Current challenges

The importance of prediction of human drug metabolism and pharmacokinetics during the preclinical stage of drug development is hard to overstate. It contributes to both efficacy and toxicity of the drug in development. Due to interspecies differences in hepatic metabolic patterns, the results obtained from rodents and dogs are not always relevant in predicting the responses of human hepatocytes. Liver microsomes, human hepatocytes in primary culture and precision cut liver slices are frequently used for early characterization of human metabolism, but do not preserve the architecture of the liver sufficiently to allow an accurate prediction of which metabolites will likely circulate.

Given the limitations of current preclinical models, human metabolites and their downstream effects often go undetected until clinical trials, the most costly and risky phase of drug development.

What is the KMT Mouse™

The KMT Mouse™ is the trade name for the proprietary chimeric mouse with humanized liver, first reported in 2001 by KMT Hepatech founders (uPA+/+/SCID mice transplanted with human hepatocytes, also known as PXB mouse).

Chimeric mouse livers contain viable, differentiating, and proliferating human hepatocytes with up to 95% of the mouse liver replaced by human hepatocytes. The replacement of mouse hepatocytes with human hepatocytes generally correlates with human albumin (hAlb) and human alpha 1-antitrypsin (hAAT) levels.

Chimeric mouse could also serve as a useful source of fresh and reproducible human hepatocytes derived from the same donor for in vitro metabolic studies. Comparative in vivo and in vitro studies with chimeric mice with the same donor prior to first time in human studies could generate useful data for resolving poorly understood phenomena and mechanisms.

What is the KMT Mouse™

- Hepatic cords
- Sinusoid-like structures
- Bile canaliculi associated with human hepatocytes
- mRNAs of 58 human phase I enzymes
- mRNAs of 26 human phase II enzymes
- mRNAs of 23 human transporters
- Lower activities of mouse P450 enzymes and high activities of human P450 enzymes
- High non-P450 enzyme activity, such as UDP-glucuronosyltransferase, sulfotransferase, aldehyde oxidase

KMT Mouse™ is your essential tool in drug metabolism studies

Relevant Publications (more references on the next page)

- Emoto C. et al. (2011) Drug metabolism and toxicity in chimeric mice with humanized liver. J. Health Sci. 57(1) 22-27
- Katoh M. et al. (2008) Chimeric mice with humanized liver. Toxicology 246(1) 9-17
- Sanoh S. et al. (2012) Prediction of human metabolism of FK3453 by aldehyde oxidase using chimeric mice transplanted with human or rat hepatocytes. Drug Metab. Dispos. 40(1) 76-82
- Schulz-Utermöhl T. et al. (2012) Evaluation of the pharmacokinetics, biotransformation and hepatic transporter effects of troglitazone in mice with humanized livers. Xenobiotica 42(6) 503-517
- Samuelsson K. et al. (2012) Pharmacokinetics and metabolism of midazolam in chimeric mice with humanized livers. Xenobiotica 42(11) 1128-1137
- Tateno C. et al. (2004) Near completely humanized liver in mice shows human-type metabolic responses to drugs. Am. J. Pathol. 165(3) 901-912

Contact Us

KMT Hepatech, Inc.
11421 Saskatchewan Drive
Edmonton, AB, Canada, T6G 2M9

Tel: +1.780.641.1919
Fax: +1.780.641.1916
Email: info@kmthepatech.com
www.kmthepatech.com
<table>
<thead>
<tr>
<th>Compounds evaluated</th>
<th>Metabolic component</th>
<th>Notes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methandienone metabolites in human and mouse urine</td>
<td>Drug, 7 metabolites, 4 metabolite isomers detected</td>
<td>The metabolite not detected in the chimeric mouse urine is variably detectable in human urine</td>
<td>[1]</td>
</tr>
<tr>
<td>Urinary excretion of cefmetazole</td>
<td>Mainly excreted in urine</td>
<td>Human transporters expressed in chimeric mouse livers</td>
<td>[2]</td>
</tr>
<tr>
<td>Metabolism of 4-Androstene-3,17-dione</td>
<td>Major: androsterone and etiocholanolone, and non-hydroxylated metabolites</td>
<td>Metabolic profiles similar to humans</td>
<td>[3]</td>
</tr>
<tr>
<td>Metabolism of 17α-Methyltestosterone</td>
<td>Metabolites 17-epimethyl-testosterone and 6-ene-epimethyl-testosterone detected by revised methodology</td>
<td>The reference proposed the utility of the chimeric mouse model for the confirmation of steroid metabolites</td>
<td>[4]</td>
</tr>
<tr>
<td>S-Warfarin conversion to 7-Hydroxywarfarin by CYP2C9</td>
<td>High 7-hydroxylase activity of microsomes inhibited by sulfaphenazole</td>
<td>The CYP2C isoform in high replacement index chimeric mice functions in vivo and in vitro as the human isoform CYP2C9</td>
<td>[5]</td>
</tr>
<tr>
<td>ADME characteristics of S-Warfarin</td>
<td>Plasma protein binding 99.1%, Urine excretion 80%</td>
<td>Bilary excretion levels in chimeric mice are consistent with the enterohepatic circulation of S-warfarin in humans.</td>
<td>[6]</td>
</tr>
<tr>
<td>Stanozolol metabolites in urine</td>
<td>LC-MS/MS detected 15 metabolites. SRM method confirmed 19 metabolites</td>
<td>The most useful metabolites for doping control were detected in both human and chimeric mouse urine</td>
<td>[7]</td>
</tr>
</tbody>
</table>

References:
3. Lootens et al. (2009) Drug Metab. Dispos. 37(12): 2367-74
5. Inoue et al. (2008) Drug Metab. Dispos. 36(12): 2429-33