VIEWPOINT

The Future of Research in Parkinson Disease

Joseph Jankovic, MD
Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas.

Todd Sherer, PhD
Michael J. Fox Foundation for Parkinson's Research, New York, New York.

There are many unanswered questions about Parkinson disease (PD), but as a result of advances in genetics, proteomics, metabolomics, epigenetics, imaging, and other novel techniques, remarkable progress is being made. In this Viewpoint, we will highlight aspects of future research aimed at addressing the following critical questions.

What is PD?

There is growing recognition that PD is not a single clinical-pathological entity but that there are PD subtypes, possibly caused by different pathogenic mechanisms.[1] Furthermore, psychiatric symptoms and cognitive impairment are increasingly recognized as major contributors to disability, and other nonmotor features, such as dysautonomia, hyposmia, and rapid eye movement sleep behavior disorder, may precede motor symptoms by several years or even decades. The traditional view that PD is defined pathologically is increasingly challenged as many genetic forms of PD phenotypes do not show the typical selective deposition of α-synuclein and the presence of Lewy bodies (LBs). Furthermore, α-synuclein pathology can be found in the brains of individuals without any symptoms of PD, the so-called incidental LB disease.

How is PD Diagnosed?

The clinical diagnosis of PD still rests on the presence of a combination of tremor, bradykinesia, rigidity, and postural instability, but by the time these motor symptoms first manifest, about 60% of nigrostriatal dopaminergic terminals are already lost. Therefore, "the holy grail" of PD research is to find diagnostic biomarkers that will identify individuals at risk for PD with high predictive value, even in the prodromal phase.[2] Based on the identification of pathology outside the central nervous system, future diagnostic techniques may include biopsies of the colon, skin, submandibular glands, and other tissues that accumulate α-synuclein. In addition to DaTscan (GE Healthcare), which has been used to differentiate PD from essential tremor and other PD-like disorders without dopaminergic deficit, there are other emerging imaging techniques that may be useful in assessing dopaminergic integrity. For example, positron emission tomography with fluorine 18–labeled 9-fluoropropyl-(1)-dihydrotetrabenazine (^{18}F-DTBZ), a radioligand targeting vesicular monoamine transporter type 2 (VMAT2), promises to be an excellent tool for the early diagnosis of PD (**Figure**).

What Causes PD and When and Where Does the Neurodegenerative Process Start?

In addition to monogenetic causes, which account for less than 10% of all cases of PD, a growing number of susceptibility genes, such as *GBA1*, have been found to markedly increase the risk of developing PD.[3] The pathological changes associated with PD have been studied to better understand the pathogenic mechanisms of neurodegenerative progression. These studies have provided evidence that pathological changes in PD may not start in the neuronal cell bodies in substantia nigra but in distal axons, supporting the notion that PD represents a form of "dying-back" axonopathy. Another recently proposed hypothesis to explain the spread of pathological process is that α-synuclein might act as a prion. This hypothesis is supported by many studies including the finding that preformed fibrils generated from full-length and truncated recombinant α-synuclein enter neurons, probably by endocytosis, and act as "seeds" that induce recruitment of soluble endogenous α-synuclein into insoluble LB-like inclusions. Furthermore, intranigral or intrastriatal inoculations into brains of animals of insoluble α-synuclein extracted from LBs of PD brains result in progressive striatal-nigral neurodegeneration.[4] Indeed, the notion that progression of neurodegenerative disease is mediated via seeding of misfolded proteins has extended to a broad range of proteins besides α-synuclein, including tau, huntingtin, SOD-1, and TDP-43.

How Can PD Be Prevented, Slowed, or Reversed?

