

Experimental Characterization of Inhibitors of the MSUT-2 Protein for the Treatment of Neurodegenerative Diseases (Year 2)

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Tauopathies are a group of progressive disorders that are characterized when a protein, called tau, builds up significantly in an individual's brain. New breakthrough research has demonstrated that tau-enabling proteins, like the MSUT-2 protein, could be linked to tau aggregation. A successful inhibitor of the MSUT-2 could serve as a disease-modifying treatment with therapeutic value for patients. In Year 1 of this research, five potential small-molecule inhibitors for the MSUT-2 protein were identified using a robust computational methodology incorporating quantum computing, molecular docking, and virtual screening. In Year 2, a myriad of tests was performed to validate the activity of top hits from Year 1. A molecular dynamics simulation modeled the stability of each of the top five compounds in complex with MSUT-2 based on RMSD fluctuation values, an important mechanistic consideration for drug development. A series of motion evaluations, mechanosensation assays, and behavioral assessments were then performed with CL2319 *C. elegans* (microscopic worms modified to overexpress neuronal tau). One of the compounds, named R128, was found to improve the health and behavior of tau mutant worms across experimental assessments. R128 was then subject to interaction analysis with MSUT-2 and QSAR-based quantitative bioactivity profiling. The DeepFrag tool was then utilized for fragment-based optimization of R128 based on an AI-based approach. Using the Year 1 pipeline, twenty originally optimized compounds from DeepFrag were narrowed to nine derivatives found to retain R128's druglikeness profile yet have improved binding affinities to MSUT-2. Retrosynthetic routes have been identified for these nine derivatives and preclinical testing and development is currently underway.

Awards Won:

Second Award of \$2,000

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