De novo Design of Broadly Neutralizing Antibodies for Rapidly Evolving Pathogens

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The rapid evolution of pathogens such as SARS-CoV-2 and influenza has consistently outpaced traditional monoclonal antibody discovery. Frequent mutations in key antigenic regions enable immune escape, reducing the long-term efficacy of therapeutic antibodies and necessitating a shift towards predictive drug design. Current antibody engineering approaches primarily focus on binding to a single, static antigen structure, limiting the antibody's effectiveness against emerging antigen variants. This project presents a computational framework for designing novel, broadly neutralizing antibodies that remain effective against diverse, mutated variants of a rapidly evolving pathogen. A deep-learning transformer was constructed to generate new antibody complementarity-determining region (CDR) sequences, specifically H3 and L3, to bind to a target antigen epitope. To model antigen evolution, mutations were introduced in the antigen's epitope regions. A molecular interaction-based scoring algorithm was developed to assess predicted antibody binding affinity to the target epitope. Antibody candidates were iteratively refined using a genetic algorithm to maximize predicted binding affinity across mutated variants. Top-performing antibody candidates were validated using ESMFold for 3D structural prediction and DiffDock for molecular docking verification. Results indicated that generated antibodies achieved significantly higher average binding affinity and greater binding consistency across a broader range of mutations compared to traditional monoclonal antibodies, while also demonstrating high target specificity. This computational antibody engineering method offers a scalable framework for real-time pandemic response and the development of broad-spectrum immunotherapies.

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