Fbw7 as a therapeutic target for treating Parkinsons disease

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Country

USA

Title of project or programme

Fbw7 as a therapeutic target for treating Parkinsons disease

Source of funding information

NIH (NINDS)

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01/06/2014

Total duration of award in years

1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Parkinson Disease, therapeutic target, parkin gene, ,

Research Abstract

DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is characterized by a spectrum of motor disorders that is caused be progressive death of dopaminergic neurons in a midbrain region known as the substantia nigra pars compacta (SNpc). Although 60,000 new

cases of PD present in the US every year and an estimated 10 million people are living with the disease world-wide, there is no known effective treatment and the disease is invariably progressive. Although most PD is sporadic in nature, a significant cohort has been shown to be transmitted genetically. By investigating the genes and mutations that cause PD, it has been hoped that an understanding of the etiology and pathology of the disease at the molecular level will lead to effective therapies. In that vein, we have been engaged in research aimed at understanding the role of parkin, a ubiquitin ligase encoded by the most frequently mutated gene in recessive hereditary PD, PARK2. Our research has led to the conclusion that the neuroprotective effect of parkin is mediated, at least in part, by targeting the substrate binding adaptor of another ubiquitin ligase, SCFFbw7, for ubiquitin-mediated proteasomal degradation. We have also determined that the critical target of the SCFFbw7 ubiquitin ligase in this context is the pro-survival Bcl-2 family member Mcl-1, essential for neuronal survival. Using an in silico approach, we have identified small molecule inhibitors of SCFFbw7. All bind to Fbw7 and prevent it from forming productive interactions with Mcl-1 in primary neurons. Most importantly, these compounds protect primary neurons from various forms of stress-induced apoptosis at sub-nanomolar concentrations. Therefore, we are proposing to use one compound with good pharmacokinetic characteristics to determine whether Fbw7 is a valid therapeutic target in vivo using established mouse PD models. Should these experiments be successful, our ultimate goal is to arrive at Fbw7 inhibitors that have druglike characteristics so that they can be developed to the stage of entering human clinical trials.

Lay Summary
PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) is characterized by a spectrum of motor disorders that is caused by progressive death of dopaminergic neurons in a midbrain region known as the substantia nigra pars compacta (SNpc). Although 60,000 new cases of PD present in the US every year and an estimated 10 million people are living with the disease world-wide, there is no known effective treatment and the disease is invariably progressive. This proposal seeks to test promising small molecule compounds in a mouse PD model in the hope of developing effective PD therapies.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Parkinson's disease & PD-related disorders

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