Evaluation of Drug-Metabolizing Potential in Experimental Animals Focused on Functions and Genetic Polymorphisms of Cytochromes P450

シトクロムP450の機能および遺伝的多型に着目した実験動物の薬物代謝能に関する基盤研究

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Main research interests

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1. Functional analyses of cytochrome P450 in a small New World monkey species, the common marmoset.

・Effects of P450 gene polymorphism on pharmacokinetics

→ **Poster Presentation P-002**
Kamimura, Uehara et al

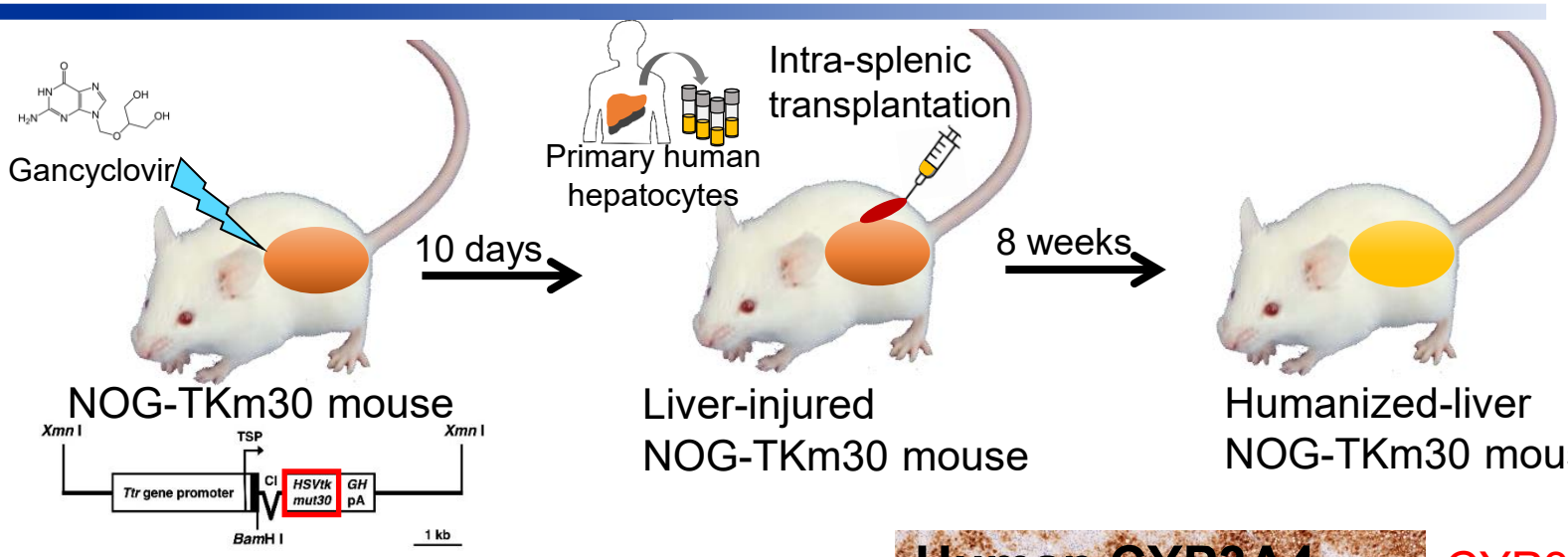
2. Development and characterization of humanized liver mouse model

・In vivo drug metabolism in humanized-liver mice

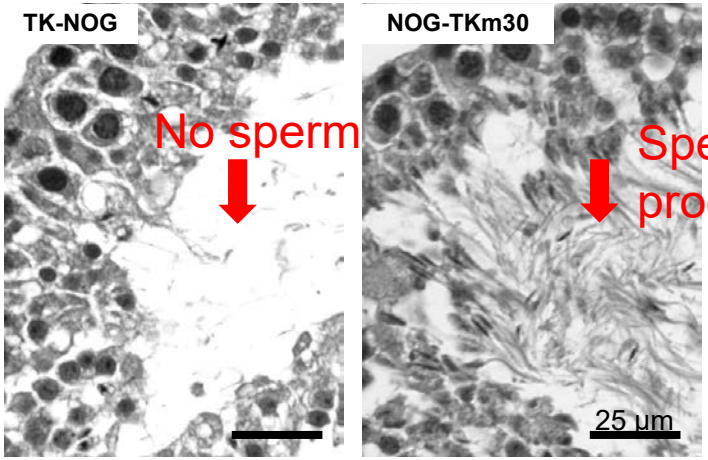
・Hepatic P450-mediated drug oxidation activity

