Designing Enhanced DNAJB6 Variants: A New Approach to Prevent Alzheimer's Disease by Inhibiting Amyloid-beta 42 Clumping

Reyes-Nieves, Amanda (School: CROEM HS)

With 50 million people suffering globally, Alzheimer’s Disease stands as one of the most devastating neurodegenerative disorders, yet no cure or preventative therapy exists (Yang et al., 2023). Fortunately, chaperone protein DNAJB6 helps prevent amyloid-beta 42 accumulation, a key contributor to Alzheimer’s (Österlund et al., 2020). However, DNAJB6 has a limited lifespan, reducing its efficiency. This investigation hypothesized that modifying unstable regions in the protein’s sequence would increase its lifespan. To test this, the 25 most unstable amino acids in DNAJB6 were pinpointed through an atomic fluctuation analysis. Then they were modified using DynaMut, which applies five different testing models to accurately predict mutations, generating 475 possible combinations. Finally, changes in stability were determined by Gibbs free energy (??G) and vibrational entropy. Molecular dynamic simulations revealed that mutation A143V had the most promising results, with a ??G of 1.117 kcal/mol that suggests an overall increase in protein stability of 7-22%. This can greatly impact resistance to unfolding. Moreover, molecular docking results showed the mutant’s HADDOCK score (-4.4 +/- 14.1) was similar to the native protein (-4.1 +/- 17.3), indicating the mutation, not only retained function, but also exhibited a slight increase in binding affinity, meaning the chaperone can now interact better with amyloids. Future work should prioritize testing in vivo, subsequently moving to disease models. By designing functional DNAJB6 variants with enhanced stability, this investigation is a stepping stone to fortifying the brain’s natural defenses against Alzheimer’s, shifting the fight from treating symptoms to molecular intervention.

Awards Won: