Humanized OATP1B1 Mouse (Model #10708)

Cre-mediated deletion of the solute carrier organic anion* transporters *Slco1a1, Slco1a4, Slco1a5, Slco1a6 and Slco1b2 combined with a random transgenic insertion for SLCO1B1 provides a unique model for drug development and toxicity studies.

Applications of the Humanized OATP1B1 Mouse

Taconic's Humanized OATP1B1 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] and they carry a homozygous transgene which expresses human SLCO1B1 under control of the liver specific human ApoE-promoter[2]. These Slco genes encode for organic anion transporter polypeptides (OATPs), which in a sodium-independent manner facilitate the transport of a wide variety of organic endogenous compounds and numerous drugs and toxins. Though within the OATP1A/1B family there are no straightforward orthologous genes between human and rodents, the Slco1b2 in the mouse Oatp1a/1b cluster is the closest homologue of human SLCO1B1/OATP1B1. OATP1B1 is involved in the hepatic uptake of important drugs, such as many statins. Pharmacological interaction with this transporter 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 OATP1B1 polymorphism in drug exposure.
- Drug-drug interaction: estimate the significance of pharmacological inhibition of OATP1B1 for drug exposure.
- Pharmacokinetics: establish the contributions of OATP1B1 to the pharmacokinetics of test compounds.
- Drug disposition: study the role of OATP1B1 in hepatic and plasma exposure of test compounds.
- Drug safety: study the role of OATP1B1 in drug-induced hyperbilirubinemia.

Features of the Humanized OATP1B1 Mouse (model #10708)

- Homozygous disruption of five established and two predicted mouse Slco1a/1b transporter genes combined with a homozygous random transgenic insertion of a liver specific human OATP1B1 expression cassette.
- Animals are viable and have normal life spans.
- Oatp1a/1b Cluster Knockout mice (#10707) are available as controls.
- Humanized OATP1B3 (#10725) animals on the same Oatp1a/1b knockout background are also available for studying the role of human OATP1B3.

Scientific Profiles of the Humanized OATP1B1 Mouse Model

Hepatic expression level of OATP1B1 is similar as in human livers. The Humanized OATP1B1 Mice showed abundant expression of human OATP1B1 in their livers, which was roughly comparable with expression of OATP1B1 in a pooled human crude liver fraction. Immunohistochemical