・Por-knockout humanized-liver mouse model

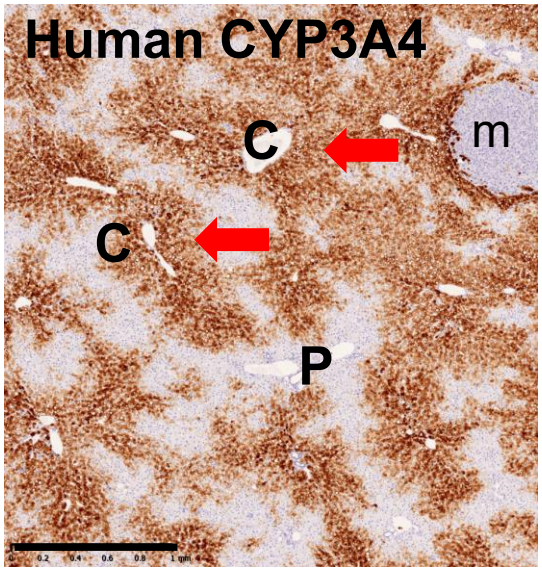
Improved Humanized-Liver NOG-TKm30 Mouse



Seminiferous tubules



Improving Infertility in male TK-NOG mouse

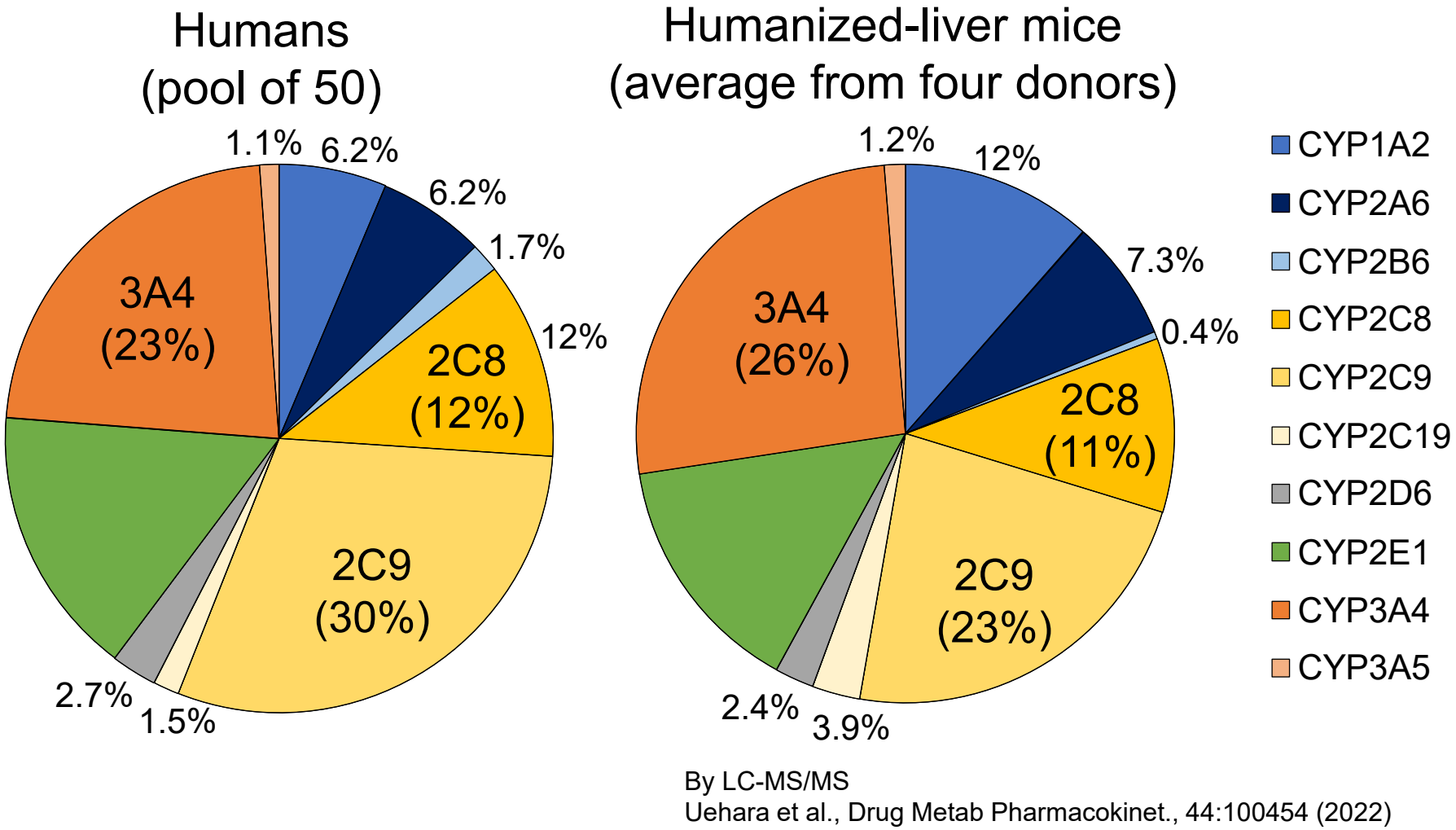


CYP3A4 localized around the central vein

Uehara et al. Drug Metab Pharmacokinet., 42:100410 (2021)

- The homozygous NOG-TKm30 mice are easily bred and contribute to a stable supply of humanized liver mice.

