DoD Neurotoxin Exposure Treatment – Parkinson's Research (NETPR) Program

Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.

Year	NETPR Contributions	Additional Information and Hyperlinks
1997	Dr. G. Webster Ross, Pacific Health Research & Education Institute, determined neurotoxic and preventive risk factors from chemical and occupational exposures. The researcher identified effect of life-style choices on Parkinson's disease (PD) risk, and that specific agricultural toxins are correlated with risk and progression for PD. With findings from other research, this work provides a basis for identifying metabolic pathways affected by environmental toxins, individuals at increased risk, and a basis for preventive and therapeutic PD treatments.	• Ross GW, Duda JE, Abbott RD, et al. 2012. Brain organochlorines and Lewy Pathology: The Honolulu-Asia Aging Study. Mov Disord Sep 15; 27(11):1418-24.
1997	Dr. Jeffery Bloomquist, Virginia Polytechnic Institute and State University, studied the effect of Permethrin, an insecticide, on dopaminergic function. He found that treated animals experienced up-regulation of dopamine transporter markers as well as, at high doses, reversibly altering nicotinic and muscarinic cholinergic receptors. Treatment also increased the toxicity of MPTP, a compound used to model Parkinson's disease (PD), but concluded that high doses may increase idiopathic disease processes, but were unlikely to enhance risk for PD.	• Karen D, Li W, et al. 2001. Striatal Dopaminergic Pathways as a Target for Insecticides Chlorpyrifos and Permethrin. Neurotoxicology 22(11):811-817. • Gillette JS and Bloomquist JR. 2003. Differential Up-Regulation of Striatal Dopamine Transporter and alpha-Synuclein by the Pyrethroid Insecticide Permethrin. Toxicol Appl Pharmacol 192(3):287-293. • Pittman J, Dodd C, and Klein B. 2003. Immunohistochemical Changes in the Mouse Striatum Induced by the Pyrethroid Insecticide Permethrin. Intl J Toxicol 22(5):359-370. • Kou J and Bloomquist JR. 2007. Neurotoxicity in Murine Striatal Dopaminergic Pathways Following Following Long-term application of Low Doses of Permethrin and MPTP. Toxicol Lett Jul 10;171(3):154-61.
2001	Dr. Gary Miller of Emory University found increased expression of VMAT2, DAT, and behavioral hyperactivity in animals dosed with Deltamethrin. Although the compound disrupts normal dopamine homeostasis, he concluded that it did not increase vulnerability to dopamine neuronal damage. In contrast to Bloomquist's studies of Permethrin, Deltamethrin did not increase toxicity of MPTP. He suggested that the increased expression of DAT, TH, VMAT2, and locomotor activity in animals exposed during development might be relevant in attention deficit hyperactivity development.	• Elwan MA, Richardson JR, et al. 2006. Pyrethroid pesticide-induced alterations in dopamine transporter function. Toxicol Appl Pharmacol Mar 15; 211(3):188-97. • Richardson JR, Taylor MM, et al. 2015. Developmental pesticide exposure reproduces features of attention deficit hyperactivity disorder. FASEB J May; 29(5):1960-72.

