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Spotlight

Targeting LRRK2 in Parkinson's disease

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Jennings et al.[1] reported that LRRK2 inhibitors can reduce kinase activity and improve lysosomal function with minor adverse effects in both animal models and human subjects. The findings provide proof of principle for LRRK2 inhibitor as a Parkinson's disease therapeutic option.

Parkinson's disease (PD) is characterized by loss of dopaminergic neurons in the substantia nigra and subsequent disruptions of the midbrain and cortical circuitry. Levodopa replacement has remained the cornerstone of PD therapeutics, but it is associated with several long-term adverse effects.[2]

Several monogenic forms of PD have been identified, and among the PD genes, leucine-rich repeat kinase 2 (*LRRK2*) attracts the most attention as a common recurrent G2019S mutation accounting for 2–7% of sporadic PD in Caucasians, and up to 40% of the cases of certain ethnicities such as Ashkenazi Jew and North African Arab.[3] Asian-specific *LRRK2* polymorphic risk variants (G2385R and R1628P) are associated with increased risk of sporadic PD.[4] Current evidence suggests that some mutations (e.g., G2019S) lead to increased kinase activity, and pharmacologic inhibition of kinase activity is able to reduce neurotoxicity in various cellular and animal PD models.[5] This provides the basis for developing drugs that target kinase activity of LRRK2.

LRRK2 inhibitors with distinct chemical structure and pharmacological properties have been developed, including a few highly potent and blood-brain-barrier-penetrating diaminopyrimidine small molecules, such as GNE-0877.[6] The safety profile of GNE-0877 in the nonhuman primate is excellent, though minor changes were seen in the lungs (cytoplasmic accumulation of lamellar bodies in type II pneumocytes). As these changes resemble those observed in the *LRRK2* knockout mice, the effect is likely due to loss of LRRK2 function instead of a toxic effect of the inhibitor.[7] In human studies, loss-of-function LRRK2 variants have been reported in healthy individuals.[8]

Jennings et al. recently conducted parallel clinical and preclinical studies using GNE-0877 (DNL201). They demonstrated that the drug reduces LRRK2 activity in human embryonic kidney (HEK) with 293 cells overexpressing LRRK2 G2019S, peripheral blood mononuclear cells (PBMCs), and brain tissues of cynomolgus macaques. DNL201 rescues lysosomal morphology in neuroglioma cells and lysosomal protein degradation in mouse astrocytes with endogenous expression of LRRK2 G2019S. LRRK2 inhibition was found to significantly increase kidney bis(monoacylglycerol) phosphate (BMP) concentrations and lower its concentrations in urine, suggesting that lysosomal function is regulated by LRRK2.[1]

In healthy subjects and patients with PD, the LRRK2 phosphorylation status and lysosome function were similarly regulated by DNL201, evidenced by a decrease in phosphorylation of LRRK2 substrates and a lower level of urine BMP. The long-term treatment of the compound was well tolerated in cynomolgus macaques. In the monkey treated with DNL201 for up to 16 mg/kg BID for 39 weeks, there was a slightly increased accumulation of lamellar bodies in type II pneumocytes and pigments in renal tubular epithelial cells, abnormalities which were fully reversible. In the phase 1 study involving healthy individuals and phase 1b study in the patients with mild to moderate PD, there were no major clinical adverse events. The investigators selected another LRRK2 inhibitor BIIB122 over DNL201 for further clinical studies due to its better pharmacokinetic profile.[1]

The findings from Jennings et al. provide important proof of principle that LRRK2 inhibitors are potentially effective and safe in both animal models and humans. However, there are still many unanswered questions that need to be further addressed. At present, the extent of kinase inhibition needed to have potential therapeutic effects remains to be elucidated. Using surrogate markers of LRRK2 activity in these studies may not fully capture the dynamic physiologic balance of the kinase activity in the neurons. "Authentic" substrates that mediate the pathogenesis of LRRK2-related PD *in vivo* have yet to be identified and validated. We also need to know if inhibition is useful for patients with normal LRRK2 kinase activity. Stratification of PD patients based on the level of basal kinase activity will be helpful to assess the therapeutic effects.

