Parkinson's Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

U.S. Army Medical Research and Development Command

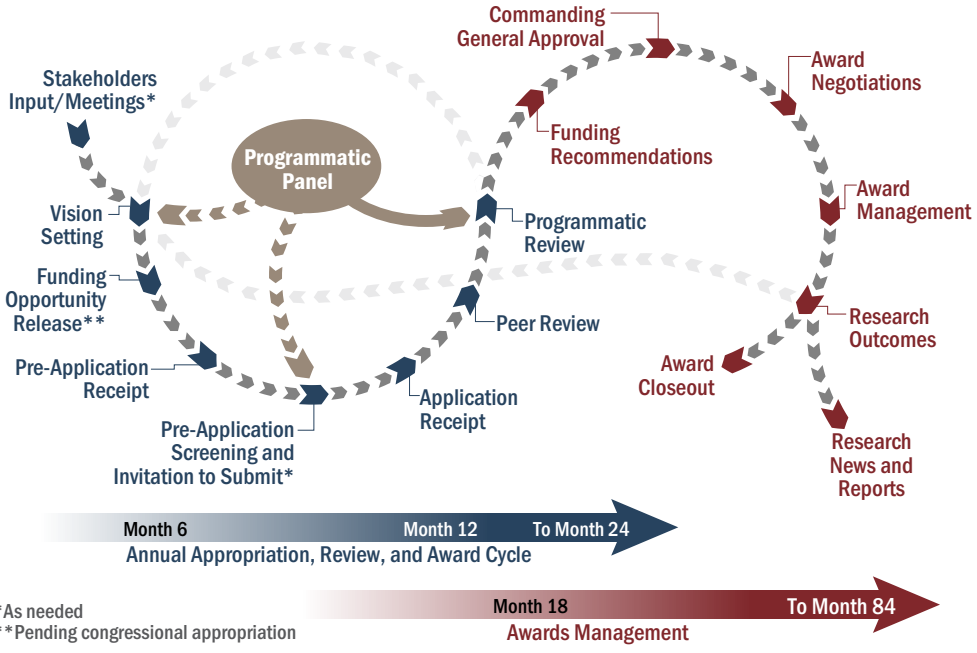
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

HISTORY

The office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, the U.S. Congress, and the military. Since its inception through fiscal year (FY) 2020, the CDMRP has grown to encompass multiple targeted programs and has been responsible for managing over $15.9 billion (B). Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs, such as the Parkinson's Research Program (PRP), is allocated via specific guidance from congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, consumers, and ad hoc programmatic reviewers as needed. The Programmatic Panel members compare applications to each other and make recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.



CDMRP Two-Tier Review Process

"Speaking for consumers, i.e., PD Patients, there is not a comparable program that I am exposed to that opens funding for creative, disruptive and challenging science. I am grateful for the funding the CDMRP offers. It's a difference maker."

Mr. Kelly Sweeney,
Parkinson's Resources of Oregon,
FY22 Consumer Programmatic Panel Member

PARKINSON'S RESEARCH PROGRAM

Vision: To increase the understanding of PD and to develop treatments towards a cure

Mission: To support high-impact Parkinson's research to benefit both the military and the American public

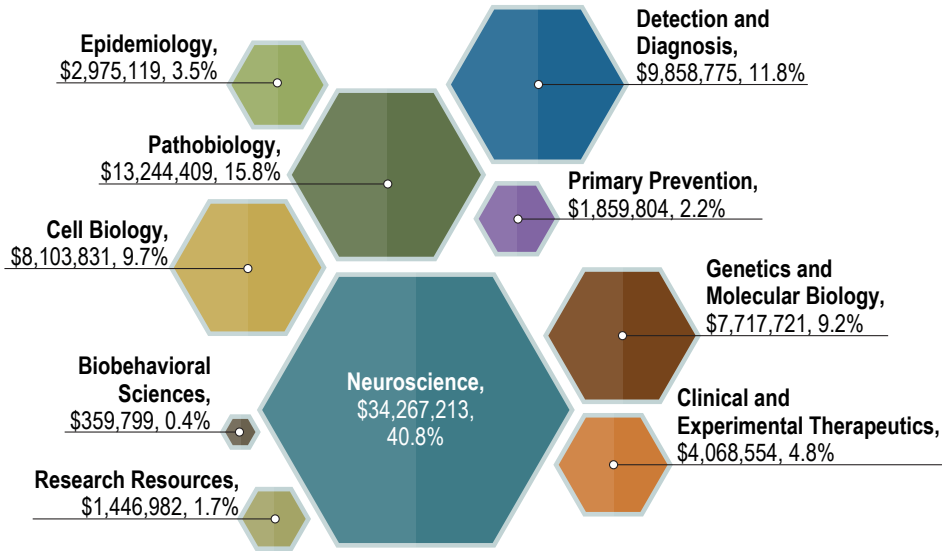
ABOUT THE PROGRAM

Parkinson's disease (PD) is a degenerative disorder of the central nervous system resulting from a loss of neurons in a region of the brain called the substantia nigra. These neurons produce dopamine, a neurotransmitter important for motor control; however, as PD progresses, the death of dopaminergic neurons results in reduced dopamine levels and impairment of motor control.

