# Advances in Therapeutics for Parkinson's Disease

## *Academia Roundtable*

May 22, 2023

Virtual Meeting

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# Executive Summary

On May 22, 2023, the National Institute of Neurological Disorders and Stroke (NINDS) held the third in a series of Advances in Therapeutics Development for PD roundtable discussions aimed at identifying challenges and opportunities for Parkinson's disease (PD) target validation and therapeutics development. These roundtables convened industry partners, nonprofit funders, academic researchers, and people with lived experience of PD. The perspectives shared during these discussions will inform a workshop and white paper focused on barriers to preclinical development of PD therapeutics.

The third roundtable was attended by academia partners and people with lived experience of PD. Topics highlighted by this stakeholder group included the need to (1) address the heterogeneity of PD in therapeutics development, (2) identify multiple biomarkers and therapeutic targets within a precision medicine approach, (3) engage research communities of other diseases to understand different therapeutics development strategies, (4) increase funding for studies that reproduce preclinical findings and characterize preclinical models, and (5) collaborate through data sharing and biorepository development.

## Challenges for Parkinson's Disease Therapeutics Development

PD is a heterogeneous disease, in which each PD patient may display unique disease pathophysiology. Many individuals carrying a leucine-rich repeat kinase 2 (LRRK2) genetic variant may test negative for α-synuclein aggregates but still display Parkinsonism. In addition, many PD patients display an acute onset of non-motor symptoms, such as Lewy body dementias, while other patients primarily display progressively severe motor symptoms. To address the heterogeneity of PD, researchers must identify appropriate therapeutic targets based on biological mechanisms and biomarkers.

The PD research community has identified multiple therapeutic targets through programs such as the Michael J. Fox Foundation's Aligning Science Across Parkinson's Initiative. However, PD research requires more funding to develop therapeutics for clinical trial testing. Researchers struggle to receive funding for predictive biomarker discovery and longitudinal studies because these studies often do not yield significant results for PD treatment. Similarly, studies that replicate and reproduce preclinical findings lack funding, resulting in a lack of characterization and validation of many transgenic rodent models. In addition to transgenic models, researchers have not reproduced findings from α-synuclein antibody assays that are critical to PD-associated α-synuclein proteoform detection and therapeutics development.

## Areas for Improving Parkinson's Disease Therapeutics Development

Because of PD heterogeneity, researchers should consider a wide range of treatment priorities among patients, including priorities of early and late onset PD patients, patients with genetic PD, patients with sporadic PD, and caregivers of patients with severe cognitive decline. In addition, increasing patient participation in PD research can help researchers understand the unique treatment priorities of each patient. To address PD heterogeneity, researchers should

implement precision medicine approaches using multiple biomarkers and combination therapies to facilitate individualized treatments.

Refining the definition of PD can help researchers identify relevant biomarkers and therapeutic targets for PD; however, identifying a single biomarker is likely not sufficient for addressing the heterogeneity of PD. Researchers should consider diagnostic biomarkers, genetic biomarkers, biomarkers of disease progression, and biomarkers of unique pathophysiology. Although reducing the clinical symptoms of PD is the ultimate goal, subtyping patients using multiple biomarkers should be a research priority within a precision medicine approach. Furthermore, researchers should validate these biomarkers in preclinical studies. Potential biomarkers identified through multi-omic analyses of clinical biofluid samples can be manipulated within preclinical model systems to reveal pathophysiological mechanisms. Researchers can also use preclinical models to develop dose-response curves for therapeutic target assays, which can translate back to clinical trials. Thus, communication between preclinical and clinical research is critical for the identification and validation of biomarkers and therapeutic targets.

Multiple diseases other than PD can provide roadmaps to FDA approvals of therapeutics and share similar disease pathophysiology that may inform future directions in PD research. Research should investigate biomarkers identified in Alzheimer's disease (AD) because PD and AD potentially share mechanisms of disease progression. For example, immune senescence and chronic inflammation occur in both AD and PD patients and potentially support disease progression. In addition, clinical trials for cancer therapeutics have historically been accelerated by investigations of biological mechanisms. However, mechanistic research in cancer is often less difficult than mechanistic research in PD; cancer research focuses on localized approaches to eliminating cells, while PD research must focus on improving knowledge of larger biological systems to prevent cell death.

Research communities studying diseases with similar pathophysiology to PD have recently formed repositories of large preclinical and clinical datasets and patient biospecimens. However, a central repository that contains collective study data from PD patients does not exist. To address this issue, the PD research community should develop a data sharing infrastructure beyond the requirements of NIH's Policy for Data Management and Sharing to maximize the value of patients' research participation. Developing data standards and annotations, as well as capitalizing on existing standards, can enable researchers to readily perform secondary analyses. In addition, developing a large searchable platform for all data repositories can enable cross-communication between data sharing efforts.