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2002	Dr. Gretchen Snyder of Intra-Cellular Therapies Inc. demonstrated that the candidate compound developed in their laboratory, ITI-007, currently in human clinical trials for treatment of schizophrenia, had negligible binding to receptors associated with cognitive and metabolic side effects of other antipsychotic drugs. Her conclusions are that studies support its development for the treatment of schizophrenia as well as other psychological and neurologic disorders, to include co-morbid conditions in Parkinson's disease.	• Snyder G, Vanover KE, et al. 2015. Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission. Psychopharmacology 232:605–621.
2002	Dr. Gretchen Snyder and Dr. Allen A. Fienberg, Intra-Cellular Therapies Inc., identified intervention points in the cholinergic system that are affected by organophosphate-type chemical agents, and they further identified candidate compounds therapeutic for such exposures. As some of the earliest epidemiological studies indicate agricultural chemicals as risk factors for Parkinson's disease, the studies provide an initial point for identifying pathways associated with risks for neurodegeneration and subpopulations most at risk for development of neurodegenerative conditions.	• Zhu H, O'Brien JJ, et al. 2010. Nerve Agent Exposure Elicits Site-Specific Changes in Protein – Phosphorylation in Mouse Brain. Brain Res June 25; 1342C:11-23.
2002	Dr. Gretchen Snyder examined signal transduction pathways that modulate striatal dopaminergic neurotransmission, which are affected in Parkinson's disease. 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 inhibition. The results suggest postsynaptic localization of adenosine A2A receptors. The findings are useful for development of A2A inhibitors as therapeutics in Parkinson's disease.	• Sahin B, Galdi S, et al. 2007. Evaluation of neuronal phosphoproteins as effectors of caffeine and mediators of striatal adenosine A2A receptor signaling. Brain Res January 19; 1129(1):1-14.
2003	Dr. Allen A. Fienberg of Intra-Cellular Therapies Inc. investigated risk factors and co-morbid conditions of Parkinson's disease. He identified two candidate compounds. One compound is a potential therapy for dysfunctions of sleep architecture associated with neurodegenerative conditions and, at higher doses, provides potential therapy for schizophrenia, for which it is currently in clinical trials. The other compound, in early studies, has potential as an adjunct Parkinson's disease therapy, allowing an administration of a lower therapeutic dose of L-DOPA.	• Håkansson K, Galdi S, et al. 2006. Regulation of phosphorylation of the GluR1 AMPA receptor by dopamine D2 receptors. J Neurochem Jan; 96(2):482-8. • Nishi A, Kuroiwa M, et al. 2008. Distinct roles of PDE4 and PDE10A in the regulation of cAMP/PKA signaling in the striatum. J Neuroscience 28:10460-71.
2003	Dr. Michael Schwarzschild of Massachusetts General Hospital examined an Adenosine A2A receptor inhibitor's effect (caffeine) on loss of dopaminergic neurons in animals exposed to maneb and paraquat, dopaminergic toxins. Caffeine was neuroprotective in this chronic pesticide exposure model of Parkinson's disease.	• Kachroo A, Prasad K, et al. 2010. Caffeine protects against combined paraquat and maneb-induced dopaminergic neuron degeneration. Exp Neurol Jun; 223(2): 657-661. • Clinical Trial: Caffeine as a Therapy for Parkinson's disease. • Clinical Trial: A 12-week Randomized Study to Evaluate Oral Istradefylline in Subjects With Moderate to Severe Parkinson's Disease.

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2005	Dr. M. Flint Beal of Weill Medical College, Cornell University, used liquid chromatography coupled with electrochemical coulometric array detection to identify metabolomic profiles of Parkinson's patients distinct from normal controls. The studies demonstrated that metabolomics profiling can successfully identify biomarkers for both diagnosis and for monitoring 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 Parkinson's disease.	• Bogdanov M, Matson WR, et al. 2008. Metabolomic profiling to develop blood biomarkers for Parkinson's disease. Brain 131:389-396.
2006	Dr. D. James Surmeier of Northwestern University identified normal peacemaking activity in the Substantia nigra (SN) due to a specific type of ion channel as a cause of mitochondrial stress and loss of SN neurons. He identified a compound which switches pace-making to different ion channels and protects neurons in animal models of Parkinson's disease. A clinical trial for a Parkinson's disease-modifying treatment based on his findings is set to enter clinical trials.	• Chan CS, Guzman JN, et al. 2007. "Rejuvenation" protects neurons in mouse models of Parkinson's disease. Nature 447(7148):1081-1086. • Surmeier DJ, Guzman JN, and Sanchez-Padilla J. 2010. Calcium, cellular ageing, and selective neuronal vulnerability in Parkinson's disease. Cell Calcium Feb; 47(2):175-82. • Surmeier DJ. 2007. Calcium, ageing, and neuronal vulnerability in Parkinson's disease. Lancet Neurol 6(10):933-938. • Chan CS, Gertler TS, and Surmeier DJ. 2009. Calcium homeostasis, selective vulnerability and Parkinson's disease. Trends Neurosci 32(5):249-256. • Guzman JN, Sanchez-Padilla J, et al. 2009. Robust pacemaking in substantia nigra dopaminergic neurons. J Neurosci 29(35):11011-19. • Guzman JN, Sanchez-Padilla J, et al. 2015. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature May 21; 521(7552):380. • Surmeier DJ, Guzman JN, et al. 2010. What causes the death of dopaminergic neurons in Parkinson‟s disease? Prog Brain Res 183:59-77. • Surmeier DJ, Guzman JN, et al. 2011. The origins of oxidant stress in Parkinson's disease and therapeutic strategies. Antioxid Redox Signal Apr 1; 14(7):1289-301.
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. Their findings further support that brain-specific gene products can be found in the peripheral blood and might be useful as biomarkers for identifying disease or injury-damaged networks.	• Ko Y, Ament SA, et al. 2013. Cell type-specific genes show striking and distinct patterns of spatial expression in the mouse brain. PNAS 110(8):3095-3100.

