

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 α -synuclein (α syn). While α syn's flexibility is functional, it enables coagulation of misfolded conformations into toxic oligomers, causing cell death in dopaminergic neurons. Current treatments fail to target α syn without disrupting function. This project aims to computationally redesign α syn to preserve function while minimizing aggregation. A computational framework was developed to generate novel protein variants using stabilizing features from homolog β -synuclein. Stable conformational ensembles of α /b-syn 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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