In silico High Throughput Identification of Novel Alpha-Synuclein Aggregation Inhibitors for Parkinson's Disease Treatments

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Parkinson’s Disease (PD), the second most common neurodegenerative disease, is caused by the depletion of dopamine as a result of toxic aggregates formed by a protein called alpha-synuclein (a-syn). These aggregates kill dopamine neurons in the substantia nigra pars compacta brain region. PD currently has only some symptomatic treatments that lose effectiveness over time. The purpose of this study was to identify drugs that bind to the non-amyloid beta component (NAC) domain of neuronal membrane bound a-syn. This will inhibit other a-syn monomers from binding to the protein and prevent further aggregation, slowing the progression of PD. Molecular docking was used to run a high throughput screening of 646 FDA approved drugs. The interactions between each drug and a-syn were analyzed and compared to those of Baicalein and SynuClean-D, two drugs that can inhibit a-syn aggregation by binding with the NAC domain but are not FDA approved. 13 drugs were identified that can potentially be used to inhibit membrane bound aggregation of a-syn and were almost 6 times more potent than Baicalein and almost 10 times more potent than SynuClean-D at binding with a-syn’s NAC domain. The Blood Brain Barrier (BBB) penetrability of these top 13 drugs was assessed, indicating the drugs with a higher likelihood of penetrating the BBB and reaching the brain. The results of this study show Telmisartan and Ibrutinib as FDA approved, BBB penetrable drugs that can inhibit membrane bound a-syn aggregation to slow the progression of PD. Verifying the results of this study through in vitro and in vivo experiments can result in the identification of a promising treatment for PD.

Awards Won:
Third Award of $1,000