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2008	Dr. Paul Greengard and colleagues from Rockefeller University identified a protein (p11) that modulates a serotonin receptor as a potential candidate for therapy in depression. Depression is both a risk factor for Parkinson's disease and co-morbid in Parkinson's disease. They found that brain levels of p11 are mirrored in blood specimens, providing easy access for diagnosis and monitoring progression. They also found that depressed individuals who reported taking non-steroidal anti-inflammatory drugs (NSAIDs) for pain, while taking an SSRI (citalopram), had a lower depression remission rate, suggesting that NSAIDs interfere with p11 function.	• Svenningsson P, Kim Y, et al. 2013. p11 and its role in depression and therapeutic responses to antidepressants. Nat Rev Neurosci Oct; 14(10):673-80. • Warner-Schmidt JL, Vanover KE, et al. 2011. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflammatory drugs in mice and humans. Proc Natl Acad Sci U S A 108(22):9262-67.
2009	Dr. Andrew Singleton's laboratory at the National Institute of Aging, using genome-wide association studies, identified novel-genetic risk loci for Parkinson's disease. These findings provide insight to the molecular cause of Parkinson's disease and could provide potential new targets for therapeutic interventions.	• International Parkinson Disease Genomics Consortium. 2011. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: A meta-analysis of genome-wide association studies. Lancet 377(9766):641-9.
2009	Dr. Andrew Singleton and a large group of expert collaborators constructed genetic risk profiles using known genome-wide association studies. They identified a strong, genetically defined level of comorbidity between Parkinson's disease and Crohn's disease, as well as between Parkinson's disease and Schizophrenia.	• Nalls M, Saad M, et al. 2014. Genetic comorbidities in Parkinson's disease. Hum Mol Genet 23(3):831-841.
2009	Dr. Andrew Singleton and collaborators discovered or confirmed 11 Parkinson's disease loci by focusing on the set of loci that passed genome-wide significance in a first-stage Gene Wide Association scan. In a second stage genotyping array, using a larger set of Single Nucleotide Polymorphisms, they identified five additional Parkinson's disease risk loci. The findings suggest potential molecular mechanisms and candidate genes for therapeutic interventions for Parkinson's disease.	• International Parkinson's Disease Genomics Consortium (IPDGC), Wellcome Trust Case Control Consortium 2 (WTCCC2). 2011. A Two-Stage Meta-Analysis Identifies Several New Loci for Parkinson's Disease. PLoS Genet June 7(6):e1002142.
2009	Dr. Andrew Singleton and collaborators tested 32 Single Nucleotide Polymorphisms previously associated with potential risk for Parkinson's disease. Twenty-four (24) replicated. Four (4) loci contained a secondary independent risk variant, resulting in replication of 28 independent Parkinson's disease risk variants. The findings suggest potential risks for Parkinson's disease; means to identify population susceptibility; and a basis for therapeutic interventions.	• Nalls M, Pankratz N, et al. 2014. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet September; 46(9):989-993.
2009	Dr. Judith Potashkin of Rosalind Franklin University of Medicine and Science, and Dr. Clemens Scherzer at Brigham and Women's Hospital identified a gene common to both dysregulated molecular pathways in Parkinson's disease and type 2 diabetes.	• Santiago JA, Scherzer CR, and Potashkin JA. 2014. Network Analysis Identifies SOD2 mRNA as a Potential Biomarker for Parkinson's Disease. PLoS One 9(10): e109042.

