A206 · AI/ML-enabled screening of FDA-approved drugs against neglected tropic disease targets

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Neglected tropical diseases (NTDs) disproportionately affect populations in low-income regions, where limited funding and infrastructure have constrained traditional drug discovery and slowed the development of effective therapies. While conventional treatments are often outdated, toxic, or non-existent for many NTDs, drug repurposing has recently emerged as a promising alternative, as illustrated by fexinidazole for sleeping sickness. Advances in AI and machine learning (ML), particularly recent progress in foundation and other deep learning models for structural biology, are creating scalable and cost-efficient opportunities, offering a powerful alternative to the conventional drug design. Here, we developed a high-throughput deep learning pipeline to characterize druggable protein targets across a broad range of NTDs and FDA-approved drugs that may be repurposed against them. The pipeline builds on a recently published graph neural network (GNN) and long-short-term memory (LSTM) architecture for predicting protein-ligand binding affinity, combined with two foundation models for structural biology: AlphaFold 3 (AF3) for modeling target protein structures and Chai-1 for modeling protein-ligand complexes. Specifically, we trained two independent GNN-LSTM models on the gold-standard protein-ligand binding affinity experimental datasets, Davis and KIBA, using contact maps derived from AF3 models to represent proteins, and SMILES strings to represent ligands. The newly trained Davis-AF3 and KIBA-AF3 models were used to predict binding affinities of 8.4 million putative protein-drug pairs between 2,939 NTD protein targets and 2,854 FDA-approved drugs or bioactive compounds. We applied a conservative target-selection criterion and restricted the analysis to the DG5 druggability class of NTD targets from the Tropical Disease Research Targets database.