Parkinson’s disease is the second most common neurodegenerative disease and it is marked by motor symptoms; rigidity, bradykinesia, postural instability, and tremor [1]. Parkinson’s disease eventually leads to death. Parkinson’s disease is marked by the progressive loss of dopaminergic neurons in the substantia nigra in the brain, but the exact etiology of the disease is unknown. Mitochondrial dysfunction is strongly linked to early-onset autosomal recessive Parkinson’s disease [2]. Dysfunctional mitochondria in normal cells are selectively degraded through mitophagy. The genes PINK1 and Parkin are involved in the signaling of mitophagy. Mutations in PINK1 can disrupt normal mitophagy in cells, which leads to the accumulation of dysfunctional mitochondria, causing cell death. This is believed to be one of the causes for dopaminergic neuronal cell death in Parkinson’s disease. It has been discovered that decreased PINK1 expression is linked to higher dopaminergic cell death, but there are no known allosteric regulatory sites for PINK1, so experimental regulation of PINK1 expression is difficult. [3]. It **is unknown** if gene therapies using wildtype PINK1 could rescue lower mutant PINK1 expression.

My **primary goal** is to determine if gene therapy (using Herpes Simplex Virus?) using functional PINK1 and an allosteric regulatory site could rescue lower mutant PINK1 expression and decrease dopaminergic cell death.

My **hypothesis** is that originally PINK1 deficient organisms can be treated with an infectious vector carrying functional PINK1 which will result in biologically significant increases in cellular PINK1 activity, which will result in higher mitophagy and lower dopaminergic cell death. My **long-term** goal is to evaluate the effectiveness of vector gene therapy as a treatment for dopaminergic cell death in early-onset Parkinson’s disease caused by mutations in PINK1.

Model organism: C. elegans, (zebrafish)

Aim 1:

Aim 2:

Aim 3:

References:

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[3] Hertz, N. T., Berthet, A., Sos, M. L., Thorn, K. S., Burlingame, A. L., Nakamura, K., & Shokat, K. M. (2013). A neo-substrate that amplifies catalytic activity of parkinson's-disease-related kinase PINK1. *Cell*, *154*(4), 737-47.