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Models For **Life.**

Oct1/2 Double Targeted Mutation Mice

Targeted deletion of genes for the two drug transporters Oct1 and Oct2 provides a unique model for ADME-Tox and oncology studies.

Applications of the Oct1/2 Targeted Mutation Mouse Model

Taconic's Oct1/2 Targeted Mutation Mice (model 006622) are homozygous for the targeted deletion of two genes: *Slc22a1* and *Slc22a2* (formerly known as *Oct1* and *Oct2*). These genes encode for the organic cation transporters 1 and 2. These two *Slc22* family members are membrane-localized, polyspecific transporters.

In rodents, *Oct1* is expressed strongly in liver, small intestine and kidney, with expression also detected in other tissues such as brain, heart, stomach and skeletal muscle, whereas in humans *Oct1* is primarily expressed in the liver. *Oct2* is primarily expressed in the kidney in both humans and rodents, but rodent expression of *Oct2* has also been detected in the small intestine, liver and brain. OCT1 and OCT2 play important roles in removal of a wide variety of compounds from the body via the liver, intestine and kidneys. OCT1 and OCT2 transport a wide variety of unrelated substrates, and non-transported inhibitors are known for both proteins.[1]

OCT1 and OCT2 participate in the absorption and excretion of food components and xenobiotic compounds in the intestine through transport at the basolateral membrane of the luminal epithelial cells. OCT1 is involved in the hepatic uptake of compounds, which can influence biliary excretion as well as biotransformation through metabolism of compounds. The role of OCT1 and OCT2 in the kidneys is especially important as these proteins play a key role in regulating renal secretion of organic cations.[1]

Applications include:

- **Pharmacology**: study the effect of OCT1 and OCT2 on elimination of drugs.
- **Toxicology**: research into possible drug-drug interactions mediated by OCT1 and OCT2 as well as decreases in systemic exposure to toxins mediated by these transporters.
- **Oral bioavailability**: study the role of OCT1 and OCT2 at the basolateral membrane of the intestine.
- **Oncology**: research into transport of chemo-therapeutics by tumor cells.
- **Pharmacokinetics**: establish the contributions of these two proteins to the pharmacokinetics of compounds of interest.
- **Neurology**: study of the role OCT1 and OCT2 play in transport of compounds across the blood-brain barrier.

Steady-state levels of TEA vary in Oct1/2 targeted mutation mice compared to wild type controls or single gene knockouts.

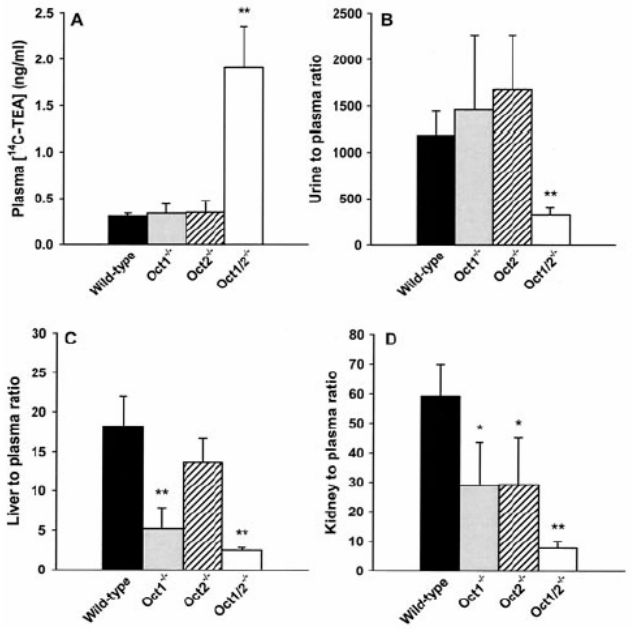

Figure 1. Steady-state pharmacokinetics of [^{14}C]TEA in wild type, *Oct1*-/-, *Oct2*-/-, and *Oct1/2*-/- mice are shown. [^{14}C]TEA was continuously infused at a rate of 27 ng/h with intraperitoneally implanted micro-osmotic pumps. (A) Steady-state levels of [^{14}C]TEA in plasma. (B) Ratios of [^{14}C]TEA concentrations in urine and plasma. (C) Ratios of [^{14}C]TEA concentrations in liver and plasma. (D) Ratios of [^{14}C]TEA concentrations in the kidneys and plasma. Results are means +/- SD (n=4). *, $P < 0.05$; **, $P < 0.01$ (compared to wild type values). Adapted from Jonker, et al., 2003.