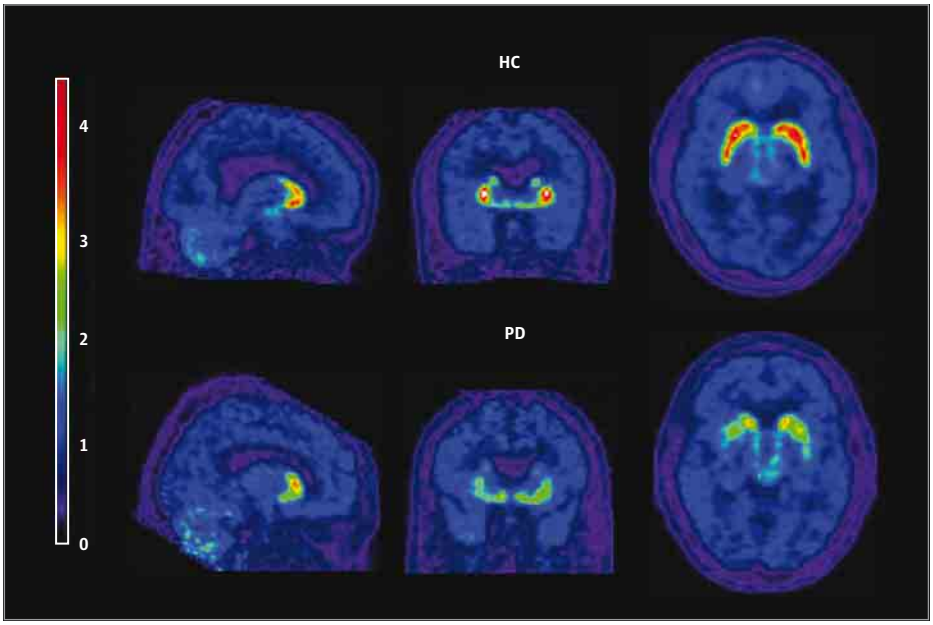
It is too early to know whether the following drugs currently undergoing clinical trials will eventually meet the standard for the designation of "neuroprotective" or "disease-modifying" agents: (1) isradipine (an antihypertensive agent shown to block L-type calcium ion channels and thus protect vulnerable dopaminergic neurons in animal models), (2) inosine (elevates urate and may act as an antioxidant), (3) AZD-3241 (myeloperoxidase inhibitor that may control activated microglia), (4) RP103 (cysteamine that acts as an antioxidant, increases brain-derived neurotrophic factor, etc), and (5) pioglitazone and exenatide (glucagon-like peptide 1 receptor agonists that may be protective against cytokine-mediated apoptosis). Unfortunately, clinical trials evaluating trophic factors, such as glial cell–derived neurotrophic factor and neurturin, have failed. ProSavin, which uses LentiVector gene technology (Oxford BioMedica) to deliver genes for 3 enzymes that are required for the synthesis of dopamine (tyrosine hydroxylase, dopa-decarboxylase, and GTP cyclohydrolase-1), has been reported to provide modest improvement in motor scores, but this gene-delivery approach is still highly experimental.[5] Anti-synuclein strategies designed to prevent α-synuclein clumping (eg, PT200-11, quinpramine, PBT434, and rifampicin), vaccine designed to elicit antibodies against α-synuclein (eg, PD01; AFFiRiS), and immunotherapy with antibodies targeting α-synuclein (eg, PRX002; Prothena) may theoretically reduce toxic α-synuclein and prevent its spread.[6]

What are the Most Promising Emerging Therapies?

Future experimental therapeutic trials will focus on new delivery techniques, using various patches, pumps, and puffs,

Corresponding Author: Joseph Jankovic, MD, Department of Neurology, Baylor College of Medicine, 6550 Fannin, Ste 1801, Houston, TX 77030 (josephj@bcm.edu).

Figure. Fluorine 18–Labeled AV-133 Positron Emission Tomography Scan of a Patient With Early Parkinson Disease (PD) Showing Marked Reduction in Striatal Dopaminergic Integrity vs a Healthy Control (HC).