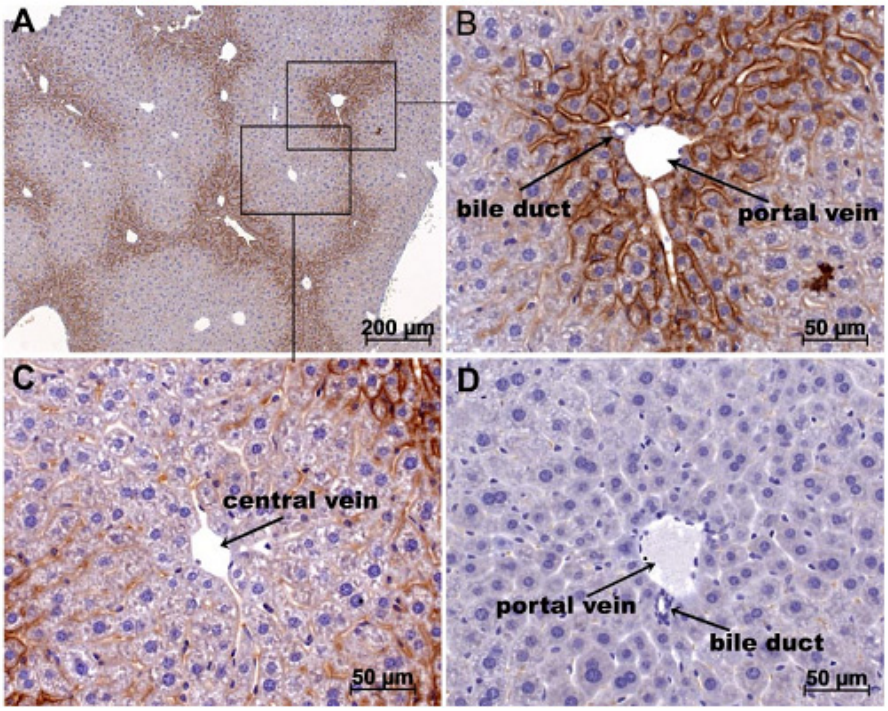

Figure 1. Immunolocalization of human OATP1B1 in the liver of SLCO1B1 transgenic mice. Paraffin-embedded liver of a SLCO1B1 transgenic mouse fed with the standard diet was sectioned (4 µm) and stained with a rabbit polyclonal antibody against human OATP1B1 (brown). Nuclei were stained with hematoxylin/eosin (blue). The picture shows a basolateral staining pattern throughout the liver lobule of SLCO1B1 transgenic mice (A), which was strongest around the portal vein (B) and weaker (but positive) at the centrolobular region (C). Wild-type liver (male) did not show staining of OATP1B1 (D). Scale bars are indicated. From van de Steeg et al., 2009.

staining was strongest around the portal vein (periportal; Figure 1B), whereas weaker staining was found toward the central vein (centrolobular; Figure 1C).

OTP1B1 in the humanized mice is functionally active. The functional activity of human OATP1B1 expressed in the liver of the humanized OATP1B1 mice was demonstrated by an increased hepatic uptake and a decreased plasma concentration of the OATP1B1 substrate methotrexate in the humanized mice compared to wild-type controls[2]. Furthermore, the increased plasma glucuronide observed in the Oatp1a/1b Cluster Knockout Mice was reversed by the human OATP1B1 transgene[3].

Note that the above immunohistochemical and methotrexate data were obtained from a publication describing the humanization for OATP1B1 with an undeleted mouse Oatp1a/1b cluster[2]. The Taconic Humanized OATP1B1 model is a combination of this original model with the Oatp1a/1b Cluster Knockout Mouse[1], which was published subsequently[3].

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. Expression of human OATP1B1 in the liver of transgenic mice was achieved by constructing an ApoE promoter-HCR1-driven expression cassette containing human SLCO1B1 cDNA followed by pronuclear injection into fertilized oocytes of FVB mice[2]. Two-cell stage embryos were implanted into oviducts of pseudopregnant F1 fosters and carried to term. A founder with stable hepatic expression of human OATP1B1 was selected for further crosses with Oatp1a/1b Cluster Knockout Mouse described above[3]. Taconic received stock in 2010. The mice were derived by embryo transfer and are maintained by incrossing of mice homozygous for both the Oatp1a/1b Cluster Knockout and the human OATP1B1 transgene.

Ready for Your Experiments

Taconic's Humanized OATP1B1 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 Humanized OATP1B1 Mice. Taconic also offers services using this model.

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.

2. van de Steeg E, van der Kruijssen CM, Wagenaar E, Burggraaff JE, Mesman E, Kenworthy KE, Schinkel AH. **Methotrexate pharmacokinetics in transgenic mice with liver-specific expression of human organic anion-transporting polypeptide 1B1 (SLCO1B1).** *Drug Metab Dispos*. 2009 Feb;37(2):277-81.

3. van de Steeg E, Stránecký V, Hartmannová H, Nosková L, Hřebíček M, Wagenaar E, van Esch A, de Waart DR, Oude Elferink RP, Kenworthy KE, Sticová E, Al-Edreesi M, Knisely AS, Kmoch S, Jirsa M, Schinkel AH. **Complete OATP1B1 and OATP1B3 deficiency causes human Rotor syndrome by interrupting conjugated bilirubin reuptake into the liver.** *J Clin Invest*. 2012 Feb 1;122(2):519-28.

- The MODELS will be used for research purposes only.
- The MODELS will not be bred except to obtain embryos or fetuses required for research purposes.
- The MODELS and biological materials derived from them will not be distributed to third parties or used for commercial purposes.

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Web information for Humanized OATP1B1 Mouse: http://www.taconic.com/wmspage.cfm?parm1=4212

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
- Oatp1a/1b Cluster Knockout Mouse (#10707): http://www.taconic.com/10707
- hOATP1B3 (#10725): http://www.taconic.com/10725

Taconic Transgenic Models Publication Reference List Humanized OATP1B1 Mouse

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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