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Promising disease-modifying therapies for Parkinson's disease

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To date, there is no disease-modifying therapy for Parkinson's disease; however, promising new agents have advanced into clinical trials.

Parkinson's disease (PD) is the second most common neurodegenerative disease. Individuals with PD have both motor and nonmotor symptoms. The motor symptoms include slowness of movement, rigidity, and tremor at rest. Nonmotor symptoms range from gastrointestinal and autonomic nervous system abnormalities to neuropsychiatric and cognitive dysfunction (*1*). Most of the neurodegenerative process of PD is driven by pathological α-synuclein, a presynaptic neuronal protein that aggregates and accumulates in Lewy bodies and Lewy neurites (*2*) in the nervous system. Although drugs that treat the motor symptoms are relatively effective and therapies addressing some of the nonmotor symptoms have shown modest efficacy, these treatments are less effective at treating advanced disease. To date, there are no disease-modifying therapies that slow, halt, or reverse the progression of PD. Development of disease-modifying agents remains a high priority. Advances in understanding the molecular pathogenesis of neurodegeneration in PD, development of new animal models, and human dopaminergic neuronal cell culture systems together with the identification of new therapeutic targets (*1*) over the past decade have led to the initiation of exploratory clinical trials. In this 11th installment of *Science Translational Medicine*'s anniversary Focus series, we highlight promising agents that have the potential for altering the progression of PD and the science behind them.

AGENTS TARGETING THE GENETIC CAUSES OF PD

Over the past two decades, there has been extensive characterization of the genetic architecture of PD, including identification of the genes encoding leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase as risk factors for PD. From this foundation, LRKK2 kinase inhibitors and agents that modulate glucocerebrosidase function have recently advanced to clinical studies.

Disease-causing mutations in *LRRK2*, which play a major causal role in the inheritance of PD, lead to enhanced activity of this kinase and neurodegeneration (*3*). LRRK2 phosphorylates a conserved threonine or serine in the switch II domain of certain Rab GTPase family members. Rab GTPases, in part, regulate vesicle trafficking (*4*). More work needs to be done to clarify the roles of individual Rab GTPases in the pathogenesis of PD. The high abundance of Rab GTPases has enabled the development of high-affinity and specific antibodies, leading to the democratization of tools to monitor LRRK2 activity. The ribosomal protein s15 is a physiological substrate of LRRK2, and phosphorylation of s15 is involved in the loss of neurons in PD through altered protein translation (*5*). Targeting LRRK2 kinase substrates for therapeutic benefit is under active exploration.

Since the identification of the causal role of LRRK2 in PD, academic and industry investigations have led to the development of LRRK2 kinase inhibitors with improved potency, selectivity, and blood-brain barrier penetration (*3*). Denali's LRRK2 kinase inhibitors, DNL-151 and DNL-201, have completed phase 1 studies in healthy volunteers (Table 1). Individuals with PD or those who are at risk of developing PD due to an LRRK2 mutation potentially could benefit from treatment with an LRRK2 kinase inhibitor. There is some evidence suggesting that LRRK2 kinase activity may also be involved in the pathogenesis of idiopathic (sporadic) PD, indicating that a substantially larger patient population potentially could benefit from treatment with these inhibitors.

A major genetic risk factor for PD is mutation of the gene that encodes the enzyme glucocerebrosidase (*6*). These mutations lead to retention of glucocerebrosidase in the endoplasmic reticulum and decreased glucocerebrosidase activity. Mutant glucocerebrosidase can lead to pathological accumulation of α-synuclein. Clinical efforts have focused on translocating mutant glucocerebrosidase from the endoplasmic reticulum into lysosomes using chemical chaperones. A phase 2 clinical trial of Ambroxol and a phase 1 study of the Allergan compound LTI-291—agents that increase the activity of glucocerebrosidase—are currently testing this idea (Table 1). In addition, Genzyme is testing the hypothesis that PD in those patients with glucocerebrosidase mutations is due to the accumulation of the glucocerebrosidase substrate glucosylceramide. Individuals with PD are being treated in a phase 2 study with ibiglustat (GZ/SAR402671, venglustat L-malate), a glucosylceramide synthase inhibitor that blocks the formation of glucosylceramide (Table 1). Given that glucocerebrosidase activity is reduced in idiopathic PD and there is an inverse relationship between glucocerebrosidase activity and the accumulation of pathological α-synuclein (*6*), agents that enhance glucocerebrosidase activity are also being explored in idiopathic PD but have yet to enter the clinic.

