High Throughput Screening to Discover Chemical Probes and Pharmacological Agents for Modulating Parkin Activity

https://www.neurodegenerationresearch.eu/survey/high-throughput-screening-to-discover-chemical-probes-and-pharmacological-agents-for-modulating-parkin-activity/

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Country

USA

Title of project or programme

High Throughput Screening to Discover Chemical Probes and Pharmacological Agents for Modulating Parkin Activity

Source of funding information

NIH (NINDS)

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01/08/2015

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2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

parkin gene, , , ,

Research Abstract

? DESCRIPTION (provided by applicant): Many neurodegenerative diseases are known to be associated with inappropriate protein aggregation. In Parkinson’s disease (PD), formation of protein aggregates in motor neurons is a hallmark of the disease. Both genetic and environmental factors have been associated with an increased risk of PD. Several susceptible genes, including alpha-Synuclein, Parkin, PINK1, LRRK2, DJ in familial PD have been identified. Mutations in Parkin are responsible for an early- onset autosomal recessive form (autosomal recessive juvenile parkinsonism; AR-JP) of PD and account for 50% all recessively transmitted early-onset PD cases. Parkin protein is a ubiquitin E3 ligase and has been shown to catalyze polyubiquitination of a variety of substrates. Parkin appears to be an integral component of cellular defense systems against misfolded proteins and damaged mitochondria. Perturbation of the Parkin activity by environmental factors or genetic mutations is the compelling mechanism for a subset of Parkinson’s disease. We hypothesized that systematic identification of small molecule probes that modulate the molecular pathways that control Parkin mitochondrial localization will help to unravel the type of environmental factors that may be associated with the development of Parkinson’s disease. In addition, availability of such specific tool compounds can help to clarify the roles of Parkin mitochondrial recruitment and mitophagy in the onset and progression of PD in model systems. We further hypothesized that identification of small-molecule inhibitors that can prevent mutant Parkin aggregation may yield nove chemical probes for the pathways that regulates Parkin aggregation and may offer new therapeutic strategies for Parkinson’s disease. Currently there are no specific pharmacological agents that can block wild type Parkin recruitment to mitochondria upon depolarization, neither are specific inhibitors that can block aggregation of Parkin mutants in cells. The overall goal of this application is to develop a set of chemical probes to permit development of the chemical genetics approaches to dissect the function of PINK1 and Parkin in Parkinson’s disease. Specificity and counter screening assays will be implemented to eliminate non-specific compounds. Deconvolution assays will be developed to allow determination of the molecular targets of the chemical probes discovered in related HTS cell based assays.

Lay Summary

PUBLIC HEALTH RELEVANCE: The overall goal of this application is to develop a set of chemical probes to permit development of the chemical genetics approaches to dissect the function of PINK1 and Parkin in Parkinson’s disease.

Further information available at:

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Investments > €500k

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United States of America

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