ALS-SynAegis: A Molecular Dynamics Study on TDP-43 Aggregation to Prevent Amyotrophic Lateral Sclerosis Onset

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Amyotrophic Lateral Sclerosis is a devastating neurodegenerative disease characterized by progressive muscle atrophy, leading to an inability to move the limbs and, in extreme cases, being unable to breathe. Current predictions show that global ALS cases will rise 69% by 2040. Prior literature has shown that the aggregation of a neuroprotein, TDP-43, leads to the onset of ALS, but the specific aggregation patterns of TDP-43 are unknown. Thus, there is limited research on the design of an inhibitor molecule targeting TDP-43. The only FDA-approved drug targeting TDP-43 aggregates, Riluzole, causes an increase in survival time of 3 months, which, in the context of ALS, is a very short time. This study utilizes Molecular Dynamics Simulations to model TDP-43 aggregation in understanding its aggregation patterns, such as contacting residues, hydrogen bonding points, and β-sheet direction. Then, Molecular Docking Analysis is used to test 5 existing inhibitors, narrowed from a set of 100, on the discovered target site. Then, the best structural and functional groups were used to design ALS-SynAegis, a new and improved TDP-43 inhibitor. This study identified 312-NFGAF-316 as a novel target site for TDP-43 aggregates. Furthermore, the docking analysis showed ALS-SynAegis outperformed current inhibitors: binding affinity increased by an average of 45.6%, cytotoxicity decreased by 44% from the FDA-approved drug Riluzole, and there are no Molecular Toxicophores in ALS-SynAegis compared to the 1 present in Riluzole. The proposed inhibitor can have a widespread effect on the pathological progression of ALS and impact the broad field of TDP-43 aggregate inhibition.