TECHNOLOGY

Novel LRKK2 GTP-Binding Domain Inhibitors for Treatment of Parkinson's Disease and Neuroinflammatory Disorders

OVERVIEW

Parkinson’s disease (PD) is an age-related disorder affecting an estimated 1-1.5 million Americans. Current therapies are only able to alleviate PD symptoms and aberrant side effects from prolonged use (5-10yrs) of these drugs can parallel the severity of the disease itself. Researchers at the University of Maryland, Baltimore have rationally designed and synthesized novel compounds that may go beyond palliative care—potentially slowing or inhibiting disease progression. With an average age of 60 at time of diagnosis, new therapies that can prolong quality of life in PD patients without adverse side effects are greatly needed.

UMB Investigators have synthesized novel small molecules rationally designed using the scaffold of Compound #68 with the aim of being one of the first FDA-approved drugs to treat a major contributing factor for the development of Parkinson’s disease— neuroinflammation. Parkinson’s disease results from insufficient dopamine signaling in the regions of the midbrain that control motor function (*substantia nigra*). While many factors contribute to the development of PD, chronic inflammation leading to the degeneration of motor neurons is a significant etiologic and progression mechanism. Mutation of the leucine-rich repeat kinase 2 (LRRK2) enzyme is commonly associated with inflammatory disorders including PD and Crohn’s disease. Activation of microglia (resident immune cells in the brain) is an early indicator of neurodegenerative diseases and increased LRRK2 activity in these cells is requisite for a full inflammatory response. Therefore, modulation of LRRK2 activity could prove a useful strategy for the attenuation of inflammatory responses leading to the progression of neurodegeneration and PD symptoms. Currently available LRRK2 kinase domain inhibitors demonstrate poor specificity and blood brain barrier (BBB) permeability. The GTP-binding domain of LRRK2 has been shown to function as a “molecular switch” regulating the activity of the kinase domain and novel #68 derivatives targeting the GTP-binding domain have LRRK2 specificity and improved uptake in the brain compared to available kinase domain inhibitors. With at least 5 LRRK2 mutations known to be directly linked to PD, a novel #68 derivative may be the first compound to successfully delay or prevent the development and progression of Parkinson’s disease

APPLICATIONS

From 2002-2011, the global PD therapeutics market grew with a CAGR of 5.8% to nearly $3B annually and is currently estimated at $3.6B. Despite increased aging populations in developed countries including the US, Japan, Brazil and Germany, future growth is expected to be constrained due to genericization of key therapies. Therefore, as current patents expire, new PD therapeutics will need to demonstrate a significant improvement in patient outcome or disease management.

ADVANTAGES

Compound #68 and novel derivatives are the only identified inhibitors of LRRK2 GTP-binding activity.

Unlike currently described LRRK2 kinase domain inhibitors, #68 derivatives demonstrate LRRK2 specificity and BBB permeability.

LICENSING POTENTIAL

UM seeks to develop and commercialize by an exclusive or non-exclusive license agreement and/or sponsored research with a company active in the area.

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PATENT STATUS

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EXTERNAL RESOURCES

- A novel GTP-binding inhibitor, FX2149, attenuates LRRK2 toxicity in Parkinson's disease models.

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