Efficacies and Pharmacodynamic Assays for LRRK2 Small-Molecule Inhibitors

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1

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Research Abstract
Summary "Efficacies and Pharmacodynamic Assays for LRRK2 Small-Molecule Inhibitors" PAR-15-071- Pharmacodynamics and In vivo Efficacy Studies for Small Molecules and Biologics/Biotechnology Products (R21/R33) Parkinson disease (PD) is a common neurodegenerative disorder pathologically characterized by dopaminergic neurodegeneration and the spread of ?-synuclein inclusions through much of the brain. More than 10 million individuals worldwide are expected to have PD by the year 2030, and currently there are no

accepted therapies that slow or halt the relentless progression of the disease. Dominant missense mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common known cause of PD, with up to 40 to 60 thousand carriers of the pathogenic G2019S-LRRK2 mutation in the United States. In model systems, the G2019S-LRRK2 mutation activates LRRK2 kinase activity. We and others have found that G2019S-LRRK2 expression exacerbates neurotoxicity and neuroinflammation associated with abnormal ?-synuclein, whereas knockout of LRRK2 expression protects from ?-synuclein. Recently, we demonstrated that pharmacological inhibition of LRRK2 kinase activity using a novel small molecule LRRK2 kinase inhibitor PF-475 provided substantial neuroprotection from ?-synuclein. In this research proposal we request support to study the effects of two structurally distinct but equally potent LRRK2 kinase inhibitors in three key areas necessary for the successful development of clinical candidate LRRK2 kinase inhibitors. First, we will create new pharmacodynamic assays to correlate kinase-inhibition profiles to phosphorylated WT and G2019S-LRRK2 levels in exosomes. Reliable target engagement assays for LRRK2 kinase inhibition are needed for the clinical development of LRRK2 kinase inhibitors in PD, and we hypothesize that our approach will allow monitoring LRRK2 kinase inhibition in the periphery and brain in a non-invasive manner. Second, we will define efficacious doses (EDs) for neuroprotection in complementary mouse models of ?- synuclein-induced neurodegeneration and aggregation. It may not be necessary to completely inhibit LRRK2 kinase activity to realize therapeutic effects, and we hypothesize that lower compound doses and incomplete LRRK2 kinase inhibition may increase therapeutic benefit by limiting undesirable effects. Third, we will vary the timing of compound administration to determine efficacies in blocking toxicities after ?-synuclein aggregation and neurodegeneration has initiated. We will utilize powerful models recently established including the ?-synuclein fibril model together with rAAV2- ?-synuclein, combined with a trio of validated congenic LRRK2 transgenics (WT-LRRK2, G2019S-LRRK2 and LRRK2-knockout [KO]). We predict that a better characterization of LRRK2 kinase inhibitor efficacy in both early and later-phases in ?-synuclein aggregation and neurodegeneration may predict the therapeutic benefits of LRRK2 kinase inhibitors in early versus established disease in clinical trials.

Further information available at:

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