Frankenstein-Synuclein: Rapid, Structure-Informed in silico Generation of de novo Replacement Protein Variants Using Benign Homologs for Parkinson's Disease Prevention

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Parkinson's disease (PD) affects over 10 million people globally. It is driven by the intrinsically disordered (IDP) protein a-synuclein (asyn). While asyn's flexibility is functional, it enables coagulation of misfolded conformations into toxic oligomers, causing cell death in dopaminergic neurons. Current treatments fail to target asyn without disrupting function. This project aims to computationally redesign asyn to preserve function while minimizing aggregation. A computational framework was developed to generate novel protein variants using stabilizing features from homolog b-synuclein. Stable conformational ensembles of a/bsyn guide design of 100 candidate chimeric sequences each loop, which are evaluated using a custom deep graph neural network for pathological property prediction. The best candidate undergoes validation via molecular dynamics for membrane/VAMP2 binding and monte carlo simulations for aggregation. Over three trials, generated variants reduced aggregation mass fraction from 80% to 30% while functional binding free energies remained around -30 kJ/mol and -17 kJ/mol for the membrane and VAMP2. Simulations revealed that the variants inhibited aggregation past specific mass fraction thresholds. DGNN predictions indicated reductions in toxicity, aggregation propensity, insolubility, and phase-separation propensities, with model accuracies over 77% generally and 95% for an IDP dataset. This demonstrate that protein function can be decoupled from toxicity, enabling two novel strategies: protein-delivery drugs to suppress aggregates in patients and preventative gene therapy for at-risk individuals. These represent some of the first ever proposed molecular interventions for PD. This framework can also be broadly applied to other neurological disorders.

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