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The development of liver toxicity knowledge base to support the assessment of drug-induced liver injury risk in humans

Drug-Induced Liver Injury (DILI) is a frequent cause of Adverse Drug Reaction (ADR) resulting in clinical trial failure, warnings and withdrawals of numerous medications. Despite the research community's best efforts, current testing strategies aimed at identifying hepatotoxic drugs prior to human trials are not sufficiently powered to predict the complex mechanisms leading to DILI. Tremendous efforts were conducted to fulfill this knowledge gap. In the FDA's National Center for Toxicological Research, we developed the Liver Toxicity Knowledge Base (LTKB), aiming to improve our understanding and the prediction of DILI risk in humans via integrative analysis of diverse drug-elicited data. In this practice, we discovered that several drug properties and toxicological properties, such as daily dose, lipophilicity and the capability to form Reactive Metabolites (RM), are strongly associated with serious DILI potential in humans. Here, we will introduce the rule-of-two model (i.e. daily dose ≥ 100 mg/day and $\log P \geq 3$) and DILI score model (i.e. a scoring model derived from daily dose, $\log P$ and formation of RM) developed by the NCTR research team. We will discuss the applications of these models in the context of regulatory processes with the discussion of independent validations reported in literature. Our studies suggest that these predictive models (e.g. RO2, DILI score) could help better assess the human DILI risk in drug development process.

Biography

Minjun Chen is a Principal Investigator working at the Division of Bioinformatics and Biostatistics of the FDA's NCTR and serve as the adjunct faculty and mentor for the bioinformatics program joint by University of Arkansas at Little Rock (UALR) and University of Arkansas for Medical Sciences (UAMS). He received the FDA award for outstanding junior investigator (2012) and the NCTR scientific achievement award (2014). Currently, he is the Editor together with Yvonne Will (Pfizer) to create a Springer book titled *Drug-Induced Liver Toxicity*. He also served as the Editorial Board Member for the journals including *Peer J* and *Chinese Herbal Medicine*. He has authored and co-authored more than 70 book chapters or scientific publications in the prestigious journals. His primary research interests encompass drug-induced liver injury, biomarker discovery, bioinformatics, and toxicogenomics..

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