Case Study: ABL1

Hit discovery
Date: 12.27 2022

Hit identification for targeting ABL Tyrosine Kinase 1

We utilized well-established AI program, DeepMatcher-Hit v1.8, to identify the best pose for targeting ABL1. Our approach involved conducting 2D/3D virtual screening, docking, and molecular dynamic simulations using a fully automated activity on a pool of one billion chemicals library. As a result, we identified 116 AI Hits, which comprise newly discovered small molecules and five TKI FDA-approved drugs(Dasatinib, Forentinib, Osimertinib, Bosutinib, and Ponatinib). Fig. 1 accurately displays the predicted 3D structure of the interaction between ABL1 and Osimertinib. Through binding energy-based association analysis and clustering, we classified these compounds into seven distinct groups (see Fig. 2). Our well-trained platform can explore the best drug-like compounds by utilizing a large-scale chemical library of over one billion compounds.

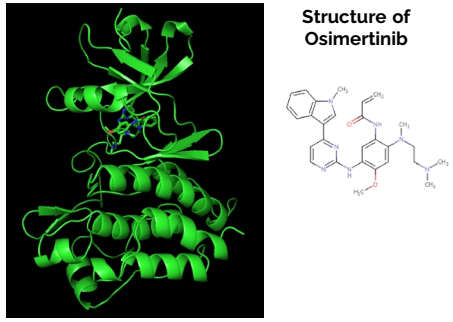


Fig.1 Predicted 3D structure of ABL1 with Osimertinib ABL1-Osimertinib, 3D structure with binding conformations of protein–ligand interactions were derived from DeepMatcher-Hit v1.8

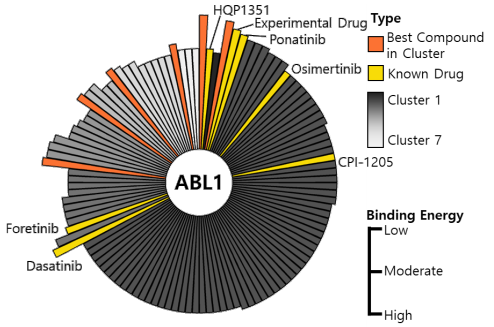


Fig.2 AI-detected compounds grouped by cluster with binding energy bars. Dark colors show clusters, orange/yellow indicate high binding energy for cluster/drug.

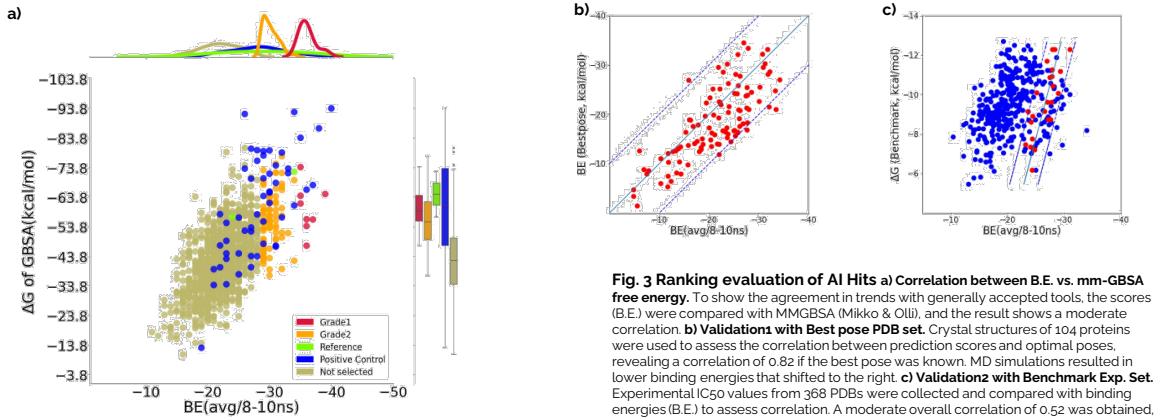
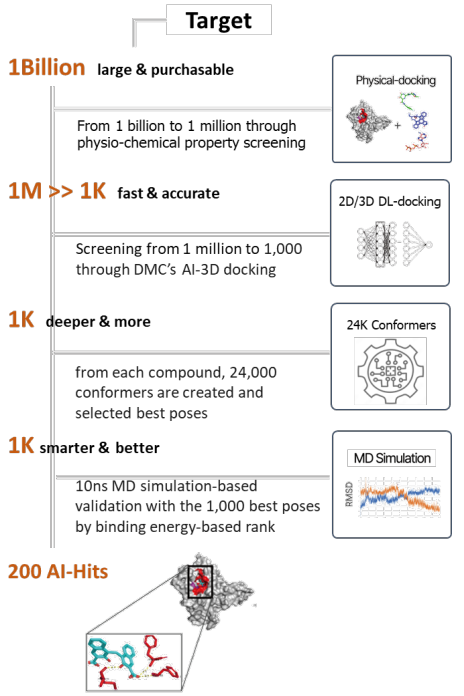


Fig. 3 Ranking evaluation of AI Hits **a) Correlation between B.E. vs. mm-GBSA free energy.** To show the agreement in trends with generally accepted tools, the scores (B.E.) were compared with MMGBSA (Mikko & Olli), and the result shows a moderate correlation. **b) Validation1 with Best pose PDB set.** Crystal structures of 104 proteins were used to assess the correlation between prediction scores and optimal poses, revealing a correlation of 0.82 if the best pose was known. MD simulations resulted in lower binding energies that shifted to the right. **c) Validation2 with Benchmark Exp. Set.** Experimental IC50 values from 368 PDBs were collected and compared with binding energies (B.E.) to assess correlation. A moderate overall correlation of 0.52 was obtained, with c-MET showing the highest correlation of 0.78. The proteins studied included BACE, CDK2, CDK8, c-MET, Eg5, JNK1, MCL1, P38, PFKFB3, PTP1B, SHP2, TNKS2, and TYK2.

AI program with DeepMatcher-Hit v1.8



- AI-based drug discovery platform "DeepMatcher®-Hit" conducts a comprehensive screening to find appropriate hit compounds using up to 1 billion compound library. The platform is fully automated and modulated into three parts for AI based 2D chemical screening, AI based 3D docking and Molecular docking simulation. Additionally, with our own high-performance computing infrastructure,
- ABL1 Tyrosine-protein kinase: ABL1 contains nuclear localization signals as well as a DNA binding domain, which enable it to carry out DNA damage-repair functions. The ABL1 gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous(https://medlineplus.gov/genetics/gene/abl1/).
- Further validation and testing are necessary to confirm the efficacy of these compounds in-vitro & in-vivo