GlueForge: A Generalizable Pipeline for Molecular Glue Discovery via Multi-Stage Screening and Geometry-Aware Ternary Learning, Demonstrated at the FBW7–MYC Interface

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Despite decades of therapeutic development, most disease-associated proteins remain therapeutically inaccessible. These so-called “undruggable” targets typically lack suitable binding pockets, preventing the application of traditional small-molecule inhibition methods. Molecular glue degraders (MGDs) offer a promising alternative by stabilizing interactions between an E3 ligase and a target protein to promote ubiquitin-mediated degradation, but rational discovery of MGDs remains difficult. This study introduces GlueForge, a computational molecular-glue discovery pipeline that integrates large-scale interface docking, pose stability filtering, diversity selection, and geometry-aware deep learning to prioritize glue-like ternary stabilizers. GlueForge was applied to identify candidate molecular glues that stabilize the interaction between the E3 ligase FBW7 and MYC, an oncogenic transcription factor deregulated in over 50% of human cancers. First, around 2 million ChEMBL compounds were screened with fast docking. Next, a diverse set of around 50,000 ligands with high predicted binding affinity was advanced to a rigorous docking stage. To move beyond docking scores, I then applied DeepGLUE, an SE(3)-equivariant graph neural network trained on ternary complex structures, to score FBW7–ligand–MYC geometry. DeepGLUE enriched interface-bridging poses by 5× in the top-ranked set compared with just docking alone. Final candidates were further prioritized using ensemble docking and ternary complex stability simulations, yielding a final shortlist of 10 high-confidence molecular glue candidates. By enriching for interface-bridging, ternary-stable candidates, GlueForge can accelerate early-stage discovery of molecular glues for oncogenic, hard-to-drug targets such as MYC.

Awards Won:

Third Award of $1,200