Matt Segall gave this presentation at the ACS Fall 2015 National Meeting & Exposition held in Boston, USA on 16th August 2015.

Abstract

Predicting the interaction of compounds with targets associated with toxicity can provide inputs to hierarchical models integrating systems toxicology, physiologically-based pharmacokinetic (PBPK) models and organ simulations to predict compound interactions with adverse outcome pathways (AOP).

For example, MRP4 (Multi-drug resistance-associated protein 4 or ABCC4) mediates the transport of signalling molecules (such as cAMP and cGMP), prostaglandins and leukotrienes (PGE1, PGE2, LTB4) and can be inhibited by drugs such as Celecoxib, Probenecid, MK-571 and Sulfinpyrazone [1]. BSEP (Bile salt export pump or ABC11) is localised in the cholesterol rich canalicular membranes of hepatocytes and its function is to eliminate unconjugated/conjugated steroidal acids from the hepatocyte into the bile. The loss of this transporter function is seen in the genetic disease progressive familial intrahepatic cholestasis type 2. Inhibition of both of these transporters MRP4 and BSEP has been identified as a risk factor in the development of cholestatic DILI (drug-induced liver injury) [2].

We have used the publically available data from ChEMBL to build categorical and continuous quantitative structure-activity relationship (QSAR) models in order to determine the molecular properties which contribute to activity at these transporters and compare these features with known hepatotoxic compounds. We have compared the results from these models with predictions from the Derek Nexus approach for knowledge-based prediction of hepatotoxicity [3]. The resulting QSAR models, along with models of other toxicity-related targets, will form part of a hierarchy of molecular-, systems- and physiologically-based models to identify compounds with an increased risk of toxicity as part of the HeCaToS project [4].

You can download this presentation as a PDF .

[1] Russel, F.G. et al. Trends Pharmacol. Sci. 29(4) pp. 200-7 (2008)
[2] Kis, E. et al. Toxicol. in Vitro. 26(8), pp. 1294-9 (2012)
[3] Greene, A. et al. SAR and QSAR in Environmental Research 10(2-3), pp. 299-314 (1999)
[4] www.hecatos.eu