

## UTILITY OF CHIMERIC MICE WITH HUMANIZED LIVER FOR PREDICTION OF HUMAN DRUG DISPOSITION

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[Purpose] Human-specific or disproportionately large human metabolites of drug candidates, that are not adequately qualified in the nonclinical safety assessment program, pose an important drug development challenge. This risk can be effectively mitigated if an accurate prediction of the human disposition of the drug candidate can be made early in the development program. However, the currently available in vitro models (e.g., liver microsomes, hepatocytes) do not always provide an adequate picture of the potential in vivo metabolic profile either due to the low metabolic turnover or lack of a good in vitro-in vivo correlation. Furthermore, the conduct of actual human ADME studies is an expensive and time-consuming endeavor that is more suited for late development when the risk of failure has been reduced. We evaluated a recently developed chimeric mouse model with humanized liver for its ability to predict human disposition of four model drugs (lamotrigine, diclofenac, a Merck drug candidate MRK-A and propafenone) that are known to exhibit human-specific metabolism routes. [Methods] ADME studies were conducted in bile-duct cannulated chimeric mice following oral administration of radiolabeled drugs. Samples of excreta (bile, urine, feces) were collected and analyzed for metabolites using LC-MS/MS and radiochromatography. [Results and Discussion] The data demonstrate that chimeric mice were able to reproduce the human-specific metabolite profile for lamotrigine, MRK-A and diclofenac. In the case of propafenone, however, the human-specific C-5 hydroxylation was not detected as a predominant pathway and the metabolite profile in non-humanized vs humanized mice was similar; this could either be due to expression of suboptimal CYP2D6 activity or presence of residual propafenone-metabolizing *mouse* enzymes in chimeric mice. [Conclusions] Overall, the data indicate that the chimeric mice with humanized liver have the potential to be a useful tool for the prediction of human-specific metabolism of xenobiotics and warrant further investigation.