NETP/PRP PROGRAM HISTORY

Based on data from the Parkinson's Foundation, almost 1 million people are living with PD in the United States, and that number is expected to increase each year by 60,000.[1] Of the more than 10 million people living with PD worldwide, an estimated 4% of that population was diagnosed before the age of 50.[1] Since 1997, the CDMRP has funded PD research through the Neurotoxin Exposure Treatment Parkinson's (NETP) Program. From FY97 through FY21, a total of 484.75 million (M) dollars appropriated for PD research.

FY16-FY21 NETP Portfolio Investment



For FY22, the U.S. Congress transitioned the NETP Program to the PRP with an appropriation of $16M. The transition broadened the research from neurotoxin exposure treatment PD research to all types of PD research. The PRP has been congressionally appropriated to support research of exceptional scientific merit in PD, and the award mechanisms include the Early-Investigator Research Award, Investigator-Initiated Research Award, and Synergistic Idea Award. For more information about PRP award mechanisms, please visit: *https://cdmrp.army.mil/prp/default.*

PROGRAM PORTFOLIO

The CDMRP NETP funded 281 awards through FY21 to support innovative research with the potential to yield new avenues of investigation and make a major impact in the understanding, prevention, diagnosis, and treatment of PD.

"As a Peer Reviewer, we have run across a great deal of creative and unexpected science with high potential for leading to important discovery that would likely not have been supported in any other way. The important breakthroughs in medicine nearly always begin as a small project in which an investigator follows a new hunch triggered by an unexpected observation of a phenomenon in nature. The PRP is paving the way for a broad array of scientists to improve now untreatable or poorly treatable diseases by providing a means for just this kind of necessary work. This is where the new ideas and treatments come from, and PRP's support will keep them coming."

David Sulzer, Ph.D.,
Peer Reviewer, Columbia University

[1] https://www.parkinson.org/Understanding-Parkinsons/Statistics

PROGRAM RELEVANCE TO MILITARY HEALTH

Several risk factors for the development of PD that are of particular interest to the military community have been identified in peer-reviewed studies. The most significant risk factors include exposure to chemicals used in the agriculture industry (including pesticides, insecticides, and solvents); traumatic injury to the head; depression; prolonged physiologic or mental stress; repeated or prolonged disruption of sleep architecture; and repeated or prolonged disruption of autonomic nervous function. These may immediately impact both physical and cognitive performance, as well as predispose susceptible Warfighters to development of neurodegenerative conditions such as PD.

Shari Bridge, Consumer, Programmatic Panel Member

I served in the Army Reserves from 1982 to 1996. I served as a medic/ambulance driver in the 477th Medical Company based in Duluth, Minnesota. My unit was deployed to the Middle East for Operation Desert Storm. We were based out of Saudi Arabia, but as ambulance drivers, we were given many temporary assignments at field hospital units all over the region.

I first noticed symptoms in about 2011. It started out as dystonia in my right foot as I was running. Initially, I didn't notice it until about 10 miles into a run (oh, how I miss being able to do that!). I was diagnosed with compartment syndrome and had a nerve release, which had no effect. Eventually, I started having other symptoms as well. My reflexes were slowing, and even simple movements were becoming increasingly difficult. I've always described it as feeling as if I was always underwater, having to push against some force that wasn't there. My fine motor skills started to deteriorate, and I developed the Parkinson's mask – the loss of expression in my face. I would look in the mirror and just saw this blank face staring back at me. I would force myself to smile. Eventually, after about 6 years of these symptoms, I saw a doctor who finally diagnosed PD. She put me on medication that almost immediately made a huge impact. I could move again without it being a struggle!

I formed a team for the Parkinson's Foundation Moving Day, which led to my becoming a research advocate for the foundation. That, in turn, led to my becoming a consumer advocate on the PRP Programmatic Panel, allowing me to provide feedback on research grant applications directly related to PD. As a non-scientific person (I am a social worker by education), this has been such a great opportunity, and I feel incredibly blessed to have it. Working with this panel, I have the chance to see what is happening now in PD research. To be able to listen to and interact with such knowledgeable experts in the field has been a great honor. The goal, of course, is to get closer and closer to a cure. One mile at a time is the running-themed mantra I always use.

