeth I01 BX005902



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GWI PROTOCOL: VA “Sister” protocol



Project IN-DEPTH

VA - NIH

INVESTIGATIVE DEEP PHENOTYPING STUDY OF GULF WAR VETERAN HEALTH



*Study Co-Chair,
Washington DC*

M. Reinhard, PsyD



*Study Co-Chair,
Miami FL*

N. Klimas, MD



*Local Site,
Palo Alto CA*

W. Ashford, MD



*NIH/NINDS,
Principal
Investigator*

B. Walitt, MD



*VA Gulf War
Program
Director*

K. Block, PhD

VA Study Team

NIH Study Team

**ORD Program
Oversight**



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Military Exposures Research Program (MERP)

MISSION STATEMENT: The VA Military Exposures Research Program seeks to advance military exposure assessments and to understand the effects of military exposures on Veterans' health outcomes to inform care and policy.

Military Exposures: Military Exposures are *toxic* agents, singly or in combination, incurred through military service (deployment, occupation, or garrison).

Exposures Assessment: Exposure assessment refers to identifying and quantifying *toxic* agent(s) to which a *Veteran* was exposed during military service.



Military Exposures Research Program (MERP)

MERP will focus on several key activities:

- Establish enterprise-level core capabilities to support funded investigator studies needing exposure assessment, data/survey tools and analysis, biospecimen collection, storage and analysis.
- Leverage ORD resources in clinical and genomic research including Cooperative Studies Program and Million Veteran Program
- Develop Capacity Building: Intra- and Inter-federal and academic partnership building are imperative to move military exposure assessment and health research forward efficiently and uniformly.
- Develop Requests for Applications (RFA) for Investigator-initiated studies: RFAs will be released broadly for investigator-initiated projects to support key gap portfolio areas.
- Support program-directed research. Program-Directed Military Exposure Research Innovation Center(s) (MERICs) will be launched to support high impact, highly innovative key priority projects.

THANK YOU & QUESTIONS



karen.block@va.gov



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Enclosure 9

National Institutes of Health

National Institute of Neurological Disorders and Stroke

Office of Neural Exposome and Toxicology

US Army CDMRP Presentation

Toxic Exposures Research Program (TERP)

Stakeholders Meeting, June 15, 2022

David A. Jett, Ph.D.

Director, Office of Neural Exposome and Toxicology

Director, NIH Countermeasures Against Chemical Threats (CounterACT)

Program Director & Scientific Team Leader, Division of Translational Research

NIH/National Institute of Neurological Disorders and Stroke

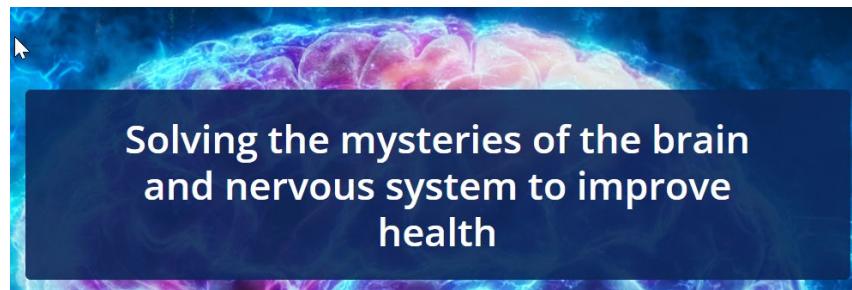
Professor Adjunct of Environmental Toxicology, Yale School of Public Health



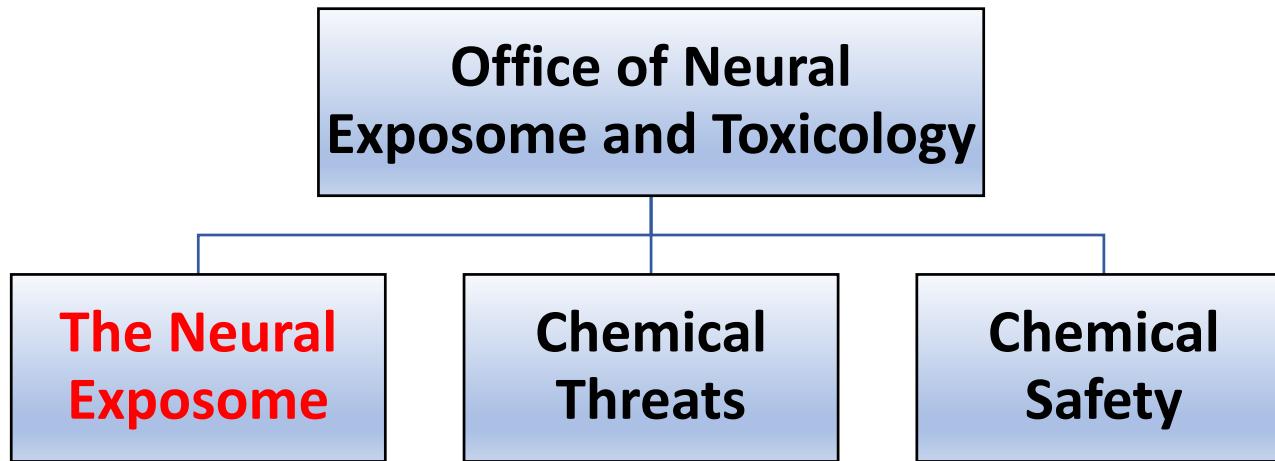
National Institute of
Neurological Disorders
and Stroke

National Institutes of Health National Institute of Neurological Disorders and Stroke

Mission is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people.



