PREDICTION OF DRUG SIDE EFFECTS MICHAEL J KEISER pdf

1: Chemistry Tree - Michael J. Keiser

These multiscale models form networks of target perturbation and biological effect that, when organized into layers of increasing complexity, comprise the drug response of a binding site, cell, tissue, organ, or entire patient in the www.enganchecubano.coms pharmacology's application to the prediction of antitarget-mediated side effects is the focus of this chapter.

Drugs can act on multiple protein targets, some of which can be unrelated by traditional molecular metrics, and hundreds of proteins have been implicated in side effects. Approximately half of the predictions were confirmed, either from proprietary databases unknown to the method or by new experimental assays. To explore relevance, we developed an association metric to prioritize those new off-targets that explained side effects better than any known target of a given drug, creating a Drug-Target-ADR network. Among these new associations was the prediction that the abdominal pain side effect of the synthetic estrogen chlorotrianisene was mediated through its newly discovered inhibition of the enzyme COX The clinical relevance of this inhibition was borne-out in whole human blood platelet aggregation assays. This approach may have wide application to de-risking toxicological liabilities in drug discovery. Adverse drug reactions ADRs can limit the use of otherwise effective drugs. Next to lack of efficacy, they are the leading cause for attrition in clinical trials of new drugs 1 â€” 3 and are more prominent still in the failure of molecules to advance from pre-clinical research into human trials. Notorious examples of off-target toxicity include that of the appetite suppressant Fen-Phen, withdrawn from the market after numerous patient deaths. These owed to the activation of the 5-HT2B receptor by one of its metabolites, norfenfluramine, leading to proliferative valvular heart disease. Methods to systematically predict off-targets, and associate these with side effects, have thus attracted intense interest, 10 â€” 16 frequently in the form of either chemical genomics 17 , 18 or informatics 19 â€” 26 approaches. Whereas the informatics methods have never been tested systematically on a large scale, in principle they can be deployed against thousands of targets. Here we present a large-scale, prospective evaluation of safety target prediction using one such method, the Similarity Ensemble Approach SEA. Because SEA relies only on chemical similarity, it can be applied systematically and, for those targets that have known ligands, comprehensively. For drugs approved for human use Supplementary Table S1 , targets were predicted from among 73 proteins Supplementary Table S2 , Supplementary Methods with established association of ADRs, 22 , 28 for which assays were available at Novartis. Encouragingly, many of the predictions were confirmed, often at pharmacologically relevant concentrations. This motivated us to develop a guilt-by-association metric that linked the new targets to the ADRs of those drugs for which they are the primary or well-known off-targets, creating a Drug-Target-ADR network. The applicability and the limitations of this approach will be considered. Testing the predictions The drugs were computationally screened for their likelihood to bind to 73 targets Supplementary Table S2 using SEA. SEA calculated the similarity of each drug versus each set of ligands for the 73 targets, comparing the overall set similarity to a model of such expected at random. Only 1, of the over 47, possible drug-target pairs had significant E-values. Of these, were already known in ChEMBL, and so were trivially confirmed; we do not consider these further. The remaining predictions represented previously unexplored drug-target associations. Table 1 New drug-off-target predictions confirmed by in vitro experiment. Representative, confirmed predictions are shown.

2: Antitargets and drug safety (eBook,) [www.enganchecubano.com]

His lab investigates forward polypharmacology for complex diseases and the prediction of drug off-target activities. The Keiser lab combines machine learning and chemical biology methods to investigate how small molecules perturb entire protein networks to achieve their therapeutic effects. In classical pharmacology, each drug was thought to strike a single note (in other words, "one drug hits one target to treat one disease").

3: Predicting new molecular targets for known drugs

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Eugen Lounkine, 1, â€ Michael J. Keiser, 2, 3, potential of this approach to predict and understand drug side effects. The method was deployed.

4: Jerome Hert - Publications List

*Large-scale prediction and testing of drug activity on side-effect targets Eugen Lounkine 1 *, Michael J. Keiser 2,3 *, Steven Whitebread, Dmitri Mikhailov, Jacques Hamon 4, Jeremy L. Jenkins 1.*

5: SeaChange | Discovery

Side Effects of Marketed Drugs: The Utility and Pitfalls of Pharmacovigilance / Steven Whitebread, Mateusz Maciejewski, Alexander Fekete, Eugen Lounkine, LÃ¡szlÃ³ UrbÃ¡n --Prediction of Drug Side Effects / Michael J Keiser --Translational Value of Preclinical Safety Assessment: System Organ Class (SOC) Representation of Off-Targets / Mateusz.

6: JoVE | Peer Reviewed Scientific Video Journal - Methods and Protocols

Divided into three major parts, the first section deals with novel technologies and includes the utility of adverse event reports to drug discovery, the translational aspects of preclinical safety findings, broader computational prediction of drug side-effects, and a description of the serotonergic system.

7: Predicting new molecular targets for known drugs â€" University of North Carolina at Chapel Hill

Discovering the unintended 'off-targets' that predict adverse drug reactions is daunting by empirical methods alone. Drugs can act on several protein targets, some of which can be unrelated by conventional molecular metrics, and hundreds of proteins have been implicated in side effects. Here we use.

8: Large Scale Prediction and Testing of Drug Activity on Side-Effect Targets

Whereas drugs are intended to be selective, at least some bind to several physiologic targets, explaining both side effects and efficacy. As many drug-target combinations exist, it would be useful to explore possible interactions computationally.

9: Michael J. Kaiser PhD | Parkinson's Disease

Predicting new molecular targets for known drugs Michael J. Keiser Retrospective drug-target predictions the drug, when they may mediate drug side effects.

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