HIGHLIGHTING RESEARCH FROM FUNDED AWARDS

Investigating Autonomic Nervous System Symptoms in Parkinson 's disease

Dr. Avraham Ashkenazi, Ph.D., Tel Aviv University

Dr. Avraham Ashkenazi, Tel Aviv University, received an award in FY21 from the CDMRP's NETP PRP. The project, "Characterizing and Targeting Molecular Signatures in Autonomic Neurons Derived from Patients with Parkinson's Disease," in collaboration with Dr. Gad Vatine, Ben-Gurion University, and Dr. Clive Svendsen, Cedars-Sinai Medical Center, will investigate questions related to initiation and progression of PD. Specifically, the award's purpose is to explore PD symptoms outside the central nervous system by targeting the autonomic neurons. Dr. Ashkenazi will use induced pluripotent stem cells (iPSCs) from sporadic PD patients to determine whether exposure of iPSC-derived autonomic neurons to neurotoxins results in distinctive PD phenotypes. If phenotypes are identified, the Principal Investigator (PI) will further investigate whether the phenotypes are associated with distinctive molecular signatures and their relationship with the propagation of alpha-synuclein in the peripheral autonomic nervous system. The PI aims to identify biomarkers of pre-motor PD and metabolic intervention points useful in the development of candidate treatments.

The Environmental Effects of Nicotine on Risk for Parkinson's Disease

Abby Olsen, Ph.D., Brigham and Women's Hospital

PD is defined by loss of dopaminergic neurons in the substantia nigra and subsequent deterioration of motor function. Many genes and environmental factors are known to influence the risk of developing PD, but the contribution of each and how they interact is unknown. An FY17 Early-Investigator Research Award from the NETP to Dr. Abby Olsen (Brigham and Women's Hospital) is supporting her investigations into the previously identified gene-environment interaction between the gene *SV2C* and smoking.[2] Smoking has been inversely associated with PD in many epidemiologic studies, but results of clinical trials testing nicotine (the presumed active ingredient in tobacco) as a therapy for PD have been mixed, perhaps in part due to genetic variation.

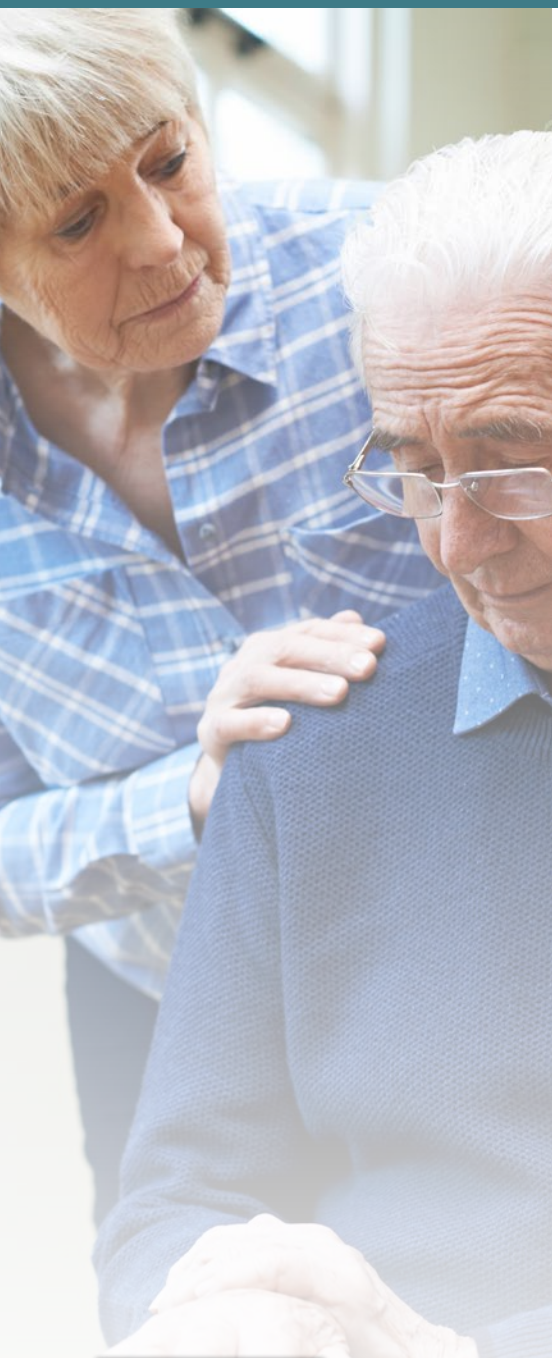
To understand how the *SV2C* gene relates to smoking, Dr. Olsen developed a unique animal model of Parkinsonism[3, 4, 5] in the fruit fly, *Drosophila melanogaster*. The flies express human alpha-synuclein and develop all the key features of PD. Taking advantage of the short life span, powerful experimental tools, and high degree of similarity between fly and human proteins, Dr. Olsen is able to use this model to discover how genes and environmental factors work together to cause PD. She identified the *Drosophila* genes that are similar to the human *SV2C* genes (orthologs) and treated the animals with nicotine. She found that nicotine treatment can rescue motor dysfunction and neurodegeneration caused by alpha-synuclein in *Drosophila*, and that this rescue depends on normal SV2C levels. When *SV2C* is knocked down, nicotine not only fails to improve neurodegeneration but, in fact, results in even fewer dopaminergic neurons and worse motor functioning than with alpha-synuclein alone. The result provides a good confirmation of the gene-environment interaction between nicotine and the *SV2C* gene as well as identifying a potential alpha-synuclein mechanistic association.

