Targeting Amyloid-β Plaques: In silico Protein Modeling of Novel Antibody for Halting Alzheimer's Disease Progression

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Alzheimer's Disease is a neurodegenerative disease in which pathological Amyloid-Beta plaques of 40 amino acids (AB40) aggregate as insoluble fibrils around cells in the neocortex. It is the most common cause of dementia, affecting 50 million worldwide. Transmembrane Amyloid Peptide Protein (APP) produces physiological Amyloid-B proteins of 42 amino acids (AB42). A missense mutation (Val717 to Ile717) in APP produces hydrophobic AB40 proteins, forming insoluble deposits. These deposits consist of a Phe residue core with Val tails. Monoclonal antibody treatments including Lecanemab use Val residues in their light chain to form soluble complexes with Phe residues in AB40. However, the binding efficacy of modern treatments declines linearly, inefficient at physiological concentrations of AB40 in Alzheimer's patients. Using protein modeling and molecular dynamics simulations with BLAST databases and SWISS-MODEL software, I designed a novel in silico antibody. The antibody uses Phe residues in its light chain, binding to AB40's Val tails. Analysis of antibody and antibody-antigen complex structures shows lowered hydrophobicity indices, increased solvent accessible area, and decreased beta sheets shown by Ramachandran plots. Previous data of marketed antibodies' binding efficacies shows a significant increase ($p < 0.01$) in the binding efficacy of our antibody and designed antibodies. Additionally, simulated blood-brain diffusion and thermodynamic equilibrium show a significant reduction ($p < 0.05$) in Ala-Gly binding rates of the designed drug on AB42, indicating selective binding to AB40. This research holds promise for advancing therapeutic interventions for Alzheimer's disease through inhibition of plaque formation and Alzheimer's progression and should be further explored.