NIH NINDS Office of Neural Exposome and Toxicology



The Exposome



Exposomic Risk Factors

- Human genetics has provided unprecedented insight into the etiologies of inherited disease
- But the majority of health risk factors cannot be explained by genetics alone
- Environmental exposures affecting the genome was coined as the “exposome” (Wild, 2005)
- Now all nonheritable factors that affect gene expression across the lifespan are considered
- This is a new frontier of biomedical research to complement the genome
- Unlock a more holistic approach to disease prevention and more effective and personalized interventions

NeuroView

A focus on the neural exposome

Amir P. Tamiz,¹ Walter J. Koroshetz,² Neel T. Dhruv,¹ and David A. Jett^{1,*}

¹Division of Translational Research, National Institute of Neurological Disorders and Stroke, NIH, 6001 Executive Blvd., Rockville, MD 20852, USA

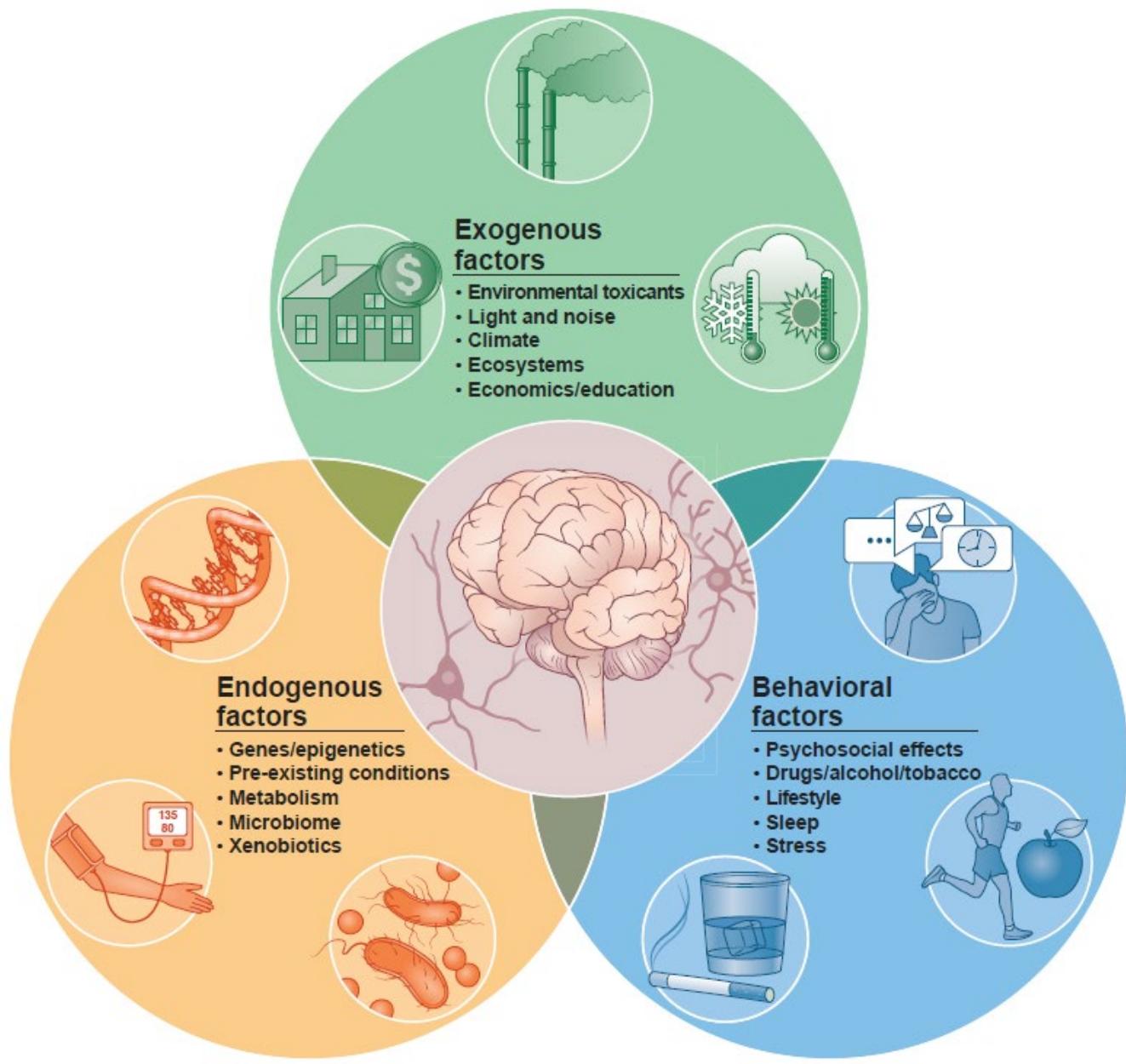
²National Institute of Neurological Disorders and Stroke, NIH, 31 Center Drive, 8A31, Bethesda, MD 20892, USA