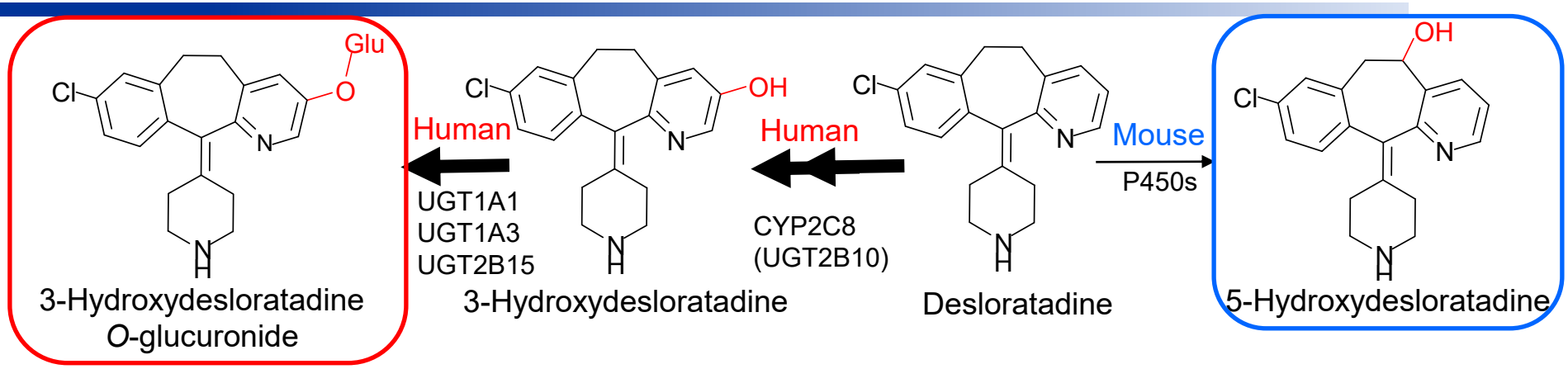
Expression Levels of Human P450 Proteins in Humanized-Liver



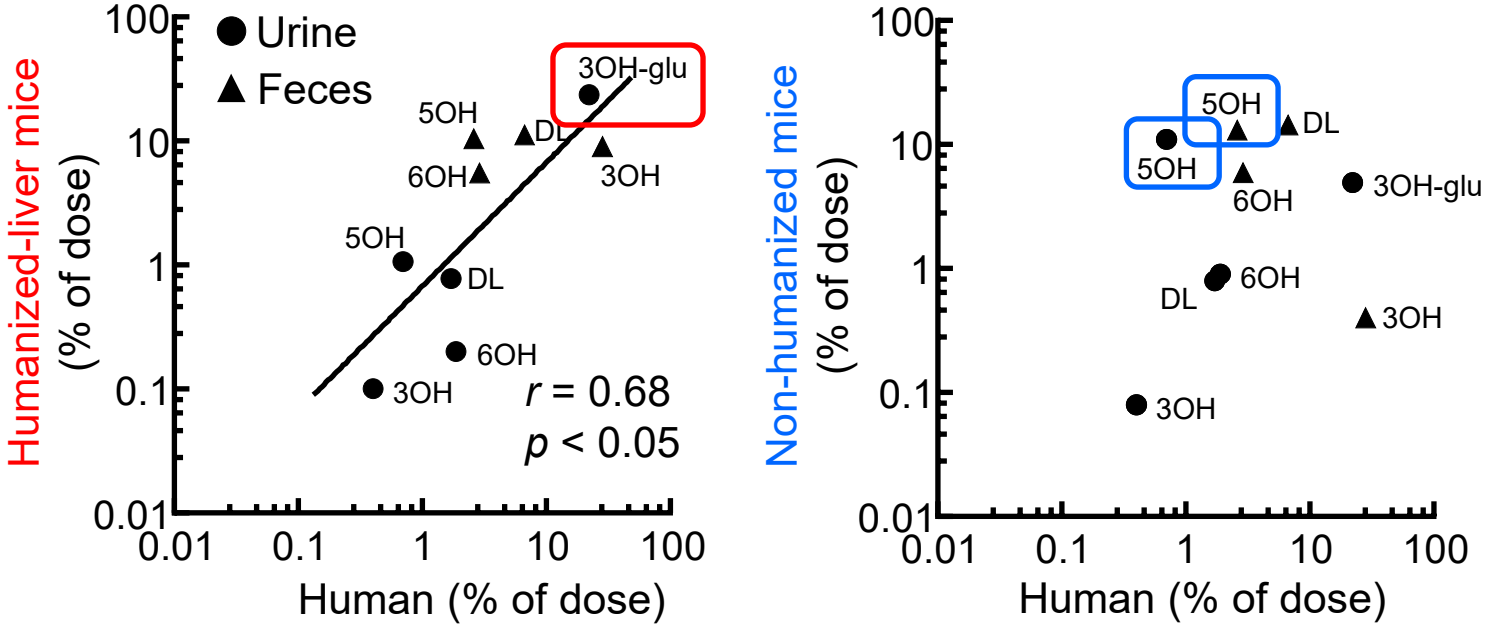
By LC-MS/MS
Uehara et al., Drug Metab Pharmacokinet., 44:100454 (2022)

