Small molecule Parkin activators to treat Alzheimers Disease

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USA

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) affects an estimated 21-35 million people worldwide; this number is predicted to double in the next decade. AD results from the degeneration and death of neurons in the hippocampus and the entorhinal cortex regions of the brain, areas that are critical for learning and memory. Patients in end stage AD lose the ability to perform basic bodily functions such as walking and swallowing and require round-the-clock care. Ultimately fatal with no cure available, AD is the sixth-leading cause of death in the

United States. Current therapeutics, which provide temporary, symptomatic relief only in patients with early stage AD, have serious side effects, and cannot prevent neuronal death and disease progression. Thus, it is necessary to identify novel therapeutics that can actually halt the progression of AD. Microscopic evidence has associated mitochondrial damage and the appearance of autophagic vacuoles with the onset of AD. Moreover, evidence suggests that mitophagy, a regulatory form of autophagic degradation which is mediated by the kinase PINK1 and the ubiquitin E3 ligase Parkin and which normally eliminates dysfunctional mitochondria, is overwhelmed and becomes inadequate to prevent accumulation of damaged mitochondria in AD-affected neurons. These results support the notion that activation of Parkin, the key element of mitophagy, is a promising therapeutic avenue that will act by enhancing compromised mitophagy in AD patients. Overexpression of Parkin in the AD mouse model APPswe/PSEN1?E9 ameliorates AD-related symptoms and restores mitochondrial integrity. Parkin exists in an auto-inhibited ‘off’ state in the cytosol via multiple intramolecular interactins; genetic disruption of these interactions stimulates Parkin activity and promotes its translocation to dysfunctional mitochondria. The goal of the present project is to mimic this effect with small molecules that activate Parkin by relieving Parkin auto- inhibition, thereby promoting mitophagy. Such activators are expected to prevent the mitophagy deficiency- induced neuronal death and consequently to hinder the progression of AD. A TR-FRET based homogeneous E3 assay will be utilized to conduct high throughput screening (HTS) of a diversity based and targeted small molecule library to identify potent and selective activators of Parkin. Subsequently, cellular proo of concept assays will be performed to measure the impact of the small molecule agonists on Parkin activation and mitophagy improvement. In Phase II, preclinical development will be pursued employing chemical optimization and efficacy/ADME studies using relevant animal models. The ultimate commercial goal is the development of a novel small molecule agonist that can be used to stop the progress of AD.

Further information available at:

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