Currently, we do not have the evidence to select the most appropriate stage of PD patients that will benefit most from LRRK2 inhibition. Early-stage PD patients may not represent the early pathological brain changes, as PD is not clinically evident until 50–60% of dopaminergic neurons are lost in the substantia nigra,[9] and the surviving neurons may also have reached a point of inevitable progression. Hence, treatment with LRRK2 inhibitors may not be efficacious when the pathological cascade in PD has become irreversible. Future clinical trials should explore patients who are more likely to be associated with high kinase activity, such as carriers of risk variants/mutations or those in the prodromal stage. However, developing a reliable and validated means to measure *in vivo* kinase activity is another challenge.

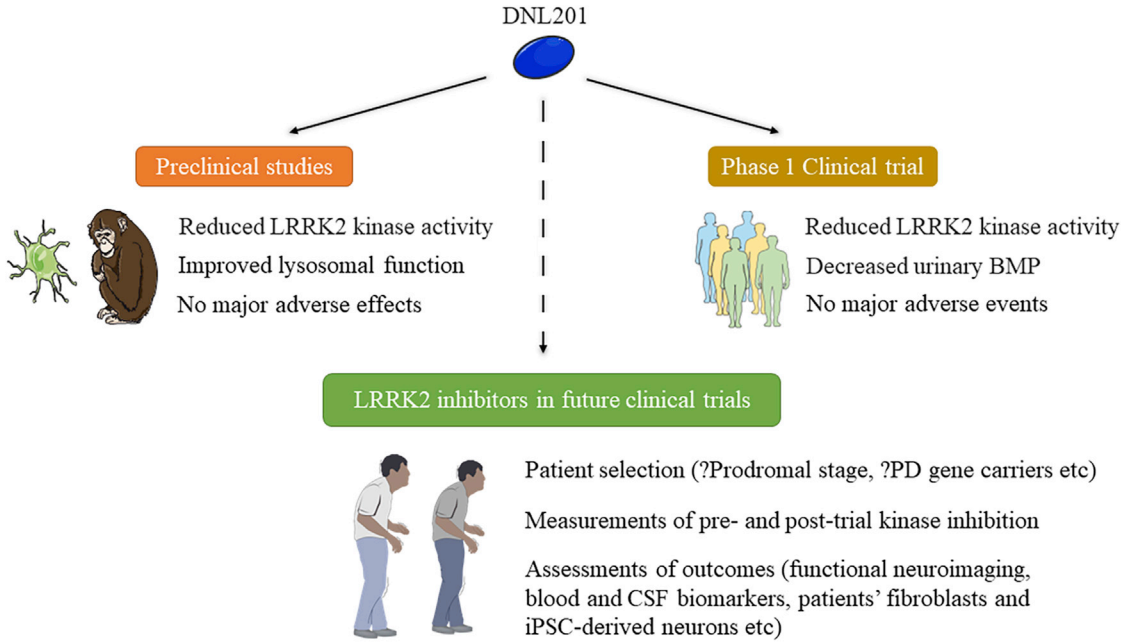

Figure 1. Success and perspective on LRRK2 inhibitor in the PD therapeutic development

DNL201 reduced LRRK2 kinase activity and improved lysosomal functions in cellular and animal Parkinson's disease models, healthy subjects, and PD patients with minimal adverse effects. Future clinical trials should explore patient selections based on LRRK2 functions. Reliable means of measuring *in vivo* kinase activity needs to be developed together with comprehensive assessment of clinical outcomes. CSF, cerebrospinal fluid; iPSC, induced pluripotent stem cell.
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In Jennings et al.'s study, lysosome function was evaluated using BMP to represent the pathophysiological changes. Even if BMP accurately indicates lysosomal function changes, it may not fully reflect the overall profile of PD-related pathological changes, as lysosomal dysfunction is only one of the cascades triggered by LRRK2 pathology, and it is unknown if lysosomal dysfunction lies upstream or downstream in the pathophysiologic pathways.[10] More comprehensive assessments using other biological, pathological, and electrophysiological markers may provide further corroborative evidence (Figure 1).

Despite these caveats and concerns, Jennings et al. have provided proof-of-concept evidence in animal models and in human studies that inhibiting LRRK2 can be a potentially viable therapeutic approach for PD.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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