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Recovering life by death: Targeting Bcl-2 family – A pharmacophore-based approach

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Introduction

The Bcl-2 family of proteins can be functionally divided into two groups, pro- and anti-apoptotic, which are positive and negative regulators of apoptosis. Those proteins are involved in the mitochondrial outer membrane stability through interactions between its members, especially between an anti- and a pro-survival protein[1]. Overexpression of pro-survival Bcl-2 proteins contributes to evasion of apoptosis in tumor cells and is an important characteristic of cancer, turning Bcl-2 family proteins an important and validated target for the design of anti-cancer therapeutics. Here we present a pharmacophore-based virtual screening (VS) approach using ligand-based and structure-based methods, consensus 3D pharmacophore model and their respective validation targeting Bcl-xL protein, a pro-survival protein, aiming to find new anti-cancer drug candidates.

Results and Discussion

The dataset used in the validation process of pharmacophore-based models was retrieved from ChEMBL database (ID: 4625, active molecules) and in PubChem Bioassay (AID: 1022, inactive molecules). We used an in-house protocol to standardize and curate all this data before generating the VS subset (36 inactives per active). Then, pharmacophore models were generated using LigandScout v3.12 (Inte:Ligand GmbH, Austria)[2] from three different Bcl-xL crystal structures available in PDB (1YSI, 1YSN and 2O1Y). The first pharmacophore model (ligand-based) was generated by aligning three known Bcl-xL inhibitors

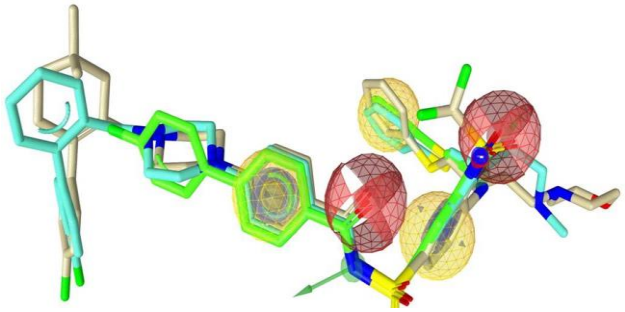

Figure 1: Ligand-based pharmacophore. Yellow spheres: hydrophobic feature; red spheres: hydrogen bond acceptor; green arrow: hydrogen bond donor

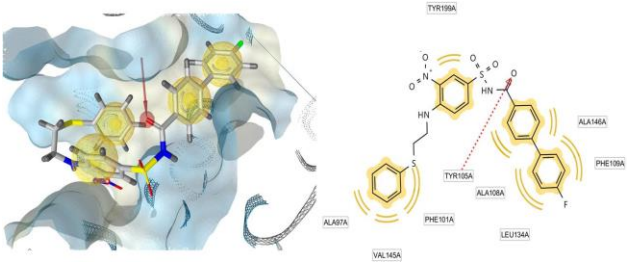

Figure 2: Structure-based model generated for PDB structure 1YSI

(ABT-263, ABT-737 and N3B) (Fig. 1); the structure-based model (Fig. 2) was generated using the crystal strutcture of Bcl-xL with N3B ligand (PDB entry: 1YSI) and the third model was based on the consensus of features between the three structures extracted from PDB. Then, a VS approach was performed to validate the three developed models using the VS subset, containing 428 active and 15,408 inactive molecules, totalizing 15,836 compounds. After the validation process[3], we performed the VS approach using the NCI chemical library database containing approximately 300,000 small molecules. The softwares FILTER[4], OMEGA[4] and QUACPAC[4] were used in the pre-processing of NCI database to filter, generate conformers and calculate partial charges, respectivelly. Then, the best pharmacophore model was used to filter NCI database, resulting in generation of a subset containing 1,000 compounds, which were visually analised. Those with favorable ADME/Tox properties predicted through an in-house protocol were selected and will be experimentally evaluated.

Conclusions

The results demonstrated a slightly superiority of ligand-based methods over the structure-based in terms of correctly classification and hit enrichment. In addition, we were able to select a small set of compounds predicted as Bcl-xL inhibitors with favorable ADME/Tox properties.

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