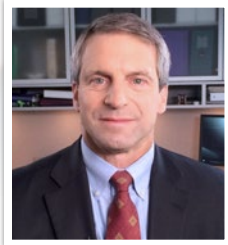
The animal model work is being paired with human studies to identify novel gene-environment interactions in the Harvard Biomarkers Study Parkinson's disease cohort. Despite added challenges due to the COVID pandemic, this research has already identified a novel possible association between asthma and Parkinson's disease, as well as confirmed links to head trauma and smoking,[6] and future work will investigate genetic variation in combination with these environmental factors.

The project has been very successful to date, and the results were selected for an oral presentation at the American Academy of Neurology annual meeting (April 2021). Multiple publications are in preparation; when completed, the work will have an important impact by clarifying the risk factors for individuals susceptible to development of Parkinson's disease and identifying efficacious therapeutic interventions in particular subsets of the Parkinson's patient population. The hope is to reach a future when certain populations of patients could be enrolled in personalized clinical trials based on the unique genetic and environmental factors driving their disease.

[2] Hill-Burns EM, Singh N, Ganguly P, et al. 2013. A genetic basis for the variable effect of smoking/nicotine on Parkinson's disease. *Pharmacogenomics J* 13(6):530–537.
[3] Ordonez DG, Lee MK, and Feany MB. 2018. α-synuclein induces mitochondrial dysfunction through spectrin and the actin cytoskeleton. *Neuron* 97:108–124.e6.
[4] Olsen AL and Feany MB. 2019. Glial alpha-synuclein promotes neurodegeneration characterized by a distinct transcriptional program in vivo. *Glia* 67(10):1933-1957.
[5] Olsen AL and Feany MB. 2021. Parkinson's disease risk genes act in glia to control neuronal α-synuclein toxicity. *Under review.*
[6] Olsen AL, Locascio JJ, and Scherzer CR. 2021. Defining the Parkinson's disease health-ome. *In preparation.*

Links: ***Public and Technical Abstracts:*** *Environmental Modulation of Alpha-Synuclein Neurotoxicity in Parkinson's Disease*





"As a psychiatrist, I enjoy being on the review panel for the PRP, as it's one of the few research programs for PD that has a specific focus on the common and problematic non-motor features of PD, including psychiatric symptoms and cognitive complications. This is crucial to improving the lives of people living with PD."

Dr. Daniel Weintraub, M.D.,
University of Pennsylvania, FY22 Programmatic Panel Member

Investigating the Gene-Environmental Interactions Related to Parkinson's Disease Susceptibility

Dr. Samuel Goldman, M.D., M.P.H.,
Northern California Institute for Research and Education
Dr. Raymond Swanson, M.D.,
Northern California Institute for Research and Education

PD is a neurodegenerative disease that progresses over time as small clusters of dopamine-producing brain cells deteriorate, causing motor issues such as tremors, loss of coordination, and difficulty speaking. The Parkinson's Foundation estimates that there are 1 million Americans currently living with PD. Although the exact cause of disease onset is unknown, it is thought that a combination of genetic and environmental factors, as well as the interaction between them, are contributors.[7] In 2010, the U.S. Department of Veterans Affairs acknowledged that exposure to Agent Orange and other neurotoxins is associated with PD.[8] However, there have been limited studies on the gene-environment interactions that contribute to a PD diagnosis and none have been replicated.

