Therapeutic Potential of Small Molecule Activators of the PINK1-Parkin Pathway

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Research Abstract

DESCRIPTION (provided by applicant): Mitochondrial DNA mutations cause a number of severe childhood-onset mitochondrial syndromes, and mitochondrial dysfunction is associated with common age-related diseases such as diabetes, Alzheimer’s disease and Parkinson’s disease. However, there are currently no curative treatments for any of these diseases. One promising avenue of therapy for mitochondrial diseases involves the use of chemical agents that can activate a cellular quality control pathway that is capable of selectively eliminating

dysfunctional mitochondria. Recent work indicates that the PTEN-induced kinase 1 (PINK1) and the E3 ubiquitin ligase Parkin function in such a pathway. Moreover, our preliminary studies demonstrate that overexpression of PINK1 and Parkin in the fruit fly Drosophila melanogaster rescues fly models of mitochondrial disease, thus validating the therapeutic potential of this pathway. The goal of our proposal is to test whether PINK1-Parkin pathway activating compounds identified from high-throughput cell culture-based screens can also rescue fly models of mitochondrial disease. To achieve this goal, we propose two aims. First, we propose to test whether PINK1-Parkin pathway activating compounds identified from cell culture-based screens can rescue an easily assayed phenotype associated with our Drosophila models of mitochondrial disease. Second, we will test whether the most promising compounds identified in our first aim act in a PINK1 and Parkin-dependent fashion, and whether these compounds can rescue other phenotypes of our mitochondrial disease models. Our work will potentially identify compounds that can be used to treat a wide variety of human diseases.

Further information available at:

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