Designing and Delivering Molecular Glue Degraders for the Total Elimination of Previously Undruggable Pathogenic Proteins

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The human proteome comprises ~20,000 unique proteins, yet only 3,000 are theoretically druggable given current therapeutic methods. Molecular glues (MGs) are therapeutics that eliminate pathogenic proteins via the proteasome without direct binding, which allows them to target the undruggable proteome. However, this unique mechanism complicates their rational design and delivery. To solve this, we developed LatentGlue, a 635M-parameter model, to learn general representations of MGs through self-supervised mask-based reconstruction using ESM-C and MoLFormer latents. Leveraging over 3 billion biomolecular sequences, LatentGlue demonstrates improvements over baselines of 21.7% (RMSE) and 40.6% (Spearman Correlation) for activity prediction averaged over three seeds with extremely localized attention. After screening 104M molecules against two major disease targets, a-Synuclein (Parkinson's) and KRAS G12D (three cancers), we identified novel MGs which we named Ceruclein and Vylodax. Ceruclein is predicted to recruit CRBN via its diazepinone ring, while Vylodax is predicted to recruit VHL by interacting with its positively charged binding site to target KRAS G12D. For clinical translation, we developed pH-responsive and biocompatible calcium-alginate microparticles (MPs) for oral delivery of MGs. Demonstrating pH-responsivity, chitosan-coated MPs remained intact in simulated gastric fluid (pH 1.2) and selectively released payload in simulated intestinal fluid (pH 6.8). We then treated major bacterial strains (E. coli and Lactobacillus) with MPs and observed no loss in colony-forming units, confirming biocompatibility with prevalent strains in the gut microbiome. For future work and reproducibility, we released all data, all code, and model weights.

Awards Won:
Second Award of $2,400