Application of Chimeric Mice with Humanized Liver for Study of Human-Specific Drug Metabolism

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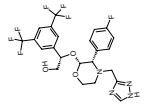
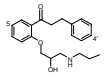
Human-specific or disproportionately larger human metabolites of drug candidates that are not formed to a significant extent by the nonclinical species used for their toxicological evaluation and, hence, are not adequately qualified in the preclinical safety assessment program pose an important drug development challenge. This risk can be effectively mitigated if an accurate assessment of significant human metabolites 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 observed 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 later in 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 that are known to exhibit human-specific metabolism routes (Table).

Drug	Structure	Elimination pathways in	
		Rodents	Humans
Lamotrigine		Oxidation	N-Glucuronidation
MRK-A		Oxidation	O-Glucuronidation
Diclofenac		Acyl glucuronidation (major), 4'-hydroxylation (minor)	Acyl glucuronidation (major), CYP2C9-mediated 4'-hydroxylation (major)
Propafenone		4'-hydroxylation	CYP2D6-mediated 5-hydroxylation

The results from these studies demonstrate that chimeric mice were able to qualitatively as well as quantitatively 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. Overall, the data indicate 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.