Oatp1a/1b Cluster Knockout Mouse (Model #10707)

Cre-mediated deletion of the solute carrier organic anion transporters Slco1a1, Slco1a4, Slco1a5, Slco1a6 and Slco1b2 provides a unique model for drug development and toxicity studies.

Applications of the Oatp1a/1b Cluster Knockout Mouse

Taconic's Oatp1a/1b Cluster Knockout Mice are homozygous deleted for the five established Slco1a and 1b genes Slco1a1, Slco1a4, Slco1a5, Slco1a6 and Slco1b2 as well as two predicted Slco1a-like mouse genes[1]. These genes encode for organic anion transporter polypeptides (OATPs), which facilitate sodium-independent transport of a wide variety of organic endogenous compounds and numerous drugs and toxins. Within the OATP1A/1B family there are no straightforward orthologous genes between human and rodents, the genes in the mouse Oatp1a/1b cluster are the closest homologues of human OATP1A2, OATP1B1 and OATP1B3. These human transporters are involved in the uptake of important drugs, such as many statins. Pharmacological interaction with these transporters or genetic polymorphisms can be associated with significant inter-individual variation in drug exposure, potentially resulting in decreased efficacy or severe toxicity.

Applications include:

- Human polymorphism: assess the potential role of human OATP1A/1B polymorphism in drug exposure.
- Drug-drug interaction: estimate the significance of pharmacological inhibition of OATP1A/1B for drug exposure.
- Pharmacokinetics: establish the contributions of OATP1A/1B to the pharmacokinetics of test compounds.
- Drug disposition: study the role of OATP1A/1B in drug tissue distribution, e.g. in liver, plasma and brain.

Features of Oatp1a/1b Cluster Knockout Mouse (model #10707)

- Homozygous disruption of five established and two predicted Slco1a/1b transporter genes.
- Animals are viable and have normal life spans, but as a consequence of hyperbilirubinemia develop signs of jaundice at approximately 12 or 85 weeks of age[1].
- Humanized OATP1B1 (#10708) and OATP1B3 (#107025) animals on the same Oatp1a/1b knockout background are available for studying direct interaction of compounds with the human transporters.

Scientific Profiles of the Oatp1a/1b Cluster Knockout Mouse Model

Expression levels of other transporters in Oatp1a/1b Cluster Knockout Mice are not or only modestly altered. Hepatic Mdr1a mRNA was modestly downregulated (~2.5-fold), while liver, kidney and small intestine expression of all other transporters analyzed (e.g. Oatp2b1, Oct1, Oct3, Oat2, Mdr1b, Bsep, Mrp2, Mrp3, Mrp4 or Bcrp) was not changed. Hepatic Ugt1a1, Aox1 and Aox3 mRNA levels were also analyzed and found to be unchanged[1].

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Studying the role of Oatp1a/1b proteins in the pharmacokinetics of drugs. Following i.v. or oral administration, plasma AUCs of the anticancer and antirheumatic drug methotrexate (MTX) were markedly (4.8- and 3.8-fold) increased in Oatp1a/1b Cluster Knockout Mice compared with wild type (WT) controls (Figure 1)[1]. In a comparable manner the pharmacokinetics of Fexofenadine[1] and Paclitaxel[2] were shown to be significantly changed in Oatp1a/1b Knockout Mice.

Establish the role of Oatp1a/1b proteins in drug-drug interactions. After rifampicin treatment, MTX plasma levels were increased and liver levels reduced in WT mice with no effect in Oatp1a/1b Knockouts, suggesting extensive inhibition of Oatp1a/1b transporters by rifampicin[1].

Origins of the Model

The Oatp1a/1b Cluster Knockout Mouse was developed in the laboratory of Alfred Schinkel of the Netherlands Cancer Institute in 2010[1]. The model was generated by insertion of loxP sites into the Slco1a5 and Slco1b2 genes at both ends of the Slco1a/1b gene cluster in E14 embryonic stem cells derived from 129P2/OlaHsd mice, followed by Cre-mediated deletion and injecting the targeted cells into C57BL/6J blastocysts. Resultant chimeras were backcrossed to FVB/N mice for at least 7 generations. Taconic received stock in 2010. The mice were derived by embryo transfer and are maintained by incrossing of homozygous mice.

