OncoBind: A Personalized Computational Pipeline Integrating Quantum Mechanics/Molecular Mechanics for Discovering Mutation-Specific Antibodies in HER2-Driven Cancers

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HER2 is associated with cancer progression in breast and gastric cancer, and, while HER2-targeted antibody therapy has improved responsiveness, approximately half of patients with HER2-positive cancer experience a relapse· Mutations in HER2 extracellular (EC) domain sequences, leading to remapping of its epitopes, are dominant mechanisms of treatment resistance· Additionally, increased expression of programmed death ligand-1 (PD-L1) offers tumor escape from destruction by the immune system· I present OncoBind, a computational pipeline for identifying mutation-specific antibody fragments targeting HER2 variants and assessing therapeutic potential for combination with PD-L1 inhibition· Structural bioinformatics of HER2 mutations defined the altered surfaces· LLM-Generated designs of the initial antibody candidates trained on the surface alterations produced candidate antibody sequences optimized to bind the altered surfaces· Candidates are identified by docking, predicting the structure of the complex, assessing developability, simulating molecular dynamics, and determining the Binding Free Energy and then refined in a custom designed quantum mechanics/molecular mechanics (QM/MM) framework· In silico modeling of the effect of HER2 and PD-L1 blockade, as monotherapy or in combination, on tumor growth, immune-mediated cytotoxicity, and signaling through cellular oncogenes in HER2-mutant cancers indicated that targeting both HER2 and PD-L1 would produce greater changes in tumor growth, immune-mediated cytotoxicity, and oncogenic signaling, than inhibition of HER2 alone· The results indicate that combining computational antibody design with multiscale simulation could ease the development of personalized therapies for HER2-mutant cancers·

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