Tackling Tau: Identifying a Novel Inhibitor for the MSUT-2 Protein based on Quantum Machine Learning for the Identification of Treatments of Neurodegenerative Diseases

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Progressive neurodegenerative disorders that are defined when a protein, called tau, builds up abnormally in a patient's brain are called tauopathies. Breakthrough research has led to the identification of MSUT-2 as a promising target for the treatment of tauopathies, as it has been linked to the enhancement of neuronal dysfunction, neuronal death, and the aggregation of tau in the brain. The focus of this research was to utilize a multi-phase computational screening approach to identify promising inhibitors of the understudied MSUT-2 target. A chemical data set (ChemBridge EXPRESS-PICK Library) was initially filtered against known drug-like metrics, eliminating approximately 30,000 compounds from the initial set. A structure-based pharmacophore similarity screen was performed, using a validated Query (trained with a starting set of partial actives and inactives) with a high AUC value of 0.98. This screen resulted in 183 compounds with favorable structural characteristics based on past experimental data. A Quantum Support Vector Machine algorithm (implemented through IBM's Qiskit framework) was then used as a binary classifier to identify drug-like compounds based on analysis of clinical data. The resulting 142 top compounds from these predictions were then subject to molecular docking with the OpenEye FRED and AUTODOCK VINA tools for an aggregate binding energy interaction score with MSUT-2. These results were then used to determine the top five overall compounds, two of which were validated in preliminary in vivo experiments with C. elegans with overexpression of neuronal tau. Not only could these two compounds serve as treatments for certain neurodegenerative disorders, but this powerful research framework can be applied to understudied disease targets efficiently.

Awards Won:

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