Courtesy of Andrew Siderowf, MD, Avid Radiopharmaceuticals Inc.

in an attempt to provide more continuous dopaminergic delivery. Of these approaches, levodopa-carbidopa intestinal gel infusion may be closest to gaining Food and Drug Administration approval. A recently completed levodopa-carbidopa intestinal gel infusion multicenter study showed that the mean on time without troublesome dyskinesia increased by nearly 2 hours compared with immediate-release levodopa-carbidopa.[7] Future therapeutic strategies will likely continue to move beyond the traditional dopamine-centric view and will lead to treatments targeting glutamate, serotonin, adenosine, and other nondopaminergic systems. For example, the Food and Drug Administration recently approved droxidopa, a prodrug of norepinephrine, for the treatment of neurogenic orthostatic hypotension. Furthermore, pimavanserin tartrate, a serotonin 2A inverse agonist, has been found to be safe, well-tolerated, and efficacious in treating levodopa-induced psychosis without worsening motor symptoms in a phase 3 trial.[8]

Improvements in deep brain stimulation (DBS) have led to the development of "closed-loop" or "adaptive" DBS systems, which may eventually significantly improve the outcomes of DBS. Furthermore, ablative techniques using focus ultrasonography are being evaluated in the treatment of various movement disorders including PD.

In conclusion, we are optimistic about the future of PD research and therapeutic development. Clinical, genetic, and molecular subtyping of the disease will allow better targeting and testing of future therapies in enriched populations most likely to benefit. One of the most exciting developments in PD research is the introduction of novel approaches targeting toxic α-synuclein into the clinic with the promise of the first therapy designed to attack the fundamental pathological mechanism in PD. Critical attention to nonmotor symptoms will lead to improved treatments for these aspects of the disease that significantly impact quality of life and patient and caregiver burden. With the application of best scientific methods and proper funding, we envision future development of transformative therapies for those affected by PD.

ARTICLE INFORMATION

Published Online: September 1, 2014. doi:10.1001/jamaneurol.2014.1717.

Conflict of Interest Disclosures: Dr Jankovic has received Research and Center of Excellence grants from Allergan, Auspex Pharmaceuticals, CHDI Foundation, GE Healthcare, Great Lakes NeuroTechnologies, Huntington's Disease Society of America, Huntington Study Group, Ipsen Limited, Kyowa Haako Kirin Pharma, Lundbeck, Medtronic, Merz Pharmaceuticals, Michael J. Fox Foundation for Parkinson's Research, National Institutes of Health, National Parkinson Foundation, Omeros Corporation, Parkinson Study Group, Pharma Two B, Prothena Biosciences, Psyadon Pharmaceuticals, St. Jude Medical, Teva Pharmaceutical Industries, UCB Inc, and University of Rochester; is a current consultant or advisory committee member for Allergan, Auspex Pharmaceuticals, Ipsen Biopharmaceuticals, Lundbeck, and Teva Pharmaceutical Industries; has received royalties from Cambridge, Elsevier, Future Science Group, Hodder Arnold, Lippincott Williams & Wilkins, and Wiley-Blackwell; and has served on editorial boards and foundation advisory boards.

REFERENCES

1. Thenganatt MA, Jankovic J. Parkinson disease subtypes. *JAMA Neurol*. 2014;71(4):499-504.

2. Wu Y, Le W, Jankovic J. Preclinical biomarkers of Parkinson disease. *Arch Neurol*. 2011;68(1):22-30.

3. Murphy KE, Gysbers AM, Abbott SK, et al. Reduced glucocerebrosidase is associated with increased α-synuclein in sporadic Parkinson's disease. *Brain*. 2014;137(pt 3):834-848.

4. Recasens A, Dehay B, Bové J, et al. Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. *Ann Neurol*. 2014;75(3):351-362.

5. Palfi S, Gurruchaga JM, Ralph GS, et al. Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease. *Lancet*. 2014;383(9923):1138-1146.

6. Tran HT, Chung CH, Iba M, et al. α-Synuclein immunotherapy blocks uptake and templated propagation of misfolded α-synuclein and neurodegeneration. *Cell Rep*. 2014;7(6):2054-2065.

7. Olanow CW, Kieburtz K, Odin P, et al; LCIG Horizon Study Group. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease. *Lancet Neurol*. 2014;13(2):141-149.

8. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis. *Lancet*. 2014;383(9916):533-540.