*Correspondence: jettd@nih.gov

<https://doi.org/10.1016/j.neuron.2022.03.019>

]

Many neurological disorders have complex etiologies that include noninheritable factors, collectively called the neural exposome. The National Institute of Neurological Disorders and Stroke is developing a new office with goals to advance our understanding of the multiple causes of neurological illness and to enable the development of more effective interventions.



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The Neural Exposome

Vision

- ⑩ A much better understanding of the causes of nervous system diseases and disorders that incorporates both genomic and exposomic factors
- ⑩ More effective therapeutics and intervention strategies

Initial Approach

- ⑩ Collaboration: Establish NINDS and trans-NIH working groups
- ⑩ Outreach and feedback from external scientific communities
- ⑩ Strategic Plan
- ⑩ Broad mechanistic Funding Announcement

•Long-term

- ⑩ Disease/Disorder-based targeted Funding Announcements
- ⑩ Translational and Clinical Funding Announcements

Opportunities for Exposome Research



Data

- > Human studies
- > Biobanks
- > Geospatial data
- > Wearables
- > Biomarkers

Tools

- > Data Bases (CTD)
- > Training
- > Analysis (HHEAR)
- > Screening
- > Omics technology

Team Science

- > Blueprint ICs
- > NIH programs
- > Consortia
- > CDC, EPA, DoD
- > Non-profits

A ladybug is shown next to a 1-millimeter-wide microflie, for scale. PHOTO: NORTHWESTERN UNIVERSITY