Ready for Your Experiments

Taconic's Oatp1a/1b Knockout Mice are produced in Isolator Barrier Unit (IBU™) facilities. Mice are shipped in Taconic Transport Cages (TTC™) and come with an up-to-date health report documenting their Murine Pathogen Free (MPF™) health status. Barrier housing conditions are recommended for maintenance of Oatp1a/1b Knockout Mice. Taconic also offers services using this model.

Role of hepatic Oatp1a/1b transporters in MTX disposition.

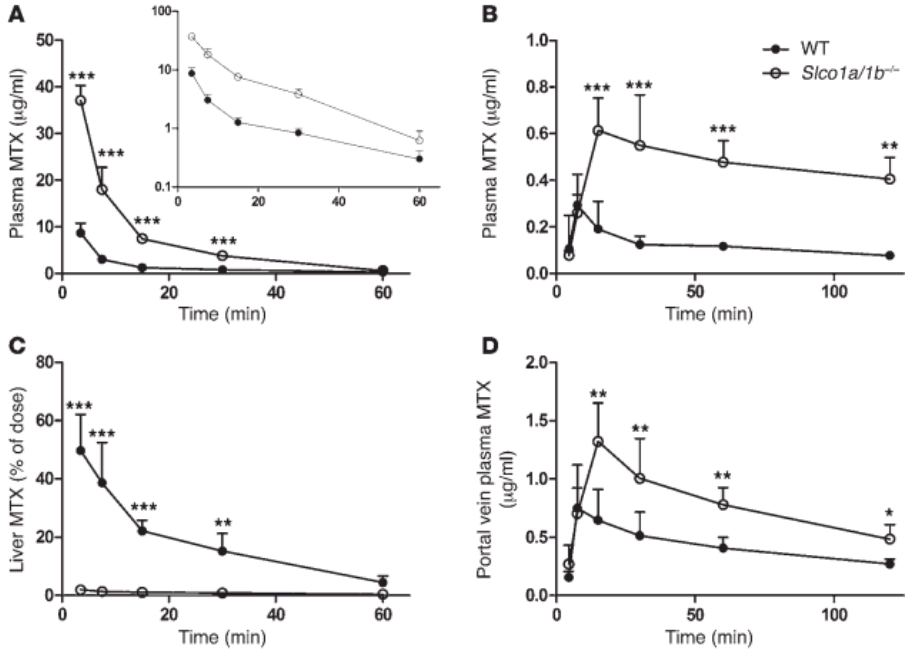

Figure 1. Pharmacokinetics of MTX (10 mg/kg) after i.v. or oral administration to female WT and Slco1a/1b–/– mice. MTX plasma concentration versus time curves after i.v. (A) or oral (B) administration, inset shows semi-log plot for i.v. data. (C) MTX liver levels (% of dose) versus time curves after i.v. administration. (D) MTX portal vein plasma concentration versus time curves after oral administration. All data are presented as mean ± SD (n = 4–8; *P < 0.05; **P < 0.01; ***P < 0.001 when compared with WT). From van de Steeg et al. 2010[1].

References cited

1. van de Steeg E, Wagenaar E, van der Kruijssen CM, Burggraaff JE, de Waart DR, Elferink RP, Kenworthy KE, Schinkel. **Organic anion transporting polypeptide 1a/1b-knockout mice provide insights into hepatic handling of bilirubin, bile acids, and drugs.** *J Clin Invest*. 2010 Aug 2;120(8):2942-52.

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Web information on the Oatp1a/1b Knockout Mouse: http://www.taconic.com/10707

Related Mouse Models from Taconic

Taconic provides a number of mouse models relevant to ADMET research. Call, fax or visit our webpage for information about these additional models:

- Mdr1a Constitutive Knock Out (#MDR1A): http://www.taconic.com/mdr1a
- Mdr1a/1b Constitutive Knock Out (#1487): http://www.taconic.com/1487
- Mrp2 Constitutive Knock Out (#6621): http://www.taconic.com/6621
- Bcrp Constitutive Knock Out (#2767): http://www.taconic.com/2767
- Mdr1a/1b-Bcrp Constitutive Knock Out (#3998): http://www.taconic.com/3998

- Mrp1 Constitutive Knock Out (#1486): http://www.taconic.com/1486
- Oct1/2 Constitutive Knock Out (#6622): http://www.taconic.com/6622
- hOATP1B1 (#10708): http://www.taconic.com/10708
- hOATP1B3 (#10725): http://www.taconic.com/10725

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Taconic Transgenic Models Publication Reference List Oatp1a/1b Cluster Knockout Mouse

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