History of the CDMRP

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, Congress, and the military. The success in managing the initial Congressional appropriations in breast cancer research, combined with additional advocacy movements and the need for focused biomedical research, catapulted the CDMRP into a global funding organization for cancer, military medical, and other disease-specific research. The CDMRP has grown to encompass multiple targeted programs and has received over $11.2 billion in appropriations from its inception through FY16. Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the PRP, is allocated via specific guidance from Congress.

Application Review Process

The CDMRP uses a two-tier review process for application evaluation, with both steps involving dynamic interaction between scientists and clinicians (subject matter experts) and consumers. The first tier of evaluation is a scientific peer review of applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Programmatic Panel, which compares applications to each other and makes funding recommendations based on scientific merit, portfolio composition, and relevance to program goals.

Consumer Advocacy Participation

A unique aspect of the CDMRP is the active participation of consumer advocates or patient representatives throughout the program's annual cycle. Consumers represent the voices and vision of individuals affected by PD, be it persons living with PD or their family members or caregivers. The PRP incorporates consumers as active participants in virtually all aspects of program execution. Consumers work collaboratively with leading scientists and clinicians in setting program priorities, reviewing proposals, and contributing their unique perspectives and a sense of urgency to the program. In addition, consumers serve as liaisons between their constituencies and the scientific community and help scientists understand the human side of how research will impact the PD community.

"The PARS study is the Parkinson's Associated Risk Syndrome (PARS) study. And that really is focused on trying to identify individuals who might be at risk to develop Parkinson's disease before they have the typical symptoms of Parkinson's disease. This is based on the premise that, for Parkinson's disease, as well as for other neurodegenerative disorders like Alzheimer's disease or Huntington's disease, there is a long period of time when there is degeneration in the brain, but symptoms have not yet arisen. . . . So the PARS study is really an opportunity to understand whether we can develop a population of individuals at risk who we could then take advantage of in clinical studies that might be used to test preventive medicines for Parkinson's disease. . . . The funding that we received for PARS was critical to enable a study to take place, and it really took great foresight from the DoD programs because this really required identification of a novel idea, that is, the idea of identifying individuals prior to the onset of symptoms, and [they] had the follow-through to enable us to continue to follow these individuals for now up to 8 years, which is really remarkable in a research project."

Kenneth Marek, M.D., Institute for Neurodegenerative Disorders

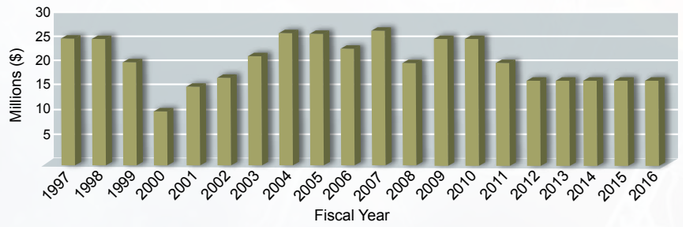
Parkinson's Research Program

Parkinson's disease (PD) is a degenerative movement 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.

Program History

The Parkinson's Research Program (PRP), funded under the Neurotoxin Exposure Treatment Parkinson's Research Program appropriation, was established by a Congressional Special Interest addition to the fiscal year 1997 (FY97) appropriation bill (October 1996). The program aims to provide support for research of exceptional scientific merit, leading to an understanding of the cause, prevention, and treatment of the loss of dopaminergic neurons in the substantia nigra that result in PD. Projects examine neurodegenerative mechanisms and compensatory effects that compromise motor, autonomic, and cognitive systems and are characteristic alterations in PD patients; as such, they also present performance and health risks for military personnel. From FY97 through FY15, $388.75 million (M) has been appropriated by Congress for PD research. The FY16 appropriation is $16M. The PRP challenges the scientific community to develop the most impactful research that will advance the understanding of the disease, with the ultimate goal of ending PD.

PRP Appropriations 1997–2016



U.S. Army Medical Research and Materiel Command

Military Relevance

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 agriculture-type chemicals (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.

1997

Dr. G. Webster Ross, of Pacific Health Research and Education Institute, determined neurotoxic and preventative risk factors for PD from chemical and occupational exposures. The researcher identified the effect of lifestyle choices on PD risk and that specific agricultural toxins are correlated with risk and progression of PD. With findings from other studies, this work provides a basis for identifying metabolomic pathways affected by environmental toxins, individuals at increased risk, and preventative and therapeutic PD treatments.

2001

Dr. Gary Miller, of Emory University, found increased expression of VMAT2, DAT, and behavioral hyperactivity in animals dosed with the insecticide, deltamethrin. Although the compound disrupts normal dopamine homeostasis, he concluded that it did not increase vulnerability to dopamine neuronal damage. Deltamethrin did not increase the toxicity of MPTP, a prodrug to the neurotoxin MPP+, in this study. He suggested that the increased expression of DAT, TH, VMAT2, and locomotor activity in animals exposed during development might be relevant in the development of attention deficit hyperactivity disorder.