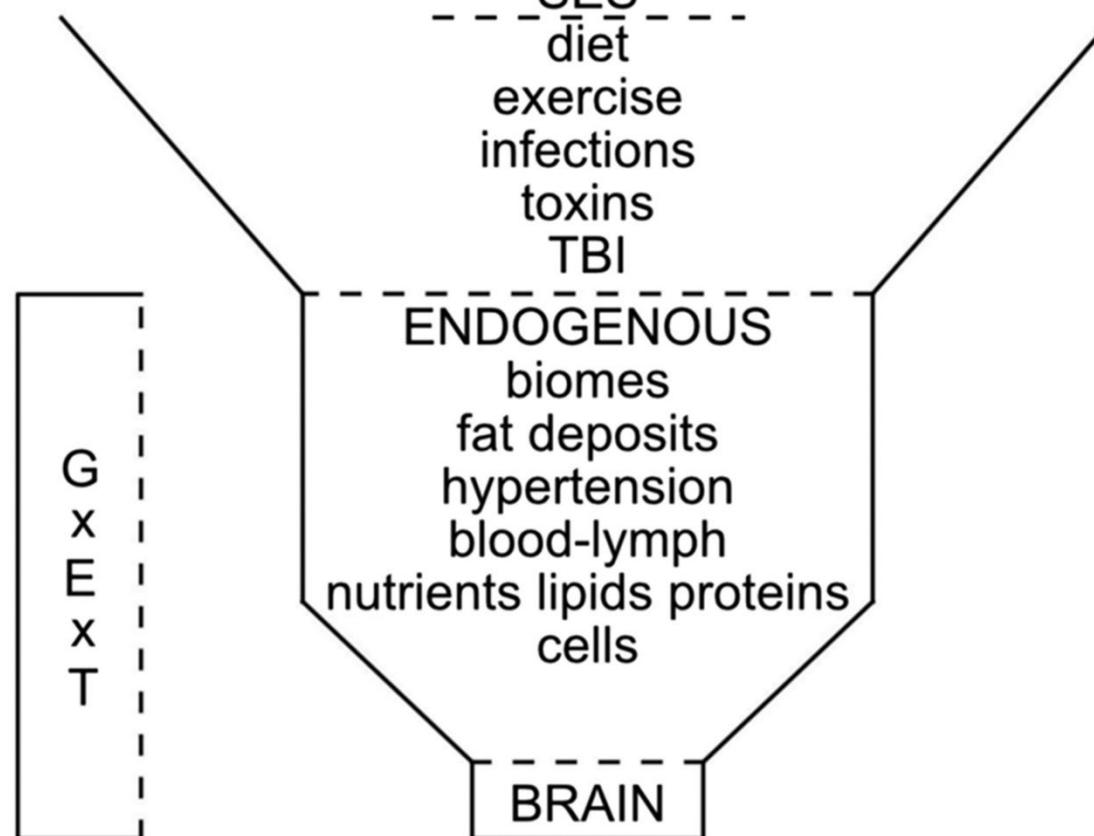
The AD Exposome

EXOGENOUS

air pollution
SES
diet
exercise
infections
toxins
TBI

ENDOGENOUS

biomes
fat deposits
hypertension
blood-lymph
nutrients lipids proteins
cells



C.E. Finch and A.M. Kulminski / Alzheimer's & Dementia 15 (2019) 1123-1132

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Exposomic Approach to Parkinson's Disease

An Agenda for Preventing Parkinson's disease

PRECLINICAL / BASIC

Examine environmentally relevant concentrations and routes of exposure



CLINICAL / TRANSLATIONAL

Measure PD incidence, and its change globally



Model combined environmental exposures



Develop biological markers of exposure and identify during prodromal phase

Consider sex as a biological variable in toxicant exposure



Perform whole-body autopsies to assess PD as a systemic disease

Utilize expansive new tools to consider gene-environment interactions



Evaluate relationship between environment and genetic risk factors

Incorporate the microbiome and diet into models of neurotoxicity



Include populations with high exposure burden



Increase investment and resources for PD prevention



Translate research into political action & policy

Exposome and Amyotrophic Lateral Sclerosis (ALS)

- Most cases are sporadic and do not have a known genetic cause
- Incomplete heritability of known mutations suggests that environmental factors are involved
- Genetic predisposition interacts with environmental exposures
- A series of steps are required for disease onset
- Factors
 - environmental pollutants (e.g., lead, heavy metals, pesticides, agricultural chemicals, and solvents)
 - medical events (e.g., brain trauma)
 - lifestyle factors (e.g., intense physical activity and military service)
- **Modifiable** risk factors to prevent disease



Lou Gehrig

Goutman SA, Hardiman O, Al-Chalabi A, Chiò A, Savelleff MG, Kiernan MC, **Feldman EL**. Lancet Neurol. 2022 Mar 22:S1474-4422(21)00414-2.
doi: 10.1016/S1474-4422(21)00414-2.

Linking Genes in Multiple Sclerosis

Journal of Neurology

<https://doi.org/10.1007/s00415-022-11072-4>

NEUROLOGICAL UPDATE

Environmental risk factors in multiple sclerosis: bridging Mendelian randomization and observational studies

Marijne Vandebergh¹  · Nicolas Degryse¹  · Bénédicte Dubois^{1,2}  · An Goris¹ 

Received: 26 February 2022 / Revised: 8 March 2022 / Accepted: 8 March 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany 2022

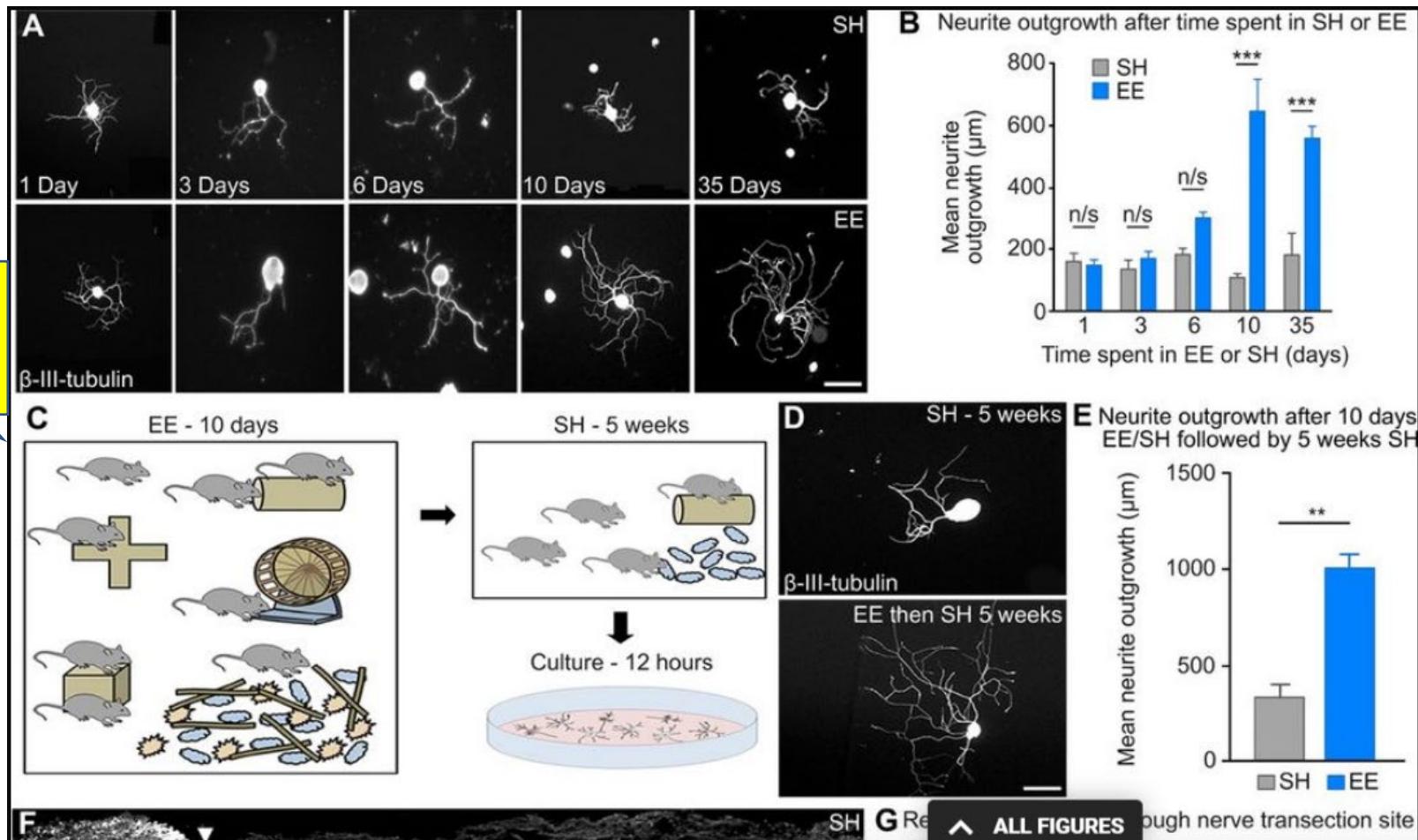
What is Mendelian randomization?

