Contribution ID: **3** Type: **not specified**

Machine learning-based prediction of hERG-mediated cardiotoxicity: a structure-based investigation

Tuesday, 7 March 2023 13:15 (30 minutes)

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Prioritizing drug candidates based on their human ether-à-go-go-related gene potassium channel (hERG) blocking potential is a mandatory step in the early preclinical stage of a drug discovery program. The hERG blockade is, in fact, considered the main cause of cardiotoxicity in post-marketing surveillance. Several ligand-based approaches were therefore developed in the last years and are currently employed in a drug discovery process for in silico cardiac safety assessment of drug candidates. Herein, the first structure-based classifiers able to discern hERG binders from non-binders will be presented.(1) LASSO regularized Support Vector Machines were applied to integrate docking scores and protein-ligand interaction fingerprints. 396 models were trained and validated based on: i) high-quality experimental bioactivity information returned by 8,337 curated compounds extracted from ChEMBL (version 25(2)) and ii) structural predictor data. Molecular docking simulations were performed by using GLIDE and GOLD software programs and different hERG structural models, namely the recently published structures obtained by cryo-electron microscopy (PDB codes: 5VA1(3)and 7CN1(4)) and two published homology models selected for comparison. Remarkably, some models return performances comparable to ligand-based classifiers in terms of accuracy (AUCMAX = 0.86±0.01) and negative predictive values (NPVMAX = 0.81±0.01) thus putting forward the herein developed computational workflow as a valuable tool for predicting hERG mediated cardiotoxicity without the limitations of ligand-based models, typically affected by low interpretability and a limited applicability domain. The study highlights the importance of using hERG structural models accounting for ligand-induced fit effects and allowed us to select the best performing protein conformation to be employed for a reliable structure-based prediction of hERG-related cardiotoxicity.

References

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Session Classification: Session