Advances in Therapeutics for Parkinson's Disease

Industry Roundtable

April 17, 2023

Virtual Meeting

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Executive Summary

On April 17, 2023, the National Institute of Neurological Disorders and Stroke (NINDS) held the first in a series of roundtable discussions aimed at identifying challenges and opportunities for Parkinson's disease (PD) target validation and therapeutics development. These roundtables will convene industry partners, nonprofit funders, academic researchers, and people with lived experience of PD, and the perspectives shared during these discussions will inform a workshop and white paper focused on barriers to preclinical development of PD therapeutics.

The first Advances in Therapeutics Development for PD roundtable was attended by industry partners and people with lived experience of PD. Topics highlighted by this stakeholder group included (1) the development of robust preclinical models and biomarkers that link to disease-modifying changes observable in clinical trials and (2) patient engagement at each stage of therapeutics research and development.

Challenges for Parkinson's Disease Therapeutics Development

Many pharmaceutical and biotechnology companies are interested in funding therapies for rare or monogenic diseases because they can guarantee major effect sizes for single target genes. By contrast, the heterogeneous pathology and clinical presentation of PD make it difficult to identify therapeutic targets for PD treatment. PD patients exhibit variable brain changes and both motor and nonmotor symptoms, and individual patients may experience a range of symptoms throughout the course of their day. Even after a target is identified, the extent to which it impacts a particular disease mechanism is difficult to assess. Furthermore, the extent to which the target *must* impact the disease mechanism in order for the therapy to be disease-modifying can only be determined after the therapy is tested in humans.

To validate therapeutic targets and determine the impact of preclinical findings on clinical outcomes, researchers must analyze large and heterogeneous patient datasets. However, rich datasets, such as those with matched antemortem cerebrospinal fluid (CSF) and postmortem brain samples, are often difficult to find and very expensive to purchase. Because neurodegenerative diseases exhibit mixed pathologies and exist on a spectrum, accessing sufficient patient samples is necessary in order to evaluate the variety of biomarkers that may be relevant to PD.

Efforts to progress therapies from preclinical to clinical development may also be hindered by lack of patient engagement throughout the research and development process. A drug designed to treat neurogenic orthostatic hypertension (nOH) was shut down during a Phase 3 trial after a significant proportion of patients showed no response to treatment. The trial included multisystem atrophy (MSA) patients and PD patients, whom investigators had assumed would respond similarly to the nOH treatment. However, post-hoc analyses revealed that only PD patients failed to respond to the treatment and MSA patients responded well. Had patients been surveyed early in the research and development process about their experiences and chief complaints, perhaps the investigators could have selected a more appropriate trial

patient population. Many potentially disease-modifying therapies may fail due to inappropriate target selection or patient stratification.

Areas for Improving Target Identification and Validation

Given the heterogeneity of PD, a graded approach to therapeutics development may be ideal. Instead of attempting to build an in vivo model capable of recapitulating every aspect of the disease, some pharmaceutical and biotechnology companies use cells to study disease mechanisms and then animals to examine the relationship between drug pharmacokinetics and pharmacodynamics. Similarly, some companies leverage in vitro phenotypic screens to identify small molecules that impact mechanisms of interest, such as those that lead to levodopa-associated dyskinesia. Afterwards, these companies test their drug in the context of disease using patient blood or CSF samples. Alternatively, another valuable graded approach may be working backwards from epidemiological studies to in vitro therapeutics development. For example, given that epidemiological studies associate smoking with decreased risk of PD, one pharmaceutical company is investigating whether an oral formulation of carbon monoxide, shown in non-PD Phase 1 and Phase 2 clinical trials to be safe and tolerable, could act as a neuroprotective agent in PD.

To efficiently validate therapeutic targets and identify biomarkers that correlate with both disease and brain pathophysiology, pre-competitive public partnerships and opportunities to access rich biorepositories of blood and CSF samples are extremely valuable. By offering a forum for pharmaceutical companies, biotechnology companies, and nonprofits to share expertise, pre-competitive public-private partnerships can facilitate the collaborative development of biomarkers for PD progression. Without sharing proprietary treatment effect data, by pre-competitively comparing biomarker changes in diseased versus control patient samples, companies can uncover the magnitude of an effect that therapeutics will need to exert in order to change the course of PD.

To facilitate the development of effective PD therapies, researchers should consider the variable clinical presentation of PD and focus on characterizing the genotypes and phenotypes of patients at different stages of disease. In addition to qualitative surveys of patient experiences, digital tools such as wearable technologies may help researchers capture a greater breadth of patient data than clinicians are able to record during standard patient encounters.