To illustrate this, if vitamin D is implicated in risk for MS, the genetic variants influencing naturally occurring vitamin D levels should also be linked to MS

- rigorously support a causal effect of **low vitamin D levels in MS susceptibility**
- support the association between an **increase in adult BMI** and **increased MS risk**
- **Observational studies have near-universally reported an approximately 50% increased MS risk in smokers versus non-smokers**

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Spinal Cord Injury and Environmental Enrichment



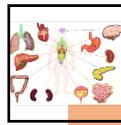
Hutson et al., Sci. Transl. Med. 11, eaaw2064 (2019) 10 April 2019

Program focus areas/ priorities



Exogenous Factors

- Chemical exposures
- Climate Change
- Health Inequities



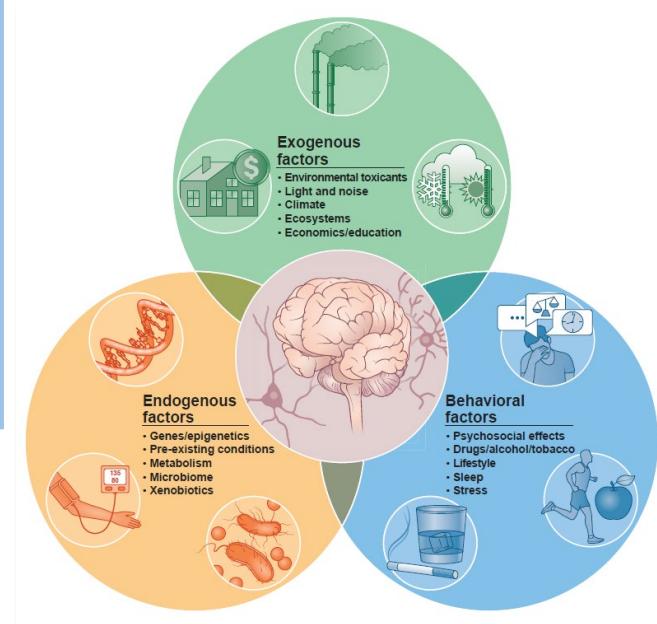
Endogenous Factors

- Genes
- Microbiome
- Metabolism



Behavioral Factors

- Psychosocial effects
- Substance Abuse
- Lifestyle

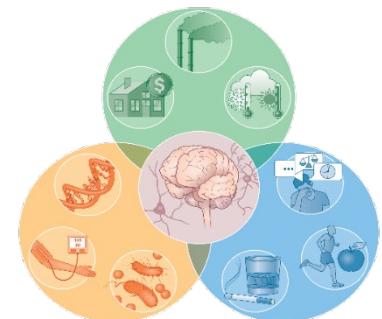


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Funding opportunities on Neural Exposome