- Hepatic human P450 contents were similar between humanized-liver mice and humans.

Metabolites in Humanized-Liver Mice after Oral Administration of Desloratadine

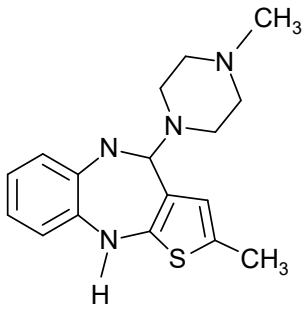


Excretion of desloratadine and its metabolites

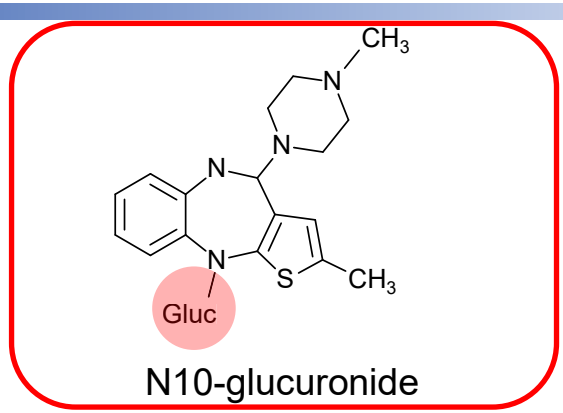


- Desloratadine metabolism mediated by P450s and UGTs in humans is roughly reproduced in humanized-liver mice. Uehara et al. Xenobiotica, 50(6):733-740 (2020)

Urinary Metabolites by UGT1A4 in Humanized-Liver Mice after Oral Administration of Olanzapine

