CDMRP

DEPARTMENT OF DEFENSE

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

Parkinson's Research Program

Advancing Parkinson's Disease Research Toward Treatments

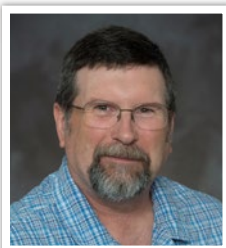For more information, please visit
cdmrp.health.mil/prp

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 2020 (FY20), 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.
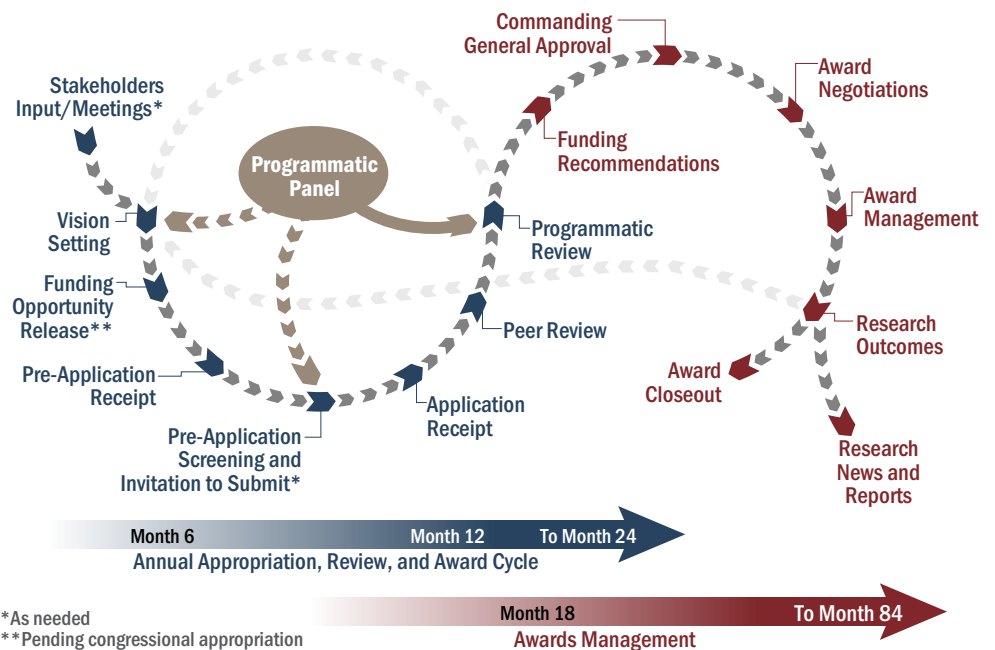
APPLICATION REVIEW PROCESS

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,
FY23 Consumer Programmatic Panel Member

PARKINSON'S RESEARCH PROGRAM

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.

Vision: To improve the health and lives of people with Parkinson's disease through innovative, clinically meaningful treatments

Mission: To support high-impact Parkinson's research that alters disease progression, improves disease symptoms, and develops treatments that benefit Service Members, Veterans, and all others living with Parkinson's disease
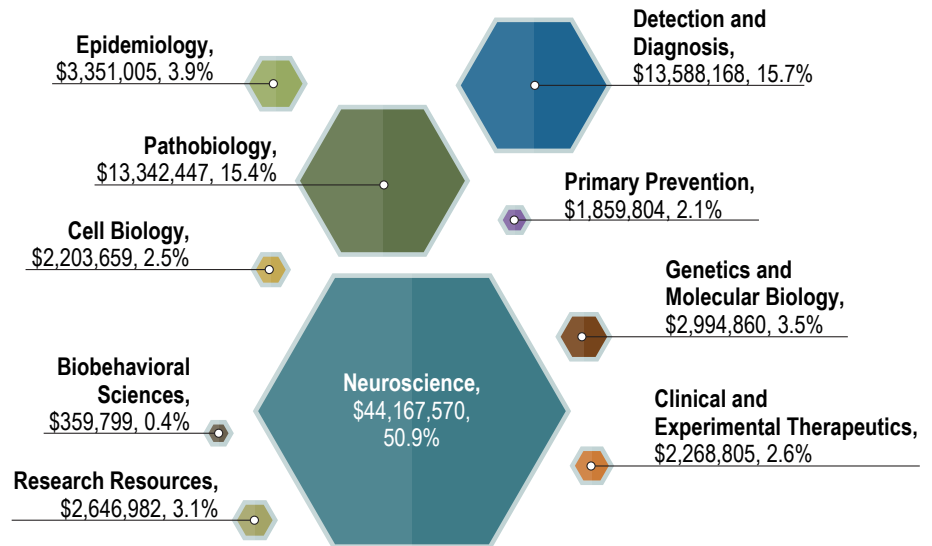
NETP/PRP PROGRAM HISTORY

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 90,000.[1] Of the more than 10 million people living with PD worldwide, an estimated 4% of that population were diagnosed before the age of 50.[1] From FY97 to FY21, the CDMRP has funded PD research through the Neurotoxin Exposure Treatment Parkinson's (NETP) Program with $484.75 million (M) of appropriations.