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2009	Dr. Howard Federoff of Georgetown University discovered and validated plasma metabolomic biosignatures in a cohort of aged individuals who were at risk for developing Mild Cognitive Impairment, and are prodromal for both Alzheimer's and Parkinson's. The identification of this 10-plasma lipid panel represents real potential for furthering diagnostics for brain dysfunction and neurodegenerative disease risks.	• Mapstone M, Cheema A, et al. 2014. Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med 20(4):415-8.
2010	Dr. D. James Surmeier of Northwestern University examined causes of vulnerability of the dopaminergic neuron from oxidant stress to mitochondria. He developed a genetically encoded ion channel indicator, targeted to the mitochondrial matrix, which permits mitochondrial calcium influx to be directly monitored in Substantia nigra dopaminergic neurons. This discovery creates an opportunity for development of disease-modifying treatments for Parkinson's that complement the treatments previously identified for ion channel antagonism.	• Dryanovski DI, Guzman JN, et al. 2013. Calcium entry and alpha-synuclein inclusions elevate dendritic mitochondrial oxidant stress in dopaminergic neurons. J Neurosci 33(24):10154-64. • Sulzer D and Surmeier DJ. 2013. Neuronal vulnerability, pathogenesis, and Parkinson's disease. Mov Disord 28(6):715-24. • Surmeier DJ and Sulzer D. 2013. The pathology roadmap in Parkinson disease. Prion 7(1):85-91. • Goldberg JA, Guzman JN, et al. 2012. Calcium entry induces mitochondrial oxidant stress in vagal neurons at risk in Parkinson's disease. Nat Neurosci 15(10):1414-21. • Sanchez-Padilla J, Guzman JN, et al. 2014. Mitochondrial oxidant stress in locus ceruleus neurons is regulated by activity and nitric oxide synthase. Nat Neurosci Jun;17(6):832-40.
2010	Dr. Michael Schwarzschild of Massachusetts General Hospital identified from epidemiological data that higher levels of blood urate were associated with a reduced risk for Parkinson's disease and a slower progression in affected individuals. His study used allopurinol to block formation of urate in a toxin model of Parkinson's. Although low urate levels did not increase neuron degeneration, exposure to both a toxin and lower urate levels negatively impacted neurons.	• Kachroo A and Schwarzschild MA. 2014. Allopurinol reduces levels of urate and dopamine but not dopaminergic neurons in a dual pesticide model of Parkinson's disease. Brain Res May 14; 1563:103-109.
2010	Dr. Michael Schwarzschild reviewed newer treatments for Parkinson's disease. His article provides background on the use of Adenosine A2A inhibitors and the use of purine compounds to ameliorate PD progression, which are both currently in clinical trials as disease modifying treatments for Parkinson's. Dr. Schwarzschild's own work on purine compound candidates entered Phase III clinical trials and may provide significant disease modification for PD patients.	• Hung AY and Schwarzschild MA. 2014. Treatment of Parkinson's disease: What's in the non-dopaminergic pipeline? Neurotherapeutics January; 11(1):34-46.
2010	Dr. Michael Schwarzschild identified the role of purine analogues as potential disease modifiers for Parkinson's disease. In particular, he has identified Inosine, a purine nucleoside, as a candidate treatment that is currently in clinical trials for Parkinson's.	• Cipriani S, Bakshi R, and Schwarzschild MA. 2014. Protection by inosine in a cellular model of Parkinson's disease. Neurosci Aug 22; 274:242-9. • Clinical Trial: Safety of Urate Elevation in Parkinson's Disease (SURE-PD).

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2011	Dr. Kenneth Marek of The Institute for Neurodegenerative Disorders validated the sequential strategy of hyposmia (deficient sense of smell) testing followed by dopamine transporter (DAT) imaging for successful identification of individuals at high risk for developing Parkinson's disease. Data suggests that hyposmic subjects are at higher risk for DAT deficit and are more likely to be identified as having non-motor symptoms compared to subjects with normal sense of smell.	• Jennings D, Siderowf A, et al. 2014. Imaging prodromal Parkinson disease: the Parkinson Associated Risk Syndrome Study. Neurology 83(19):1739-46.
2012	Dr. Judith Potashkin of Rosalind Franklin University of Medicine and Science, and Dr. Clemens Scherzer of Brigham and Women's Hospital found that expression of seven splice variant markers were dysregulated in whole cellular blood of Parkinson's disease patients. The panel of markers may prove useful in diagnostic testing for Parkinson's disease.	• Santiago JA, Scherzer CR, and Potashkin JA. 2014. Network Analysis Identifies SOD2 mRNA as a Potential Biomarker for Parkinson's Disease. PLoS One 9(10):e109042.
2012	Dr. Judith Potashkin identified a transcription factor associated with gluconeogenesis and diabetes, and a binding protein involved in the translation of insulin as potential biomarkers for Parkinson's disease. The up-regulation of the gluconeogenesis-associated transcription factor and the down-regulation of the binding protein were confirmed in blood analysis with 90% sensitivity and 80% specificity. With further investigation, the discovery could lead to the development of a blood test for the detection of Parkinson's disease.	• Santiago JA and Potashkin JA. 2015. Network-based metaanalysis identifies HNF4A and PTBP1 as longitudinally dynamic biomarkers for Parkinson's disease. Proc Natl Acad Sci U S A Feb 17; 112(7):2257-62.