Features of Oct1/2 Targeted Mutation Mice (model 006622)

- Homozygous disruption of two cation transporter genes in the solute carrier family 22.
- Knockout mice can serve as more specific tools to replace experiments using wild type animals treated with OCT inhibitors. These inhibitors are often non-selective, so use of Oct1/2 mice can provide more relevant information and reduce the number of experiments needed.
- Animals are healthy and develop normally.[3]
- Clinical chemistry and histology of the mice showed no abnormalities.[3]

Scientific Profile of the Oct1/2 Targeted Mutation Mouse Models

Oct1/2 mice have decreased renal excretion of TEA compared to Oct1 targeted mutation mice. Tetraethylammonium (TEA) is a small organic cation. IV administration of [^{14}C]TEA to *Oct1* single knockout mice and *Oct1/2* double knockout mice resulted in fourfold higher levels of TEA in the plasma of the *Oct1/2* double knockouts versus plasma levels in the *Oct1* single knockout mice. Renal elimination of the labeled compound was decreased in the double knockout versus the single. Study animals were on a mixed FVB x 129 background.[3]

Steady-state levels of TEA in plasma were sixfold higher in *Oct1/2* double knockout mice compared to wild type, or the *Oct1* or *Oct2* single knockouts in one experiment. TEA was infused at a steady rate, so only the rate of elimination could affect steady-state levels. Thus elimination was impaired only in the double *Oct1/2* targeted mutation mice, but not in animals with only *Oct1* or *Oct2* disruptions. Oct1/2 targeted mutation mice showed a lower liver to plasma TEA ratio, urine to plasma TEA ratio and kidney to plasma TEA ratio compared to wild type controls. Study animals were on a mixed FVB x 129 background.[3]

Oct1/2 targeted mutation mice show essentially no renal tubular secretion of TEA. Glomerular filtration of TEA did not differ substantially between Oct1/2 mice and wild type controls. Study animals were on a mixed FVB x 129 background.[3]

Oct1/2 double knockout mice may serve as good models for human deficiencies in OCT2. Whereas both OCT1 and OCT2 are present in the rodent kidneys, humans only have OCT2 in the kidney. Single gene knockouts might not be good models for human OCT2 deficiency due to the observed redundancy in OCT1 and 2 in rodents for some compounds, seemingly due to substrate overlap. Study animals were on a mixed FVB x 129 background.[3]

Oct1/2 targeted mutation mice may be useful to explore the role of OCT1 and OCT2 in efflux of compounds across the blood brain barrier. Expression of both *Oct1* and *Oct2* has been seen in the choroid plexus, but expression of these genes at the blood brain barrier is currently unknown.[2]

Oct1/2 mice may be useful for studying hepatic uptake of various compounds. *Oct1/2*-deficient mice demonstrated impaired liver accumulation of TEA. Study animals were on a mixed FVB x 129 background.[3]

***Oct1/2*-deficient mice have higher airway epithelial acetylcholine content than wild type controls.** However, the serotonin-induced broncho-constriction response is not altered in the knockout mice compared to wild types.[4]

Origins of the Models

The Oct1/2 mouse was developed in the laboratory of Alfred Schinkel of the Netherlands Cancer Institute. The model was created through sequential targeting of the Slc22a1 and Slc22a2 genes 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 doubly homozygous mice.

Ready for Your Experiments

Taconic's Oct1/2 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 Oct1/2 Targeted Mutation Mice.

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Meeting Your Research Needs

Call on Taconic's Customer Service or Technical Representative to provide the information you need to incorporate Oct1/2 Targeted Mutation Mice into your experimental protocols. Inquire about updates from continuing studies using the Oct1/2 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. Koepsell, H., Lips, K., Volk, C. (2007) **Polyspecific Organic Cation Transporters: Structure, Function, Physiological Roles, and Biopharmaceutical Implications**. *Pharm. Res.*, May 1, epub ahead of print.
2. Kusuhara, H., Sugiyama, Y. (2005) **Active Efflux across the Blood-Brain Barrier: Role of the Solute Carrier Family.** *NeuroRx*, Vol.2, pp. 73-85.
3. Jonker, J.W., Wagenaar, E., van Eijl, S., Schinkel, A.H. (2003) **Deficiency in the Organic Cation Transporters 1 and 2 (Oct1/2 [Slc22a1/Slc22a2]) in Mice Abolishes Renal Secretion of Organic Cations.** *Mol. Cell. Biol.*, Vol. 23, pp. 79022-7908.
4. Kummer, W., Wiegand, S., Akinci, S., Wessler, I., Schinkel, A.H., Wess, J., Koepsell, H., Haberberger, R.V., Lips, K.S. (2006) **Role of Acetylcholine and Polyspsecific Cation Transporters in Serotonin-induced Bronchoconstriction in the Mouse.** *Respir. Res.* Vol. 7, pp. 65-77.

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)** – carries 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*.
- **Mrp2 Targeted Mutation Mouse (model 006621)** – carries a disruption of the *Abcc2* gene, which encodes the multidrug resistance protein 2.

For more information or to place an order contact:

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Taconic Transgenic Models
Publication Reference List
Oct1/2 Targeted Mutation Mice

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