Mrp2 Targeted Mutation Mice

Targeted deletion of gene for the drug transporters Mrp2 provides a unique model for pharmacokinetic, toxicology and oncology studies.

Applications of the Mrp2 Targeted Mutation Mouse Model

Taconic's Mrp2 Targeted Mutation Mice are homozygous for the targeted deletion of the *Abcc2*, formerly called *cMoat* or *Mrp2*. This gene encodes the multidrug resistance protein 2 (MRP2), which participates in active transport of compounds in the liver, small intestine and kidney. MRP2 controls the biliary excretion of various classes of xenobiotic and endogenous compounds including chemo-therapeutics and antibiotics.

Applications include:

- **Pharmacokinetics**: study the role of the MRP2 drug transporter in compound uptake and excretion.
- **Oncology**: research into drug resistant tumors.
- **Toxicology**: study the role of MRP2 in limiting exposure to dietary carcinogens.

Features of Mrp2 Targeted Mutation Mice (model 006621)

- Homozygous disruption of the drug transporter gene *Abcc2*.
- Animals are healthy and develop normally, but display mild hyperbilirubinemia and decreased bile flow as well as elevated liver size.[1]
- Knockout mice can serve as more specific tools to replace experiments using wild type animals treated with Mrp2 inhibitors. These inhibitors are often non-selective, so use of Mrp2 mice can provide more relevant information and reduce the number of experiments needed.

Scientific Profiles of the Mrp2 Targeted Mutation Mouse Model

***Mrp2*-/- mice have decreased bile flow compared to wild type mice.** Bile flow in *Mrp2*-deficient mice was measured at only 37% of that in wild type controls. Study animals were on a mixed FVB x 129 background.[1]

Bilirubin Levels in Plasma of Mrp2 Targeted Mutation Mice

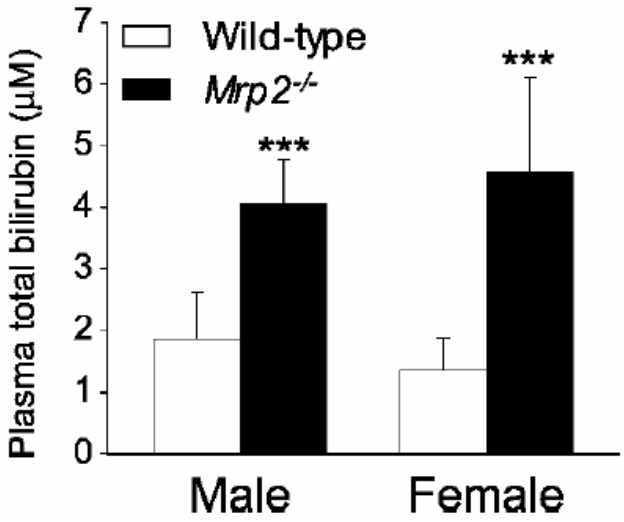

Figure 1. Plasma values of total bilirubin in wild type (open bars) and *Mrp2* knockout mice (closed bars). Means +/- SD, n = 5-6, *** P < 0.001. Adapted from Vlaming, et al., 2006.[1]

Mrp2 targeted mutation mice have impaired secretion of certain compounds into bile. *Mrp2*-deficient mice displayed decreased total bilirubin and glutathione in bile compared to wild types. The *Mrp2*-deficient mice also had increased levels of bilirubin in urine, indicating that urinary excretion may serve as an alternate excretion pathway for certain compounds in these mice. Study animals were on a mixed FVB x 129 background.[1]

Mrp2 mice have impaired elimination of the anticancer drugs methotrexate and doxorubicin compared to wild type mice. For methotrexate, this effect was found to be dose-dependent. Study animals were on a mixed FVB x 129 background.

MRP2 plays a role in chemotherapeutic resistance in tumors through active export of drugs. Mrp2 targeted mutation mice may be useful for the study of drug resistance mechanisms.[1]

However, Mrp2 targeted mutation mice show no differences in plasma clearance of the cancer drugs irinotecan and SN-38. Pharmacokinetics of these two compounds after IV administration did not differ between knockout and wild type mice. This finding is different from that in *Mrp2*-deficient rats (EHBR), which were shown to have slower plasma clearance of these compounds compared to wild type rats.1

Mrp2 targeted mutation mice have increased plasma levels of certain dietary carcinogens. *Mrp2*-deficient and wild type control mice received orally-administered PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine) and IQ (2-amino-3-methylimidazo[4,5-f]quinoline). Plasma levels of these compounds were higher in the Mrp2 targeted mutation mice versus the controls. Study animals were on a mixed FVB x 129 background.[1]