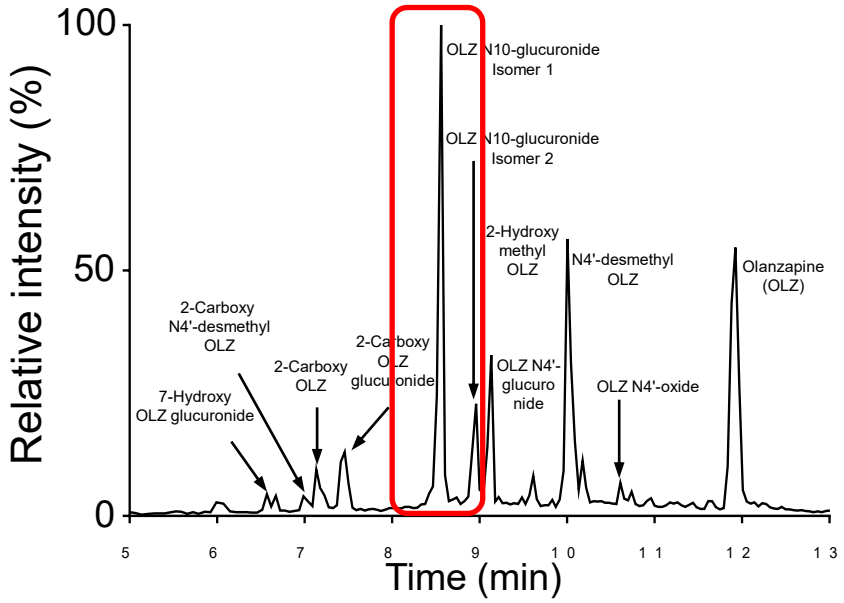


UGT1A4

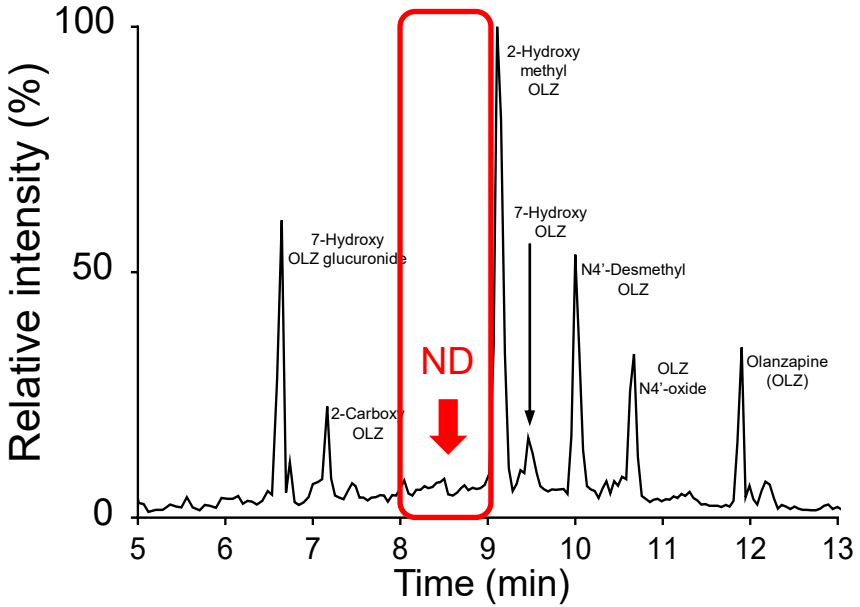


Unique human metabolite

Olanzapine
Humanized-liver mice



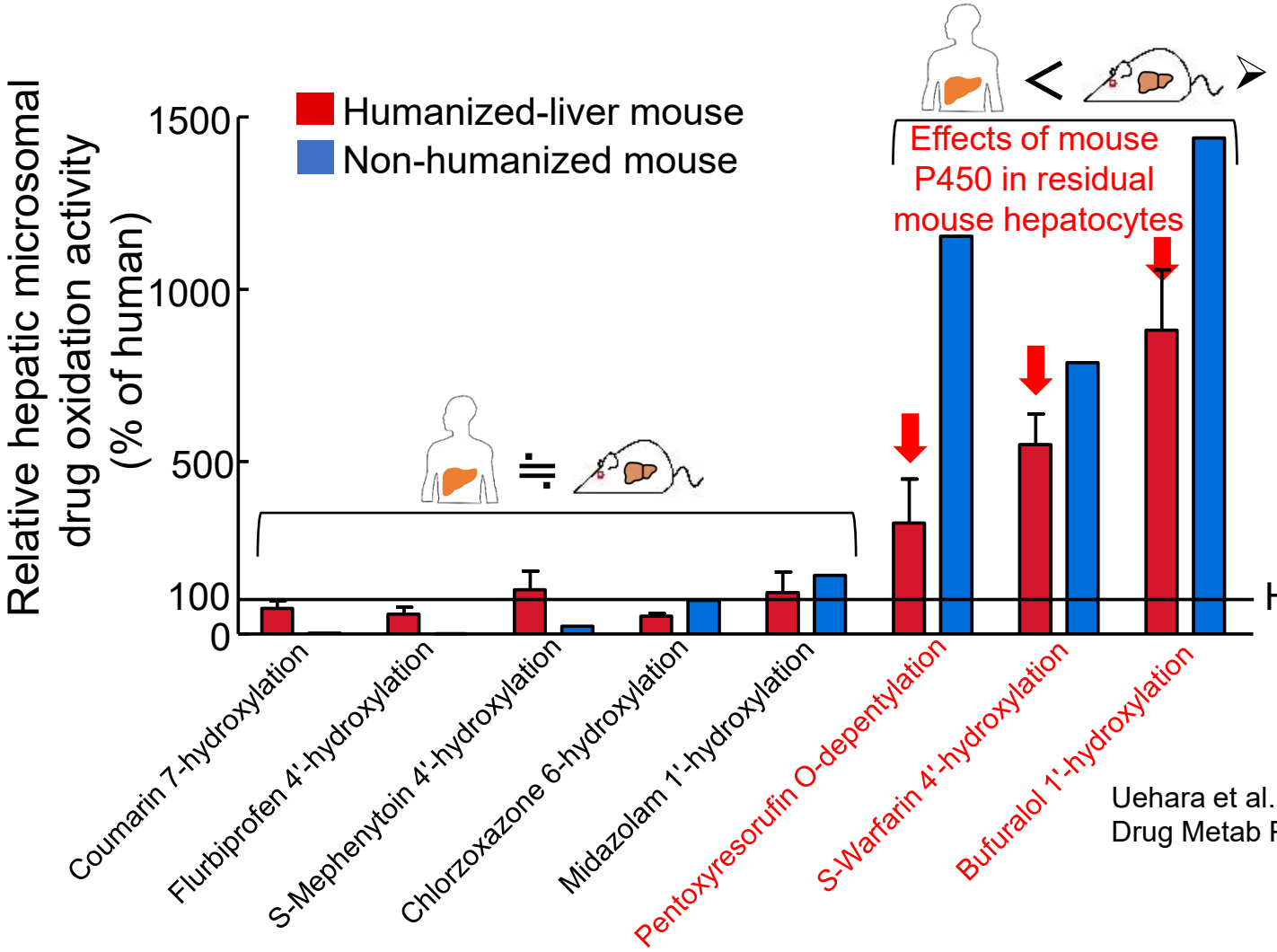
Non-humanized mice



- Humanized-liver mouse may be a suitable model for studying UGT1A4-dependent biotransformation of drugs in humans.

