Ameliorating Alpha-Synuclein Aggregation in Parkinson's Using Optimized Chaperones: An in silico Approach

Pate, Jeremiah

The aggregation of misfolded alpha-synuclein protein is a key feature of Parkinson's Disease which afflicts over 53 million globally. There is no cure and the current treatment, Levodopa, has changed little in the 50 years since introduced. Chaperone proteins represent the cell's own response to misfolded proteins. This project intended to identify and tailor chaperone modifications to target misfolded alpha-synuclein. My integrative research introduced a novel in silico approach to indicate potentiated small heat shock protein/chaperone variants that have the ability for therapeutic refolding of pathogenic alpha-synuclein. The genetic optimization used within this in silico approach data-mined publicly available protein sequence databases to identify helpful mutations. With the aid of this data-driven metaheuristic approach, the algorithm enabled computer-assisted drug discovery and development of chaperone-centric and protein-based therapeutics. As a proof-of-concept, the identified high-performance chaperones were biomanufactured in transformed E. coli Dh5-alpha competent cell cultures, and tested with in vitro methods to confirm therapeutic protein refolding. A novel integrated and translational in vivo assay was designed using transgenic Drosophila expressing the A53T and A30P synuclein mutation. The assay was shown to have a statistically significant larval turning phenotype ($p<.05$). The chaperone modification strategy was tested in vivo; both upregulated chaperones and small molecular enhancers demonstrated rescue from Parkinson's phenotype. As affirmed by the novel in vivo and in vitro assays, this integrated approach of in silico protein-based therapeutic development results in a promising avenues for Parkinson's therapies and a manner to arrest the progression of the disease.

Awards Won:

University of Arizona: Tuition Scholarship Award

Intel ISEF Best of Category Award of $5,000