***Mrp2*-deficient mice may express differing levels of other drug transporters compared to wild type mice.** *Mrp2* knockout mice did not demonstrate upregulation of MDR1A, MDR1B or BCRP in the the liver, but MRP3 protein levels in the liver were ~2-fold higher than in wild types. MRP4 levels in the kidney were ~2-fold higher in *Mrp2*-deficient mice compared to controls. Study animals were on a mixed FVB x 129 background.[1]

Mrp2 mice may serve as a model for Dubin-Johnson Syndrome (DJS). DJS is a hereditary disease characterized by bilirubinemia and chronic jaundice. Patients who suffer from this recessive syndrome have two defective copies of the ABCC2 gene.[3-4]

Origins of the Model

The Mrp2 mouse was developed in the laboratory of Alfred Schinkel of the Netherlands Cancer Institute. The model was created through targeting of the Abcc2 gene in 129/Ola-derived E14 ES cells and injecting the targeted cells into C57BL/6 blastocysts. Resultant chimeras were backcrossed to FVB/N for seven generations (N7). Taconic received stock in 2006, and the line was embryo transfer derived. The colony is maintained by mating of homozygotes.

Ready for Your Experiments

Taconic's Mrp2 Targeted Mutation Models 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 Mrp2 Targeted Mutation Mice.

Meeting Your Research Needs

Call on Taconic's Customer Service or Technical Representative to provide the information you need to incorporate Mrp2 Targeted Mutation Mice into your experimental protocols. Inquire about updates from continuing studies using the Mrp2 Targeted Mutation Mouse Models.

Molecular Analysis Services

Taconic Biotechnology provides genotypic and phenotypic assays for characterization of transgenic and knockout lines. Assays include Southern Blots, Slot Blots, PCR and Immunoassay. An optional GLP-compliant Molecular Analysis Report can be provided.

References Cited:

1. Vlaming, M.L.H., Mohrmann, K., Wagenaar, E., de Waart, D.R., Oude Elferink, R.P.J., Lagas, J.S., van Tellingen, O., Vainchtein, L.D., Rosing, H., Beijnen, J.H., Shellens, J.H.M, Schinkel, A.H. (2006) **Carcinogen and Anticancer Drug Transport by Mrp2 in Vivo: Studies Using *Mrp2* (*Abcc2*) Knockout Mice.** *J. Pharmacol. Exp. Ther.*, Vol. 318, pp. 319-327.
2. Chu, X.Y., Kato, Y., Niinuma, K., Sudo, K.I., Hakusui, H., Sugiyama, Y. (1997) **Multispecific Organic Anion Transporter is Responsible for the Biliary Excretion of the Camptothecin Derivative Irinotecan and its Metabolites in Rats.** *J. Pharmacol. Exp. Ther.*, Vol. 281, pp. 304-314.
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Related Mouse Models from Taconic

Taconic provides a number of mouse models relevant to immunology. Call or fax for information about these additional models:

- **Bcrp Targeted Mutation Mouse (model 002767)** – carrying a disrupted *Abcg2* gene. Associated with multi-drug resistance. Useful for studies of drug uptake and cellular transport.
- **Mdr1a Targeted Mutation Mouse (model MDR1A)** – carrying a disrupted *Abcb1a* gene, a multi-drug resistance-associated transport protein, conferring a deficiency in the blood-brain barrier; useful in neurotoxicology and in studies of drug design, cellular transport and testing
- **Mdr1a/b Targeted Mutation Mouse (model 001487)** – carrying disruptions of two genes, *Abcb1a* and *Abcb1b* and lacking cellular transport mechanisms by their two multi-drug resistance-associated protein products, conferring a deficiency in the blood-brain barrier; useful in neurotoxicology and in studies of drug design, cellular transport and testing.
- **Mdr1a/b-Bcrp Targeted Mutation Mouse (model 003998)** – carries disruptions of three genes; *Abcb1a*,*Abcb1b*, and *Abcg2*, that encode for three drug-extruding transporters.
- **Mrp1 Targeted Mutation Mouse (model 001486)** – carrying a disruption of the *Abcc1a* (multi-drug resistant associated protein gene), an ATP dependent drug-extruding transporter. This mouse exhibits impaired inflammatory stimulus response and is useful for studying the role of MRP1 in mediating inflammation responses and testing drug disposition *in vivo*.
- **Oct1/2 Targeted Mutation Mouse (model 006622)** – carrying a disruption of the *Slc22a1* and *Slc22a2* genes, which encode the organic cation transporters 1 and 2. This model is important for a wide range of ADME-tox and oncology studies.

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Taconic Transgenic Models
Publication Reference List
Mrp2 Targeted Mutation Mice

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