→ **Poster Presentation P-052**

Hepatic Microsomal Drug Oxidation Activities in Humans, Humanized-Liver Mice, and Non-Humanized Mice



Several drug oxidation activities are much higher in humanized liver mouse microsomes than human liver microsomes.

Uehara et al.,
Drug Metab Pharmacokinet., 44:100454 (2022)

⇒ To eliminate the adverse effects of hepatic mouse P450s, we generated a novel humanized liver mouse.

We Generated P450 Oxidoreductase (Por) Conditional Knockout (cKO) Mouse

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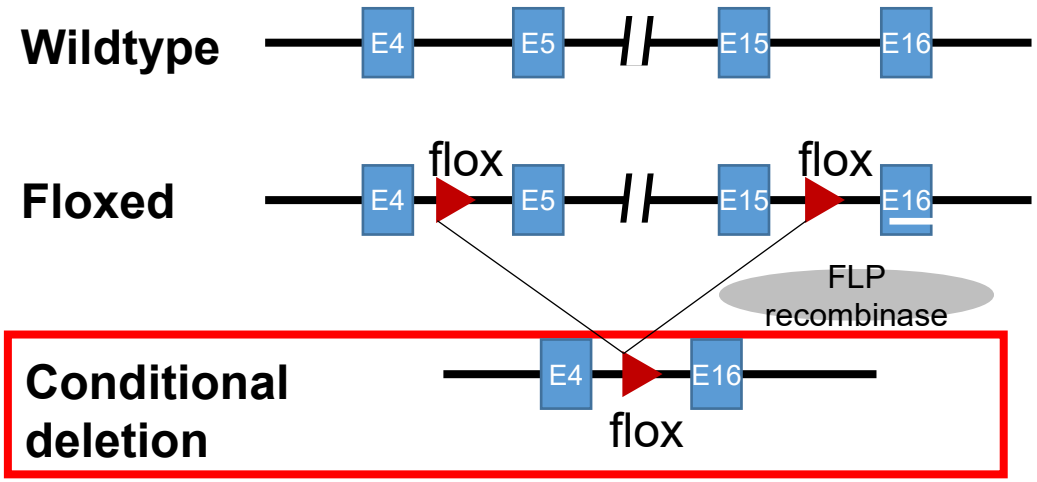
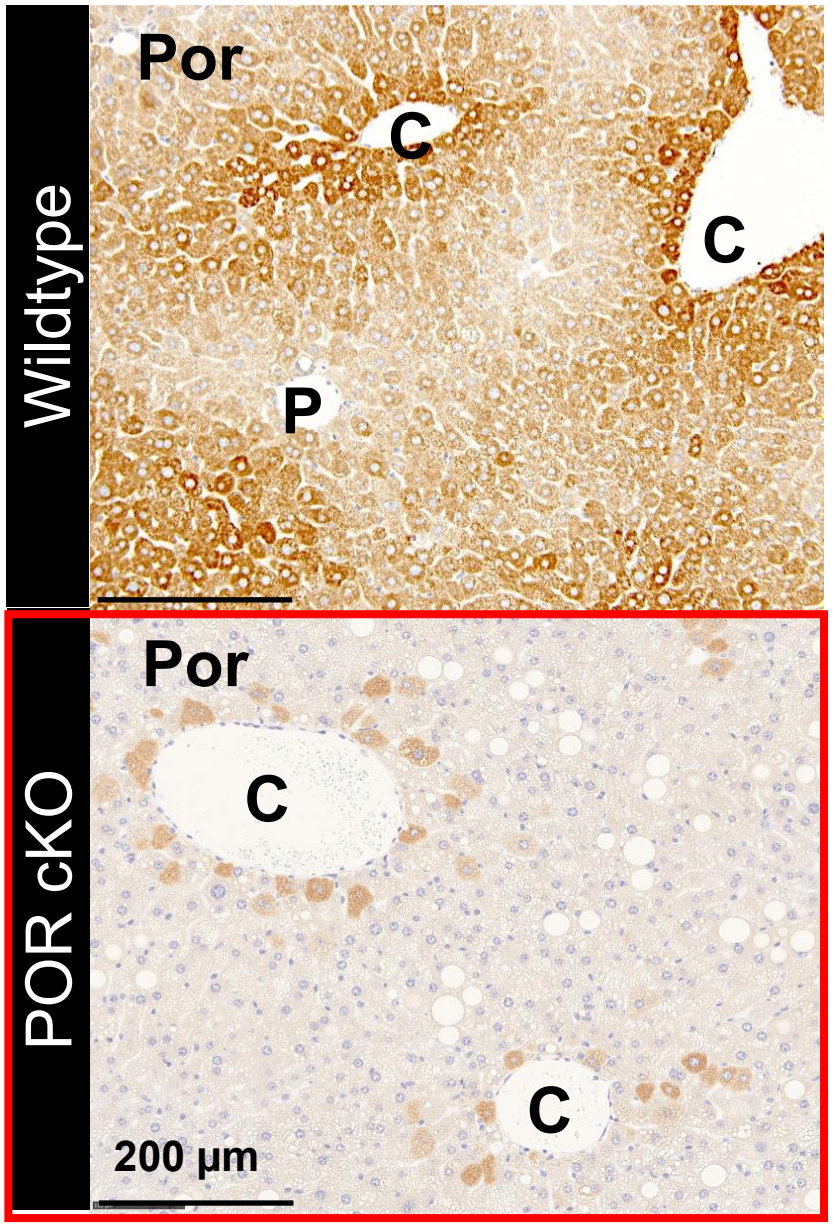
Por gene