AGENTS EXPLOITING THE CELL BIOLOGY OF PD

Research focused on how pathological α-synuclein leads to neurodegeneration in idiopathic PD has also resulted in agents that are now in clinical trials. Under physiological conditions, α-synuclein exists in both a soluble and membrane-bound state with the

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Table 1. Agents in clinical trials for PD.

Target	Action	Agent	Trial phase	Clinical trial identifier
LRRK2	Decrease LRRK2 kinase activity	Denali—DNL-151	Phase 1	NCT04056689
		Denali—DNL-201	Phase 1	NCT03710707
Glucocerebrosidase	Chemical chaperone to translocate mutant enzyme from the endoplasmic reticulum into lysosomes	Ambroxol	Phase 2	NCT02941822 and NCT02914366
		Allergan—LTI-291	Phase 1	Netherlands Trial NL7061
	Block accumulation of the glucocerebrosidase substrate, glucosylceramide	Genzyme/Sanofi—Ibiglustat (GZ/SAR40267)	Phase 2	NCT02906020
α-Synuclein	Anti–α-synuclein monoclonal antibodies to lower α-synuclein concentrations and block cell-to-cell transmission	Biogen—Cinpanemab	Phase 1/2	NCT03318523 and NCT03716570
		Hoffmann–La Roche/Prothena—Prasinezumab	Phase 2	NCT03100149
		Abbvie—ABBV 0805	Phase 1	NCT04127695
		Takeda/AstraZeneca—MEDI1341	Phase 1	NCT03272165
		Lundbeck—Lu-AF-82422	Phase 1	NCT03611569
	Inhibitors of pathological α-synuclein aggregation	Enterin—ENT-01	Phase 1	NCT03938922
		Alterity Therapeutic—PBT434	Phase 1	U1111–1211-0052
		Neuropore Therapies Inc./UCB S.A.—NPT200-11	Phase 1	NCT02606682
c-Abl kinase	c-Abl kinase inhibition	SPARC—K0706	Phase 2	NCT03655236
		Novartis—Nilotinib	Phase 2	NCT02954978 and NCT03205488
		1ST Biotherapeutics, Inc—FB-101	Phase 1	NCT04165837
GLP-1 receptor	GLP-1 receptor agonist, decreases inflammation	Amylin Pharmaceutical/AstraZeneca—Exenatide	Phase 3	NCT03456687, NCT04154072, and ISRCTN14552789
		Novo Nordisk—Liraglutide	Phase 2	NCT02953665
		Sanofi—Lixisenatide	Phase 2	NCT03439943
		Neuraly—NLY01	Phase 2	NCT04154072

monomer in an inherently unfolded state. α-Synuclein can transition between nontoxic monomers and tetramers and toxic oligomers and fibrils. There is growing evidence that the central role of α-synuclein in α-synucleinopathies and PD is mediated by the aggregated α-synuclein fibrils. Pathological α-synuclein toxicity may be partly engendered through cell-to-cell transmission, in which pathological α-synuclein may act like a prion (*2*). Thus, monoclonal antibodies against α-synuclein are being used to reduce concentrations of α-synuclein and to prevent cell-to-cell transmission of pathological α-synuclein (Table 1). Biogen's Cinpanemab (BIIB 054) and Hoffmann–La Roche/Prothena Biosciences' Prasinezumab (PRX002) monoclonal antibodies are currently in phase 2 clinical trials. Meanwhile, Abbvie's ABBV 0805, AstraZeneca's and Takeda's MEDI1341 (TAK-341), and Lundbeck's Lu-AF-82422 monoclonal antibodies against α-synuclein are in phase 1 trials (Table 1). Preclinical studies using these different monoclonal antibodies and an immunotherapy approach are testing the hypothesis that lowering α-synuclein or interfering with cell-to-cell transmission may have a beneficial effect on disease progression and severity. There is a concern that the timing of immunotherapy could affect the efficacy of this approach. A distinct challenge for anti–α-synuclein monoclonal antibodies to lower α-synuclein in the brains of individuals with PD exists, because α-synuclein is predominantly an intracellular protein. Small-molecule inhibitors of α-synuclein, which in theory would prevent the formation of pathological aggregated α-synuclein, have entered phase 1 trials. These include Enterin's ENT-01, Alterity Therapeutic's PBT434, and Neuropore/UCB's NPT200-11 (UCB0599) (Table 1). Ideally, treatment initiated during the early stages of the disease would be optimally efficacious in limiting seeding and misfolding of α-synuclein; however, extensive work still needs to be done to identify presymptomatic subjects. Phase 2 and 3 studies will ultimately determine the usefulness of these approaches in modifying the course of disease in individuals with early symptomatic PD.

