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TDI - DDI risk assessment from *In Vitro* to *In Vivo* - Application of PBPK modeling and simulation tool

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Time-dependent inhibition (TDI) is an important consideration in the drug development process. To date, methods to accurately predict the magnitude of a clinical drug-drug interaction (DDI) from pre-clinical TDI data have been lacking. Until relatively recently, the application of PBPK modeling in support of drug discovery and early development was somewhat limited due to the resource-intensive ADME data required to fully populate PBPK models and the mathematical complexity of the model itself. However, advances in *in silico/in vitro*-based prediction tools, in particular those for absorption, distribution and hepatic clearance, have enabled the use of PBPK modeling at an earlier stage of drug discovery. In addition, the emergence of software tools, such as GastroPlus™ and the Simcyp® simulator, allow for a broader use of PBPK models. Although more complex prediction algorithms have been developed, the accuracy has still improved little. Historically, human liver microsomes have been used to generate inhibition kinetic data used for *in vivo* DDI predictions. Recently, it has been suggested that human hepatocytes TDI kinetic data may provide a better prediction for assessing clinical DDI related to TDI. Our work evaluates and optimizes a human hepatocyte assay for the assessment of CYP3A4 TDI using pooled cryopreserved human hepatocytes. Using two different optimized methods, the time-dependent inhibition kinetic parameters for four known CYP3A4 TDI, diltiazem, erythromycin, verapamil, and troleandomycin, were determined. When drug interactions were simulated with Simcyp PBPK model, the predictions using the kinetic parameters from human hepatocyte resulted in a much better simulated change in pharmacokinetics when compared with observed clinical data.

Biography

Yuan Chen, Ph.D., is currently a Senior Scientist in the Department of Drug Metabolism and Pharmacokinetics at Genentech. Yuan has more than 10 years of pharmaceutical industry experience in the DMPK discipline working at Roche and Genentech. She has been DMPK project lead for many discovery and early development projects, and contributed significantly to the clinical candidate nomination and filing of IND to the regulatory authorities. Yuan has broad experience in field of in vitro and in vivo drug metabolism and investigative ADME to understand mechanism of drug disposition. Her recent research focuses are on mechanistic-based modeling (PBPK model) for the prediction of human PK and drug-drug interaction.

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