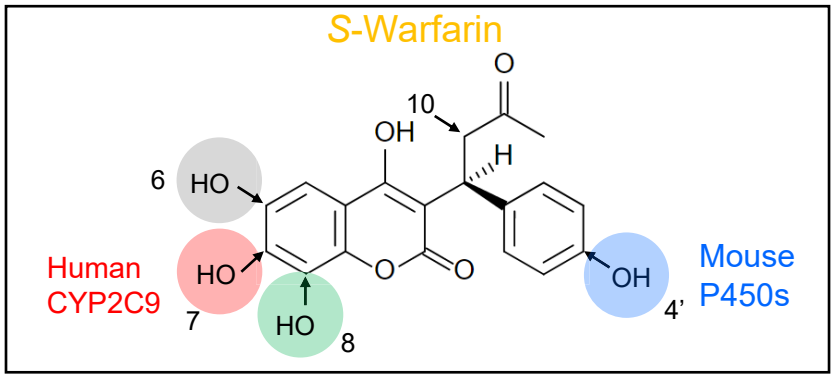


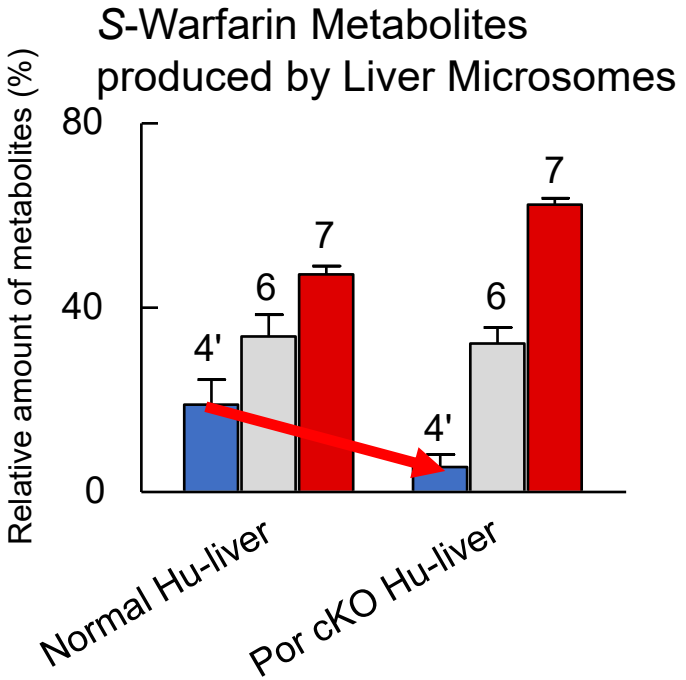


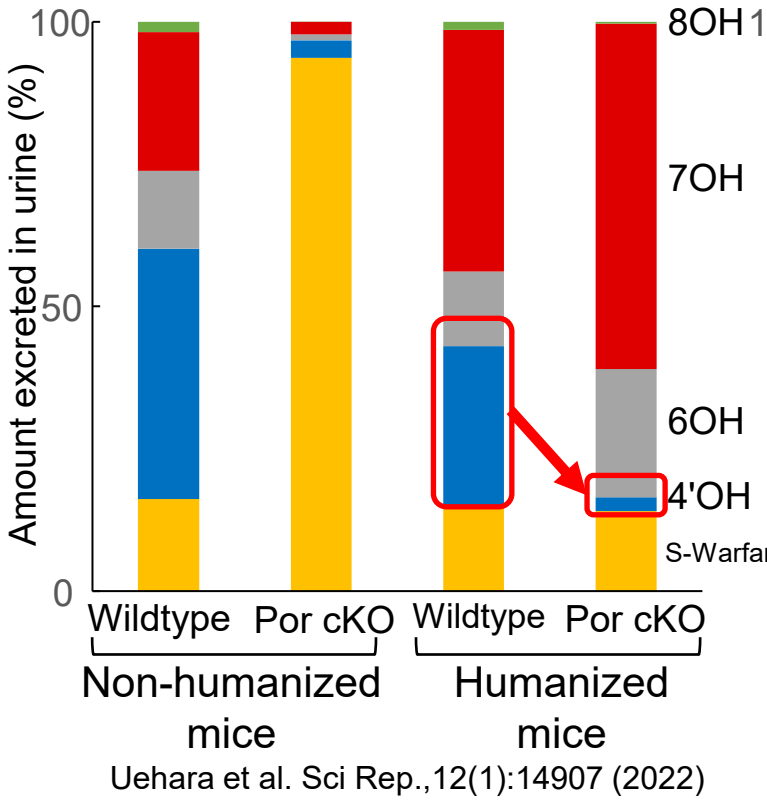
- Liver-specific deletion of Floxed exons of the Por gene is achieved by restricting Flp recombinase expression using Cyp3a11 promoter.
- The number of Por-expressing cells was remarkably reduced in the liver of Por cKO mouse.

Uehara et al. Sci Rep.,12:14907 (2022)

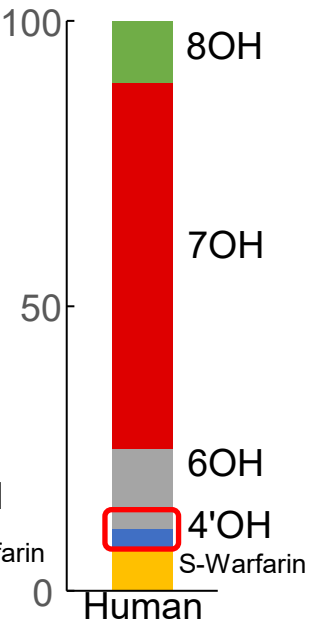
In Vitro and In Vivo *S*-Warfarin Metabolism in Por cKO Humanized-Liver Mice







Uehara et al. Sci Rep.,12(1):14907 (2022)

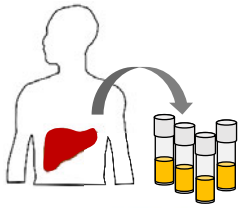


*Data from humans
Miller et al., Chem Res Toxicol., 22:1239-1245 (2009)

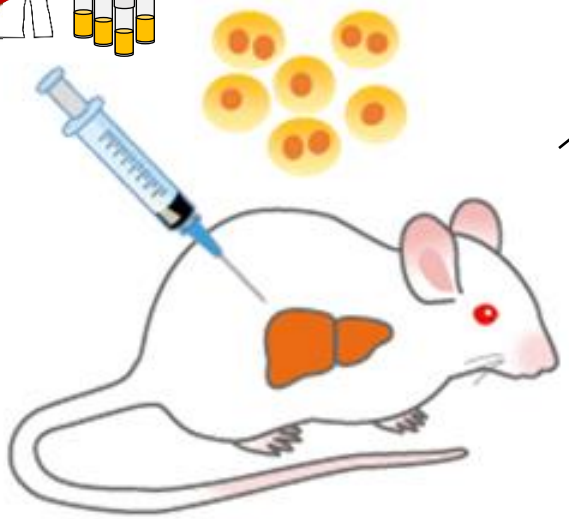
- Novel humanized-liver mouse lacking Por activity, with minimal interference from mouse hepatic P450 oxidation activity, is a valuable model for predicting human drug metabolism.

→ **Oral Presentation O-03**

Perspective on Future Directions



Primary human hepatocytes



Humanized liver mouse

Pharmacokinetics (PK)

•Prediction of metabolic clearances and distribution volume

Drug-drug interactions

•Induction and inhibition of P450 enzymes

Metabolites/Clearance pathways

•Identification of major metabolites/clearance pathways
•Identification of unique human metabolites

Hepatotoxicity

•Formation of reactive metabolites
•Detection of direct hepatotoxicity

- We will focus to develop advanced humanized liver mice with genetic modifications for drug metabolism and hepatotoxicity.

- We hope to globally contribute to the acceleration of drug discovery and development through humanized liver mouse model.

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Liver Engineering Laboratory
In Central Institute for Experimental Animals (Jan. 2022)

37th JSSX Annual Meeting
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