Contribution ID: **100** Type: **Flash presentation**

Prediction of hERG-Mediated Cardiotoxicity based on the integration of docking scores and protein–ligand interaction fingerprints

Wednesday, 14 September 2022 12:05 (5 minutes)

Drug-induced cardiotoxicity is a common side effect of drugs in clinical use or under post-market surveillance and is commonly due to off-target interactions with the cardiac Human-Ether-a-go-go-Related (hERG) potassium channel. Several ligand-based models were developed in the last years and are today used in the early stages of a drug discovery program for in silico safety assessment of drug candidates. We present the first structure-based classifiers able to discern hERG binders from nonbinders and based on the integration of docking scores and protein–ligand interaction fingerprints [1]. In particular, 396 models were trained and validated based on: (i) high-quality experimental bioactivity information returned by a curated dataset extracted from ChEMBL (version 25) and (ii) structural predictor data. Docking simulations were performed using two software programs (i.e., GLIDE and GOLD) and four different hERG structural models, namely two recently published structures obtained by cryoelectron microscopy (PDB codes: 5VA1 and 7CN1) and two homology models selected for comparison. Remarkably, performances comparable to ligand-based classifiers in terms of area under the ROC curve (AUCMAX = 0.86 ± 0.01) and negative predictive values (NPVMAX = 0.81 ± 0.01) were returned by some models, thus supporting the robustness of the proposed computational workflow. From a more methodological point of view, the study represents the first example of successful integration of docking scores and protein–ligand interaction fingerprints (IFs) through a support vector machine (SVM) LASSO regularized strategy and highlights the importance of employing hERG structural models accounting for ligand-induced fit effects. Finally, the obtained data allowed us to select the best-performing protein conformation to be used in the future for structure-based predictions of hERG-related cardiotoxicity.

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Session Classification: MS

Track Classification: Crystallographic and Spectroscopic Advanced Tools Applied to Pharmaceuticals