FY17-FY22 Portfolio Investment

Epidemiology, $3,351,005, 3.9%

Detection and Diagnosis, $13,588,168, 15.7%

Pathobiology, $13,342,447, 15.4%

Primary Prevention, $1,859,804, 2.1%

Cell Biology, $2,203,659, 2.5%

Genetics and Molecular Biology, $2,994,860, 3.5%

Biobehavioral Sciences, $359,799, 0.4%

Neuroscience, $44,167,570, 50.9%

Clinical and Experimental Therapeutics, $2,268,805, 2.6%

Research Resources, $2,646,982, 3.1%

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 received another $16M dollar appropriation in FY23. 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.health.mil/prp/.*

PROGRAM PORTFOLIO

The CDMRP funded PD research through the NETP and PRP for a total of 295 awards through FY22 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

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[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

Mechanisms of Specific Lipid-Induced Degeneration Causing Non-Motor Symptoms of Parkinson's Disease

Ole Isacson, M.D., Ph.D., and Penelope Hallett, Ph.D., McLean Hospital

In a normal, working central nervous system, the enzymes ß-hexosaminidase (HEX) and glucocerebrosidase (GCase) are important for the storage and removal of lipids. Changes to these enzymes are suspected to contribute to Lewy body formation, and genetic mutations in GCase are a strong risk factor for PD in humans. With an FY19 NETP PRP Investigator-Initiated Research Award, Drs. Isacson and Hallett used research mice to evaluate the role of these enzymes in neuron destruction. They found that loss of HEX activity in mice led to synapse-associated protein α-synuclein (aSYN) accumulation in the brain. Moreover, overexpression of HEX and aSYN in the brains of rats led to reduced accumulation of aSYN and prevented protein-lipid interactions by aSYN, as well as providing protection of midbrain dopamine-releasing neurons from aSYN-induced degeneration.

The team then explored the possibility that altered lipid trafficking plays a role in PD progression and is likely driven by the enzyme GCase. The researchers observed that mice treated with GCase inhibitors accumulated aSYN aggregates and exhibited a higher neutral lipid content in dopaminergic neurons and lower neutral lipid content in neighboring brain cells compared to untreated mice. To identify a GCase as a potential biomarker, Drs. Isacson and Hallett generated a cell model of PD using skin cells from idiopathic PD patients and PD patients with a mutation in the gene encoding the GCase enzyme. Compared to skin cells from healthy controls, idiopathic or mutated PD cells exhibited decreased GCase activity and exhibited a decrease in the protein that regulates the activity and function of GCase. These results suggest that the reduction in GCase activity in idiopathic PD cells is driven by a different mechanism than that in genetic PD cells.

The work of Drs. Isacson and Hallett and their research team promises to provide clinicians with novel diagnostics, treatments, and therapeutics that will enable them to restore lipid equilibrium in the brains of PD patients by targeting glycolipid dysfunctions that play a role in triggering PD and related neurodegenerative diseases. The development of such agents could significantly improve patient outcomes and quality of life.

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. Dr. Abby Olsen used PRP funding to support her investigations into the previously identified gene-environment interaction between the gene SV2C and smoking. 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, which develop all the key features of PD. Dr. Olsen used 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 and treated the animals with nicotine. The results indicated 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 expression is reduced, 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 PD cohort. This research has identified a possible novel association between asthma and PD, as well as confirmed links to head trauma and smoking. Future work will investigate genetic variation in combination with these environmental factors. When completed, the work will have an important impact by clarifying the risk factors for individuals susceptible to development of PD and identifying efficacious therapeutic interventions in particular subsets of the PD patient population.

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.[2] In 2010, the U.S. Department of Veterans Affairs acknowledged that exposure to Agent Orange and other neurotoxins is associated with PD.[3] However, there have been limited studies on the gene-environment interactions that contribute to a PD diagnosis and none have been replicated.

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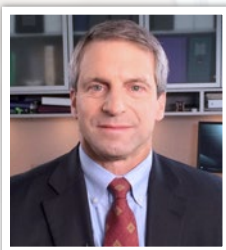
"As a psychiatrist, I enjoy being on the review panel for the PRP, as it's one of the few research programs for PD that has a specifi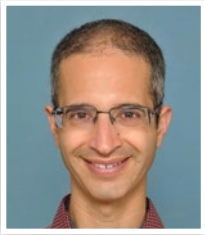c focus on the common and problematic non-motor features of PD, including psychiatric symptoms and cognitive complications. This is crucial to improving the lives of people living with PD."