Through a NETP FY19 Investigator-Initiated Research Award, Drs. Samuel Goldman and Raymond Swanson at the Northern California Institute for Research and Education aim to uncover the link between genetic and environmental factors as they contribute to individual risk for PD. The team will use whole-genome sequencing and bioinformatics to investigate the genetic variants involved in susceptibility to PD. First, the investigators will use induced pluripotent stem cell (iPSC) cell lines exposed to toxins such as paraquat and permethrin to determine whether glutathione S-transferase theta-1 (GSTT1) deletion increases susceptibility. They will also assess samples from the National Institute of Environmental Health Sciences Farming and Movement Evaluation (FAME) study database to examine other genes that contribute to increased susceptibility to pesticides and other persistent organic pollutant exposures, which will be characterized both historically and through serum analysis. Drs. Goldman and Swanson plan to use whole-genome sequencing and novel machine learning and bioinformatics approaches for the FAME database analysis and will also focus on Service-related neurotoxin exposures. They will use iPSC-derived neuronal cell lines to confirm the genes that are shown to confer susceptibility and the extent to which those genes play a role in individuals of varying genetic backgrounds.

Over 300 samples from the FAME study database will be examined in this groundbreaking study with the goal of conclusively linking environmental risk factors and susceptibility to PD. If successful, this project could provide the framework for PD risk identification and prevention strategies based on combined environmental and genetic data at the individual level, which is especially important for military personnel with known neurotoxin exposures.

[7] https://www.niehs.nih.gov/health/topics/conditions/parkinson/index.cfm

[8] https://www.research.va.gov/topics/parkinsons.cfm

FY20 EARLY-INVESTIGATOR RESEARCH AWARD RECIPIENTS

Dr. Deepak K. Gupta, M.D., Larner College of Medicine, University of Vermont

Dr. Deepak Gupta is a movement disorders neurologist and physician informatician who has been devoted to PD since his medical career started. While making several strides in the PD field, driven in major part from personal experiences of supporting his late father, Ashok Gupta, in living with PD for 13 years, Dr. Gupta is now dedicating his efforts to developing a niche in the application of clinical informatics to advance PD research. With the support from an Early-Investigator Research Award, he plans to develop a multi-institutional clinical informatics research tool, the Ontology-based, Real-time, Machine learning Informatics System for PD (ORMIS-PD), that will be used for predicting an individual PD patient's diagnosis probability and prognosis score by using the Movement Disorders Society criteria, open-access PD databases, and artificial intelligence methods. The ORMIS-PD tool will assist clinicians and researchers in forecasting two of the most important questions to the patient and their caregivers: how accurate is the patient's diagnosis and how will the patient's disease progress in the future? Dr. Gupta's ORMIS-PD platform from this proposed research project will potentially form the foundation of a much needed point-of-care clinical decision support system for PD and provide new information on potential differences between neurotoxin-associated PD and idiopathic PD in Veterans and non-Veterans.

Dr. Kathryn Cross, M.D., Ph.D., University of California, Los Angeles

A physician-scientist who has a particular interest to understand the individual differences and heterogeneity in PD, Dr. Kathryn Cross is looking to apply her research experience and training in Movement Disorders neurology in human brain mapping. Specifically, Dr. Cross is looking to study Freezing of Gait (FOG), a heterogeneous, common, and yet poorly understood symptom of advanced PD. With support from an Early-Investigator Research Award, Dr. Cross plans to unravel phenotypic subtypes of FOG and elucidate dynamics of cortical neural activity throughout the freezing episode. This research study will include PD patients who will wear sensors on their limbs and an electrode cap on their head while neural activity is recorded using electroencephalography as they walk in a clinical setting to characterize detailed movement kinematics. This research will potentially increase the understanding of heterogeneity and neurophysiological mechanisms in FOG.

Dr. Su Jeong Kim, Ph.D., University of Southern California

Dr. Su Jeong Kim is investigating genetic variants and mitochondrial-derived peptides within PD that are related to pesticide exposure. Though not everyone exposed to pesticides will develop PD, exposure does have the capability of increasing the risk of PD based on inhibitors and stressors that contribute to mitochondrial dysfunction contained in the pesticide. This research, supported by an Early-Investigator Research Award, seeks to identify the mitochondrial gene-environment interactions (pesticide exposure) and potentially discover novel mitochondrial genetic targets to be used as possible PD treatment targets. Specifically, Dr. Kim is investigating the potential role of SHLP2, a peptide derived from the mitochondria, in determining its therapeutic potential for PD progression. If successful, Dr. Kim's research will create a genomic analysis-based personalized therapeutic approach to treat PD through rapid translation into clinical and population studies.

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