Previous Initiatives

- **PAR-22-048: Clinical Relevance of the Linkage between Environmental Toxicant Exposures and Alzheimer's Disease and Related Dementias (R01)**
 - **Expired: March 11, 2022**
 - **Budget: Direct costs may not exceed \$500,000/ year**
 - **Project Period: May not exceed 5 years (no renewals)**
- **NOT-NS-22-050: Notice of Special Interest (NOSI) in NINDS mission relevant Pain Research**
Role of the Gut Microbiome in Chronic Neuropathic Pain
 - **Expired: May 8, 2022**
 - **Budget and Project period limits: Must adhere to rules of parent announcement**



Funding opportunities on Neural Exposome

Current/Active Initiatives

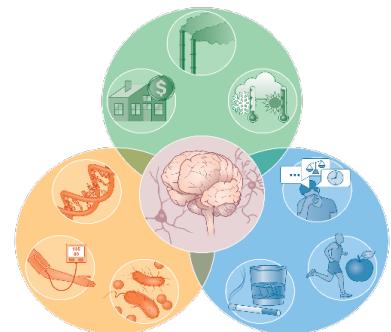
- **NOT-NS-22-088: Notice of Intent to Publish a Funding Opportunity Announcement on the Impact of the Microbiome Gut-Brain Axis on Alzheimer's Disease Related Dementias (R01)**
 - Estimated Due Date: September, 2022
 - Budget: Total costs may not exceed \$750,000/ year
 - Project Period: May not exceed 5 years (no renewals)
- **PAR-21-349 / PAR-21-350: Research on Biopsychosocial Factors of Social Connectedness and Isolation on Health, Wellbeing, Illness, and Recovery (R01)**
 - Due Date: June 21, 2022
 - Budget: Application budgets are not limited but need to reflect the actual needs of the proposed project
 - Project Period: May not exceed 5 years (no renewals)
- **NOT-AG-22-048: Notice of Special Interest (NOSI): Administrative Supplements to Support Research Infrastructure on Exposome Studies in Alzheimer's Disease (AD) and AD-Related Dementias (ADRD)**
 - Estimated: Summer, 2022
 - Budget and Project period limits: Must adhere to rules of parent announcement
- **NOT-ES-22-006: Notice of Special Interest (NOSI): Climate Change and Health**
 - Estimated: Summer, 2022
 - Budget and Project period limits: Must adhere to rules of parent announcement