2002

Dr. Gretchen Snyder, of Intra-Cellular Therapies, Inc., examined signal transduction pathways that modulate striatal dopaminergic neurotransmission, which are affected in PD. Dr. Snyder found that the phosphorylation state of all post-synaptic, but not pre-synaptic, targets were up-regulated in a time- and dose-dependent manner by treatment with the A2A receptor inhibitor. The results suggest post-synaptic localization of adenosine A2A receptors. The findings are useful for development of A2A inhibitors as therapeutics in PD.

2005

Dr. M. Flint Beal, of Weill Medical College, Cornell University, used liquid chromatography coupled with electrochemical coulometric array detection to identify metabolomics profiles of Parkinson's patients that were distinct from normal controls. The studies demonstrated that metabolomics profiling can successfully identify biomarkers for both diagnosis and monitoring of disease progression and may be extended to identify therapeutic intervention points. This work was instrumental to later studies that were successful in identifying blood-based biomarkers for PD.

2007

Dr. Leroy Hood, of the Institute for Systems Biology, compared gene expression patterns from the Allen Brain Atlas to cell type-specific genes for neurons, astrocytes, and oligodendrocytes from previously published transcriptome profiling studies. His findings further demonstrate that brain-specific gene products can be found in the peripheral blood and might be useful as biomarkers for identifying disease or injury-damage networks.

2010

Dr. Michael Schwarzschild, of Massachusetts General Hospital, investigated the role of purines, in particular, adenosine, caffeine, and urate, in the progression of PD in an effort to develop improved therapeutic strategies. With his epidemiological collaborators, he demonstrated that higher serum urate concentrations are a predictor of slower clinical decline, as well as a lower risk of developing PD. Convergent preclinical evidence from his laboratory demonstrated the neuroprotective effects and mechanisms of urate in animal and cellular models of PD and substantiated the rationale for clinical development of urate-elevating therapy as a candidate disease-modifying strategy in PD. He currently leads a Phase III randomized clinical trial of the urate precursor inosine to investigate its potential to slow disease progression.

2012

Dr. Judith Potashkin, of the Rosalind Franklin University of Medicine and Science, worked on the development of diagnostic strategies for PD, specifically, investigating potential biomarkers. Analysis of changes in messenger RNA (mRNA) levels in whole blood led to the identification of hepatocyte nuclear factor (HNF4A) and polypyrimidine tract-binding protein 1 (PTBP1) mRNAs as promising biomarkers of early-stage PD. The same study indicated that both markers may be useful in monitoring disease progression, and HNF4A showed promise as a biomarker to monitor disease severity. Identification of these biomarkers contributes to the understanding of the molecular mechanisms of disease and can help track the therapeutic efficacy of potential disease-modifying treatments.

2012

Dr. James Surmeier, of Northwestern University, researched the effects of calcium entry through L-type channels in the dopaminergic neurons of the substantia nigra during pacemaking. Loss of these neurons, thought to be caused by mitochondrial oxidative stress, results in PD. Dr. Surmeier's research revealed that calcium entry through L-type channels elevates mitochondrial oxidant stress. Inhibiting L-type channels reduces mitochondrial stress and increases neuronal resistance to other insults. Epidemiological work shows that use of L-type channel inhibitors is associated with a significant reduction in the risk of developing PD. These studies have led to a 56-center, 5-year Phase III clinical trial to determine whether a Food and Drug Administration–approved L-type channel inhibitor can slow the progression of early-stage PD.

2013

Dr. Howard Federoff, of the University of California at Irvine, has focused on developing a therapeutic intervention targeting a new target, PGC-1α, which is correlated with the initiation and progression of Parkinsonian neurodegeneration. Preliminary research indicates that reduction in the molecular functions of the protein PGC-1α occurs during the initiation and progression of Parkinsonian conditions. Development and validation of PGC-1α's altered molecular function in PD may provide a means of preventing disease progression in susceptible populations and/or mitigating the consequences of diminished function in PD patients, offering the possibility of a disease-modifying treatment. Dr. Federoff has applied for a patent covering the use of a candidate compound targeting PGC-1α as a potential treatment for PD.

CDMRP
Department of Defense

PRP VISION:
Slow the progression of, prevent, and cure Parkinson's disease in order to lessen personal and societal impact of the disorder

FY16 RESEARCH FOCUS AREAS

- Studies of neurovascular units (including neurons, glia, the microvasculature, and the blood-brain barrier) in PD and changes associated with its treatment
- Identification and evaluation of mechanisms in early PD involving olfactory, microbiome, gastrointestinal, and/or autonomic nervous systems
- Mechanisms of neuroplasticity and compensation in PD, such as influences of sleep, exercise, and diet
- Underlying factors influencing PD progression in specific community-based populations (e.g., Veterans) to identify heterogeneity

SCOPE OF THE DISEASE

- 14th leading cause of death in the United States[1]
- 60,000 Americans are diagnosed each year with PD[2]
- 1 million people in America and 7–10M people worldwide live with PD[2]

[1]U.S. Centers for Disease Control and Prevention
[2]Parkinson's Disease Foundation