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Mdr1a Targeted Mutation Mice and Mdr1a/b Double Targeted Mutation Mice

Blood Brain Barrier Deficient Models for Central Nervous System Research

THE TACONIC Mdr1a MOUSE AND THE Mdr1a/b DOUBLE TARGETED MUTATION MOUSE CARRY A FUNCTIONAL DEFICIENCY IN THE BLOOD BRAIN BARRIER through disruption of endogenous Abcb1a and Abcb1b genes. These Targeted Mutation Mice are applicable to a wide range of central nervous system research and toxicology research.

Potential Applications of the Mdr1a Targeted Mutation and the Mdr1a/b Double Targeted Mutation Mouse

- **Neurotoxicology** Investigate central neurotoxicity of compounds.[1]
- **Drug transport** Test new drug design approaches for pro-moting or minimizing access to the brain.
- **Oral Bioavailability** Study the pharmacological activity associated with the use of P-glycoprotein inhibitors in drug therapies.[2]
- **Multi-drug resistance** Evaluate how the Mdr1a and Mdr1a/b P-glycoproteins confer multi-drug resistance to cancer cells and test therapies to increase penetration of anti-tumor cells.[1,2]
- **Teratology** Evaluate the barrier function of P-glycoprotein in placental transport and susceptibility to chemically-induced birth defects.[3]
- **Pharmacokinetics** Establish the principal contributions of the mdr P-glycoproteins to the pharmacokinetics of drugs of interest.
- **Colitis** The Mdr1a Targeted Mutation mouse serves as a model of spontaneous colitis

Tissue Concentrations of Ivermectin in Mdr1a (+/+) and (-/-) mice 24 hr after Oral Injection of a Dose of 0.2 mg/kg [1]

Tissue	Mdr1a (+/+)	Mdr1a (-/-)	Ratio (-/-):(+/+)
Brain	1.5 ± 1.2	131 ± 16	87
Muscle	9.6 ± 3.3	48 ± 3	5.0
Heart	25 ± 10	100 ± 23	4.0
Kidney	47 ± 14	141 ± 27	3.0
Liver	130 ± 45	497 ± 74	3.8
Gall Bladder	147 ± 17	1376 ± 804	9.4
Lung	23 ± 6	91 ± 24	4.0
Stomach	63 ± 60	107 ± 46	1.7
Small Intestine	31 ± 13	121 ± 30	3.9
Colon	31 ± 12	108 ± 30	3.5
Fat (neck)	188 ± 62	486 ± 78	2.6
Fat (organ)	126 ± 77	152 ± 41	1.2
Testis	9.4 ± 4.2	70 ± 7	7.4
Epididymis	59 ± 20	164 ± 17	2.8
Spleen	13 ± 4	48 ± 10	3.7
Thymus	43 ± 13	121 ± 49	2.8
Plasma	16 ± 6	52 ± 8	3.3

Results are expressed as means ± SD(n-1) in nanograms per gram of tissue. Three mice were analyzed in each group. All mice were male, between 10 and 14 weeks of age.

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Mdr1a and Mdr1a/b Targeted Mutation Mice
Background Strains

Taconic Model Name	Model Number	ILAR Designation	Gene(s) of Interest	Genotype	Background Strain
Mdr1a	MDR1A	FVB.129P2-*Abcb1a*^{tm1Bor} N7	*Abcb1a*	Homozygote	FVB.129P2
Mdr1a/b	001487	FVB.129P2-*Abcb1a*^{tm1Bor}-*Abcb1b*^{tm1Bor} N12	*Abcb1a* & *Abcb1b*	Homozygote/ Homozygote	FVB.129P2

Scientific Profile of Mdr1a Targeted Mutation Mouse

The Mdr1a Targeted Mutation Mouse has been shown to lack the protective function of the P-glycoprotein. When treated with drugs which normally do not penetrate the blood brain barrier, the brain and nervous system were found to contain elevated levels of the drug. For example, treatment with ivermectin, resulted in a 90-fold higher concentration in the brains of the Mdr1a Targeted Mutation Mouse when compared to normal mice.[1] Treatment of mice with vinblastine, a human anti-cancer compound, led to brain concentrations 20-fold higher in the Mdr1a Targeted Mutation Mouse than in normal mice.[1]