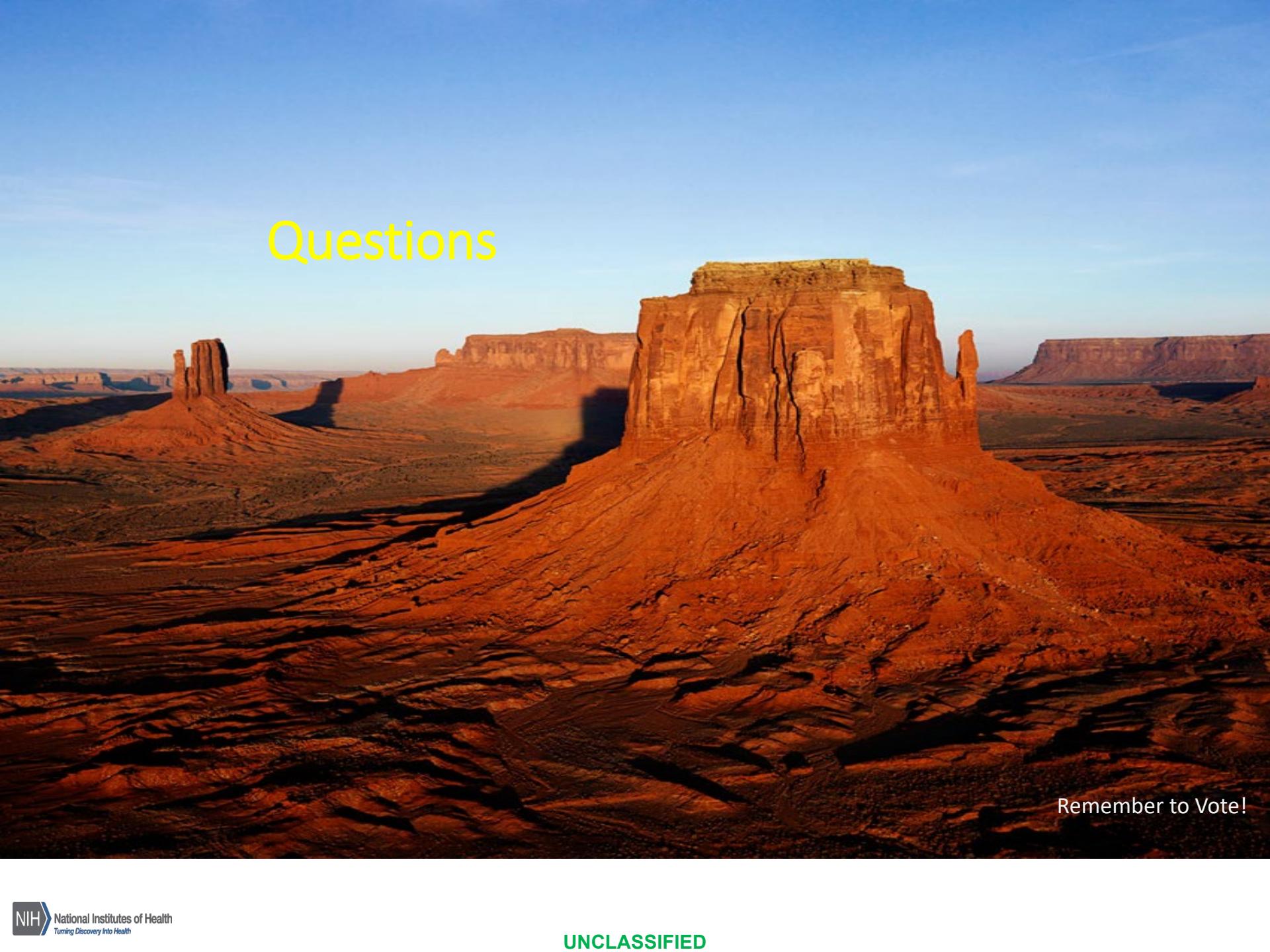


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Areas you'd like fund in but are not currently supporting

- **Data Repositories**
- **More Disease-Specific Clinical Relevance of Environmental Exposures (Mechanistic)**
 - [Parkinson's; ALS; Epilepsy; Renew AD/ADRD](#)
 - [Stroke; Spinal Cord Injury; Traumatic Brain Injury](#)
- **Epidemiology and Mechanistic Team Science in Environmental Neuroscience**
 - [Environmental influences on Child Health Outcomes \(ECHO\)](#)
 - [HEALthy Brain and Child Development Study \(HBCD\)](#)
 - [All-of-Us](#)
- **Biomarkers of the Effect of the Neural Exposome**
 - [Exposures, Effects, Diagnostic, Prognostic](#)





Questions

Remember to Vote!

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Enclosure 10
Military Operational Medicine Research Program
Performance in Extreme Environments



Performance in Extreme Environments

Dr. Ronald W. Matheny Jr. Portfolio Manager

Military Operational Medicine Research Program (MOMRP)
15-16 Jun 2022





MOMRP Overview



MOMRP portfolio serves to ensure Service members are

responsive to the challenges of training
resilient to the rigors of combat
resistant to longitudinal stressors

Develops capabilities and delivers solutions to:

- Prepare for the fight and stay in the fight
- Enable Service members to overcome external and internal stressors
 - *External factors* include heat, cold, blast and repeated impacts (operating weapons systems, physical injury)
 - *Internal factors* are both physiological and psychological





Environmental Threats Encountered by Warfighters



Extreme Operational & Training Environments

- Heat
- Cold
- Altitude
- Underwater



Toxic Operational & Training Environments

- Pollution
- Subterranean/Enclosed Space
- Industrial Chemical Exposures
- Burn Pits





Environmental Toxic Exposure Impact on Health and Performance



- In-theatre exposure to toxic industrial products and environmental pollutants has the potential to result in immediate adverse health effects
 - Temporary degraded physical state (respiratory issues, irritated eyes)
 - Decreased cognitive performance
 - Incapacitating injury (e.g., organ failure, systemic toxicity) requiring evacuation from theater
- Some exposures may have long term impacts affecting future performance and readiness (i.e., asthma)
- Individual variation in response after being exposed to a toxicant, pollutant or other harmful mixture of chemicals complicates decision making



UNCLASSIFIED



Research Gaps

- Gap #5: Identify, characterize, and understand the short- and long-term health effects of single and multi-environmental stressors, threats, and hazards, to include but not limited to impacts to cognition, impacts of hazardous exposure, impacts of medical care received, and impacts on reset/recovery between missions.
- Gap #8: Identify, characterize, and understand the risk factors, effects of injuries, exposures, and health risk assessment and management of exposures of different environmental stressors, threats, and hazards on SMs and their health, readiness, and performance.
- Gap #11: Identify, characterize, and understand environmental hazards (e.g., flora, fauna, environmental conditions not used as threats by humans), and determine the operational risk they present to SMs.
- Gap #13: Revise existing and/or develop new environmental hazard exposure and RTD guidelines to protect SMs and sustain operations in all hazardous environments.



Environmental & Occupational Exposure Monitoring in the Environmental Health & Protection Portfolio Strategic Plan



- Prevent illness and optimize performance when operating in environmentally-toxic environments
 - *Greater operational effectiveness and ability to move decisively during operations in toxic environments*
 - *Enhanced occupational exposures screening*
 - *Development or refinement of toxic chemical and material exposure guidelines*
 - *Improved force health readiness and fewer lost duty days*

- Identify and develop assays for verified biomarkers of exposures to military-relevant chemicals, materials, or mixtures.
- Identify/improve and demonstrate technology for rapid screening of toxic chemicals and materials for use towards the development of exposure guidelines.
- Provide novel health or toxicological data to fill data gaps and demonstrate their use towards the development or revision/refinement of exposure guidelines/limits to militarily-relevant chemicals, materials, and environmental hazards.



