Humanized OATP1B3 Mouse (Model #10725)

Cre-mediated deletion of the solute carrier organic anion* transporters *Slco1a1, Slco1a4, Slco1a5, Slco1a6 and Slco1b2 combined with a random transgenic insertion for SLCO1B3 provides a unique model for drug development and toxicity studies.

Applications of the Humanized OATP1B3 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 SLCO1B3 under control of the liver specific human ApoE-promoter. 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 SLCO1B3/OATP1B3. OATP1B3 is involved in the hepatic uptake of important drugs, such as many statins. Pharmacological interaction with this transporter can be associated with significant inter-individual variation in drug exposure, potentially resulting in decreased efficacy or severe toxicity.

Applications include:

- Drug-drug interaction: estimate the significance of pharmacological inhibition of OATP1B3 for drug exposure.
- Pharmacokinetics: establish the contributions of OATP1B3 to the pharmacokinetics of test compounds.
- Drug disposition: study the role of OATP1B3 in hepatic and plasma exposure of test compounds.
- Drug safety: study the role of OATP1B3 in drug-induced hyperbilirubinemia.

Features of the Humanized OATP1B3 Mouse (model #10725)

- 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 OATP1B3 expression cassette.
- Animals are viable and have normal life spans.
- Oatp1a/1b Cluster Knockout mice (#10707) are available as controls.
- Humanized OATP1B1 (#10708) animals on the same Oatp1a/1b knockout background are also available for studying the role of human OATP1B1.

Scientific Profiles of the Humanized OATP1B3 Mouse Model

Hepatic expression level of OATP1B3 is similar as in human livers and OTP1B3 in the humanized mice is functionally active. Liver levels of transgenic OATP1B3 proteins were similar to those seen in pooled

human liver samples and the increased plasma glucuronide observed in the Oatp1a/1b Cluster Knockout Mice was reversed by the expression of human OATP1B3[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[2]. 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 OATP1B3 in the liver of transgenic mice was achieved by constructing an ApoE promoter-HCR1-driven expression cassette containing human SLCO1B3 cDNA followed by pronuclear injection into fertilized oocytes of FVB mice. Two-cell stage embryos were implanted into oviducts of pseudopregnant F1 fosters and carried to term. A founder with stable hepatic expression of human OATP1B3 was selected for further crosses with Oatp1a/1b Cluster Knockout Mouse described above[1]. 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 OATP1B3 transgene.

Ready for Your Experiments

Taconic's Humanized OATP1B3 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 OATP1B3 Mice. Taconic also offers services using this model.

References cited

1. 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.

2. 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 for Humanized OATP1B3 Mouse: http://www.taconic.com/10725

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
- hOATP1B1 (#10708): http://www.taconic.com/10708

Taconic Transgenic Models Publication Reference List Humanized OATP1B3 Mouse

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.

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