Dr. Daniel Weintraub, M.D.,
University of Pennsylvania, FY23 Programmatic Panel Member

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

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

FY21 EARLY-INVESTIGATOR RESEARCH AWARD RECIPIENTS

Avraham Ashkenazi, Ph.D., Tel Aviv University

Dr. Avraham Ashkenazi's research focuses on developing new diagnostic and therapeutic techniques for PD by identifying and understanding the cellular mechanisms that enable neurons to survive. With support from an Early-Investigator Research Award, Dr. Ashkenazi plans to use stem cell technology to explore how exposure to environmental toxins and certain types of proteins affect peripheral autonomic neurons, which are responsible for the functioning of the heart, bladder, intestines, and blood vessels. Because many PD patients will develop gastrointestinal, cardiovascular, or even psychiatric disorders before they experience the onset of motor symptoms, a better understanding of dysfunction in peripheral autonomic neurons not only could help physicians to predict and diagnose PD earlier, but also could lead to the development of novel therapeutic treatment strategies.
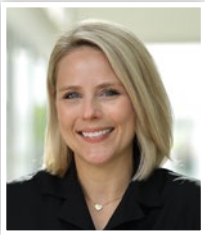
Margaret Caulfield, Ph.D., Michigan State University

The success of cell-based therapies in treating PD, such as grafting new dopamine neurons into the brain of a person with PD, can vary widely from patient to patient. Dr. Margaret Caulfield's study, supported by an Early-Investigator Research Award, seeks to better understand how an individual's unique genetics impacts the success of dopamine cell replacement therapy. Focusing on a specific genetic variation called rs6265 (also called Val66Met), Dr. Caulfield will test how the presence of the rs6265 gene variant, which suppresses the release of brain-derived neurotrophic factor (BDNF), a growth factor that is critical for normal neuron development and function, influences therapeutic outcome of grafting. Curiously, this rs6265 variation has both clinically positive and negative influences on dopamine cell therapy. Ultimately, Dr. Caulfield seeks to determine whether "the positive" associated with the rs6265 variation is related to a unique factor that improves the likelihood that dopamine cell replacement therapy will be successful. She also will examine whether supplementing levels of the BDNF in rs6265 subjects can mitigate "the negative." Understanding how to harness the positive aspects, while modifying the negative, will provide for optimized therapeutic development for PD.

Karen L. Eskow Jaunarajs, Ph.D., University of Alabama at Birmingham

Levodopa (L-DOPA) treatment is one of the few effective drug therapies for PD, but long-term use of this treatment leads to abnormal uncontrollable movements and postures, called L-DOPA-induced dyskinesia and dystonia (LIDD). Dr. Karen Jaunarajs studies the role that the striatum — the brain's primary motor area — plays in movement disorders. With the help of an Early-Investigator Research Award, she seeks to understand how L-DOPA treatment affects gene expression and transcription in individual cells in the striatum by affecting the three-dimensional availability of DNA as LIDD develops. A more complete understanding of how gene expression changes are affected by L-DOPA and LIDD could lead to the development of new therapies and treatment options for PD.
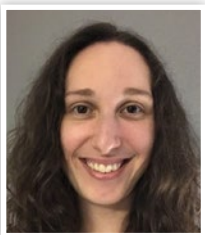
Danielle Mor, Ph.D., Medical College of Georgia at Augusta University

One of the hallmarks of PD is the formation of Lewy bodies, which are abnormal deposits of the protein α-synuclein in the brain. However, the role of α-synuclein in PD remains unclear. Recent research suggests that α-synuclein may first appear in the neurons of the digestive tract before spreading to the brain. As part of her research into the efficacy of early interventions in the treatment of PD, Dr. Danielle Mor seeks to apply her Early-Investigator Research Award to test this "gut-to-brain" hypothesis using the nematode worm Caenorhabditis elegans (C. elegans) to understand how α-synuclein affects learning and memory, identify how gut-derived α-synuclein enters neurons, and develop novel treatments more quickly than can be accomplished using more traditional rodent models.
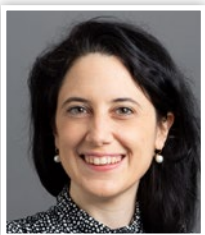
Giulietta M. Riboldi, M.D., Ph.D., New York University Grossman School of Medicine

Early identification of PD is crucial for successful disease management. However, researchers have yet to fully understand the mechanisms responsible for the development of PD as well as particular biological characteristics, called biomarkers, that would allow early detection of ongoing disease processes. With support from an Early-Investigator Research Award, Dr. Giulietta Riboldi seeks to study how environmental exposures impact the behavior of immune cells by affecting the way their genes work in a cohort of people with certain non-motor clinical presentations (such as impaired sleep cycles and loss of sense of smell) or who carry specific PD-associated gene mutations that indicate an increased risk of developing PD. By correlating environmental exposures with genetic changes in the immune system, Dr. Riboldi hopes to better understand the role the immune system plays in the development of PD and identify biomarkers that clinicians can use to identify the presence of the disease earlier and target suitable preventive interventions.

For more information, please visit
https://cdmrp.health.mil
or contact us at:
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