After α-synuclein misfolds, it sets in motion both cell-autonomous (action within a cell) and non–cell-autonomous (action outside a cell) pathways, which contribute to neurodegeneration. The nonreceptor tyrosine kinase c-Abl, which is overactive in idiopathic PD, may play an important role in cell-autonomous death of neurons because loss or inhibition of c-Abl is protective in multiple animal models of pathological α-synuclein–induced neurodegeneration (*7*). c-Abl phosphorylates several substrates that

may contribute to the neurodegenerative process, including the ubiquitin E3 ligase, parkin, which leads to its inactivation. Inactivation of parkin induces accumulation of the parkin substrates PARIS (ZNF746) and aminoacyl tRNA synthetase complex interacting multifunctional protein 2 (AIMP2), which down-regulate peroxisome proliferator–activated receptor-gamma coactivator-1α and activate poly(ADP-ribose) polymerase-1, respectively. This kills neurons through formation of poly(ADP-ribose) and activation of parthanatos. c-Abl also phosphorylates α-synuclein on tyrosine 39, turning it into a pathological species. Other c-Abl substrates that may participate in the neurodegenerative process include cyclin-dependent kinase 5 and p-38 kinase (*7*). Enhanced c-Abl activity also impairs the autophagic degradation of pathological α-synuclein through unclear mechanisms (*7*). c-Abl inhibitors were developed for the treatment of cancer and are poorly brain penetrant. A small phase 1b study with Novartis's nilotinib suggested that individuals with PD who received nilotinib experienced a slight benefit (*7*). There are two phase 2 trials attempting to confirm this initial report (Table 1). Efforts to develop safer and brain-penetrant compounds have resulted in Sun Pharma Advanced Research's brain-penetrant c-Abl kinase inhibitor, K0706, which is currently in phase 2 clinical trials and 1ST Biotherapeutics' FB-101, which is in a phase 1 trial.

Non–cell-autonomous cell death is gaining traction as an important contributor to the pathogenesis of PD. Recent studies suggest that glucagon-like peptide-1 (GLP-1) receptor agonists, which lower blood glucose in diabetes, could be disease-modifying agents in PD. GLP-1 receptor agonists have diverse targets, but their primary mechanism of action may be through preventing pathological microglial activation and secretion of the proinflammatory cytokines tumor necrosis factor, interleukin-1α, and complement component 1q, which in turn prevents the conversion of resting astrocytes to the toxic and reactive A1 phenotype (*8*). Amylin Pharmaceuticals' and AstraZeneca's GLP-1 receptor agonist exenatide has been through a double-blinded and placebo-controlled phase 2 trial in patients with moderate PD. Individuals with PD who received exenatide experienced a slight improvement in motor function. However, it remains unclear whether the improvement was due to symptomatic relief or modification of the disease process (*9*). Exenatide has advanced to a phase 3 clinical trial. Other GLP-1 receptor agonists in phase 2 trials include Novo Nordisk's Liraglutide, Sanofi's Lixisenatide, and Neuraly's NLY-01. LRRK2 inhibitors and agents targeting glucocerebrosidase may also interfere with non–cell-autonomous cell death because both LRRK2 and glucocerebrosidase are enriched in glia and immune cells (*3*, *6*).

POINTS TO CONSIDER

The presence of multiple potential disease-modifying therapies in early-phase clinical trials is exciting. One GLP-1 receptor agonist, exenatide, has already advanced to a definitive phase 3 clinical trial. Barring safety concerns or phase 2 trial futility, it is likely that many of the agents highlighted in Table 1 will advance to phase 3 clinical trials. However, as has been observed in prior clinical studies founded on sound science that failed to meet primary end points, major impediments to success remain. These include the heterogeneity of the clinical course of PD and the lack of biomarkers for diagnostic certainty and monitoring of disease progression. Development of tools for diagnosis and monitoring of disease progression beyond clinical assessments that are used by master clinicians will be critical to identify disease-modifying compounds that have small to modest but significant effects (*10*). An agent that halts disease progression may obviate the need to address these issues. However, because of the inherent challenges to achieve success, tools to aid in the diagnosis and monitoring of disease progression will ultimately be essential for identifying, proving, and accelerating the clinical use of agents that modify the course of PD. Finally, genetics and rigorous cell and animal studies have identified many additional disease targets not mentioned here. Agents directed at these targets are in the drug development pipeline. We remain optimistic that ultimately agents will be identified that can slow and alter the course of PD.

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