Some Mdr1a$^{-/-}$ mice may spontaneously develop colitis when housed under specific pathogen free conditions (SPF). The intestinal inflammation is similar to that seen in human inflammatory bowel disease (IBD). Symptoms included loose stool and anal mucous discharge. Inflammation along the entire length of the colon, mucosal thickening and inflammatory cell infiltrates into the lamina propria were observed. Treatment with broad spectrum antibiotics reduced the observed incidence of colitis.[2]

Infection with specific agents influences the colitis phenotype. Infection with *Helicobacter bilis* accelerates development of colitis, with evidence of diarrhea by 3 weeks post-infection. Infection with *Helicobacter hepaticus* delays development of colitis in these mice. *H. hepaticus*-infected mice had less severe IBD than unaffected Mdr1a$^{-/-}$ controls.[3] A portion of Mdr1a Targeted Mutation Mice infected with both agents developed IBD with foci of low- to high-grade dysplasia. This may make the Mdr1a mouse a good model to study the link between human ulcerative colitis and colorectal cancer.[4]

Scientific Profile of Mdr1a/b Double Targeted Mutation Mouse

The Mdr1a/b Double Targeted Mutation Mouse was generated by sequential gene targeting in ES cells. The Mdr1a/b Double Targeted Mutation Mouse and the Mdr1a Targeted Mutation Mouse both exhibit normal development, viability and fertility. The Mdr1a/b showed (male). In addition the Mdr1a/b Double Targeted Mutation Mouse showed a significant increase in accumulation of digoxin in the ovaries and adrenal glands over plasma levels and over levels in wild type mice,[5] an increase similar to the Mdr1a Targeted Mutation Mouse in accumulation of digoxin in the brain and testis

Ready for Your Experiments

Taconic's Mdr1a Targeted Mutation Mouse and Mdr1a/b Targeted Mutation Mouse are on a congenic FVB.129P2 background and are available Murine Pathogen Free (MPF™). Taconic's quality program assures that each Mdr1a Targeted Mutation Mouse and Mdr1a/b Targeted Mutation Mouse is the proper genotype. Taconic mice are shipped in Taconic Transport Cages (TTC™) and include an up-to-date health report. Clean housing conditions are recommended for these mice.

Related Mouse Models from Taconic

- **HRN Mouse (models 007293 and 007353)** – carries a liver-specific deletion of the Por gene, resulting in a mouse that lacks hepatic cytochrome P450 activity.
- **Mrp1 Targeted Mutation Mouse (model 001486)** contains 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 MRP 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
- **Bcrp Targeted Mutation Mouse (model 2767)** carrying a disrupted *Abcg2* gene. Associated

with multi-drug resistance. Useful for studies of drug uptake and cellular transport.

- **Mdr1a/b-Bcrp Targeted Mutation Mouse (model 003998)** carries disruptions of three genes; *Abcb1a*,*Abcb1b*, and *Abcg2*, that incode for three drug-extruding transporters.
- **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.

Origins

- **Mdr1a Targeted Mutation Mouse** was developed in the laboratory of Alfred Schinkel of the Netherlands Cancer Institute. The model was created by targeting the *Abcb1a* gene in E14 ES cells. Resultant chimeras were backcrossed to FVB for seven (N7) generations. Taconic received stock in 1994 and derived the line by Caesarean transfer. The colony is maintained by incrossing homozygous mice.
- **Mdr1a/b Targeted Mutation** was developed in the laboratory of Alfred Schinkel of the Netherlands Cancer Institute. The model was created through sequential targeting of the *Abcb1a* and *Abcb1b* genes in E14 ES cells. Resultant chimeras were backcrossed to FVB/N for seven (N7) generations. Taconic received stock in August 1997. The mice were then backcrossed five more generations (N12) to FVB/N. The colony is maintained by mating doubly homozygous mice.
- **Mdr1a/b-Bcrp Targeted Mutation** was developed in the laboratory of Alfred Schinkel of the Netherlands Cancer Institute. The model was created through crossbreeding of the Mdr1a/b targeted mutation mouse and the Bcrp targeted mutation mouse in the Schinkel lab. The Mdr1a/b model was created through sequential targeting of the *Abcb1a* and *Abcb1b* genes in E14 ES cells. Resultant chimeras were backcrossed to FVB/N for seven generations (N7). The Bcrp model was created by targeting the *Abcg2* gene in E14 embryonic stem cells derived from 129P2/OlaHsd mice and injecting the targeted cells into FVB blastocysts. Resultant chimeras were backcrossed to FVB/N for seven generations (N7). Taconic received stock of the triple targeted mutation line in April 2005. The colony is maintained by mating animals homozygous for all three mutations.

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Rev. 03/08

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