Service-Specific Performers

Agency/Service	Research Efforts	Coordination
Army	USARIEM: Risks and solutions to cold, heat and high altitude injuries. WRAIR: Risks and screening for toxic exposures	Coordination of efforts occurs at the programmatic level. WG research is complementary and leverages expertise and efforts from the Army labs.
Navy	NEDU, NHRC: Risks and solutions to heat, cold, underwater NSMRL, NAMRU-D: Risks and screening for toxic exposures	Coordination of efforts occurs at the programmatic level. WG research is complementary and leverages expertise and efforts from the Navy funded efforts.
AF	711HPW: Risks and screening for toxic exposures	Coordination of efforts occurs at the programmatic level. WG research is complementary and leverages expertise and efforts from the AF labs.

USARIEM: US Army Research Institute of Environmental Medicine; NEDU: Navy Experimental Dive Unit; NHRC: Naval Health Research Center;
NSML: Naval Submarine Medical Research Laboratory; NAMRU-D: Naval Medical Research Unit – Dayton; 711HPW: 711th Human Performance Wing (Air Force)



Portfolio Status



- Baseline portfolio funding in FY22 similar to previous years
- Received additional restoral funds for toxic exposure research
- Leverage non-DHP funds for this topic, focus core investments with 6.2 and 6.3 research



Portfolio Underfunded Areas



- Extreme Operational Environments
 - Subterranean and/or enclosed spaces
 - Undersea
 - Space
- Contaminant Exposure Monitoring
 - Biomarker assay development
 - Low level/long term exposures



Portfolio Future Directions



- Focusing future environmental toxic exposure thrust areas:
 - Assay development
 - Rapid screening
 - Exposure guidelines
 - Health effects of exposures in the dense urban environments
- Move toward individualized exposures and responses
- Partnering with Millennium Cohort for research
 - 20 years of survey data for thousands of active duty/veterans
 - Health Issues
 - Mental Health Issues
 - Resident research staff for collaboration
 - Great support for epidemiological and prospective/retrospective research



Questions/Comments

For further questions/information please contact:

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Performance in

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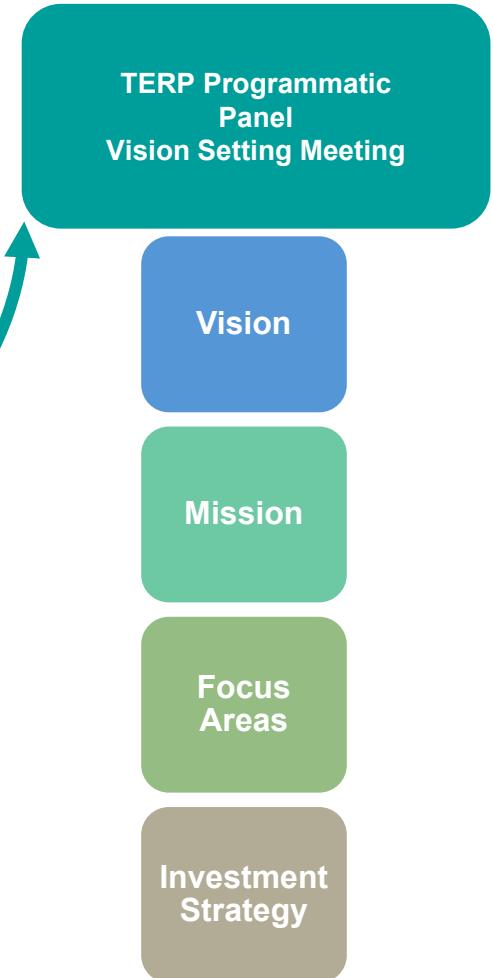
Enclosure 11
Stakeholders Conclusions

Meeting Outcomes and Overarching Themes

Expectations: TERP Stakeholders Meeting

Outcomes

- ✓ Summary of relevant gaps, refinement of the state of the science in service-related toxic exposures, identification of potential challenges, and opportunities for success.



Next Steps

1. Prioritized list of gaps from each breakout group will be discussed at the TERP FY22 Vision Setting Meeting and will inform the focus areas and investment strategy of the program
2. All outcomes will be made available to the TERP Programmatic Panel for strategic planning
3. Outcomes may ultimately inform TERP's Strategic Plan (near and long term plans and goals)
4. Stakeholder book, presentation slides and outcomes from the Stakeholders meeting will be made publically available on the TERP website

TERP Vision Setting Meeting

Vision

Mission

Focus
Areas

Investment
Strategy

TERP Further Information

Website

<http://cdmrp.army.mil/terp>

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Thank you!