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演題: CYP で代謝される医薬品におけるヒト肝細胞移植キメラマウスを用いた体内動態の個人差予測

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## Title

Inter-individual pharmacokinetic differences of CYP substrates in chimeric mice transplanted with human hepatocytes

## Abstract

**[Purpose]**
Differences between individuals in their metabolic activities could affect efficacy and safety based on pharmacokinetics (PK). Therefore, it is important to predict drug metabolism and PK in different individuals. We focused on chimeric mice with humanized livers (PXB mice (R)) developed by PhoenixBio, Co., Ltd. The livers of chimeric mice consist of approximately 80% human hepatocytes. Human drug-metabolizing enzymes such as CYPs, transferases, and transporters are expressed in the livers of these mice.

**[Methods]**
Chimeric mice transplanted with hepatocytes (BD85 and BD195, Corning Japan KK; IZTand PDC, BioreclamationIVT) were used. Midazolam, verapamil, bufuralol, and tamoxifen were used as CYP model substrates. PK and mRNA expression levels of CYPs in the livers of chimeric mice were evaluated.

**[Results and Discussion]**
In vitro metabolic activities and mRNA levels of CYP3A4 were similar between BD85 and BD195 chimeric mice livers. In the PK study, the two strains differed by less than twofold in midazolam and verapamil clearances. On the other hand, the plasma concentrations of CYP2D6 metabolite after the administration of bufuralol in IZT (CYP2D6 poor metabolizer) chimeric mice were slightly lower than those in BD195 chimeric mice. The plasma concentration of unchanged tamoxifen was slightly higher in IZT than in BD195 chimeric mice after dosing with tamoxifen. The contributions of other compensatory metabolic pathways and metabolic activities in residual mouse hepatocytes may affect PK in livers of chimeric mice.
[Conclusion] To predict inter-individual differences of PK, we need to examine the effects of expression levels and polymorphism in drug-metabolizing enzymes on PK profiles using chimeric mice transplanted with various of hepatocytes.