

Lipoprotein/Atherosclerosis Microinjected Animal Models

Taconic offers four animal models developed by Xenogen Biosciences (now Caliper Life Sciences) that exhibit the critical human characteristics of lipoprotein metabolism, and are available for compound screening and evaluation of new drug candidates.

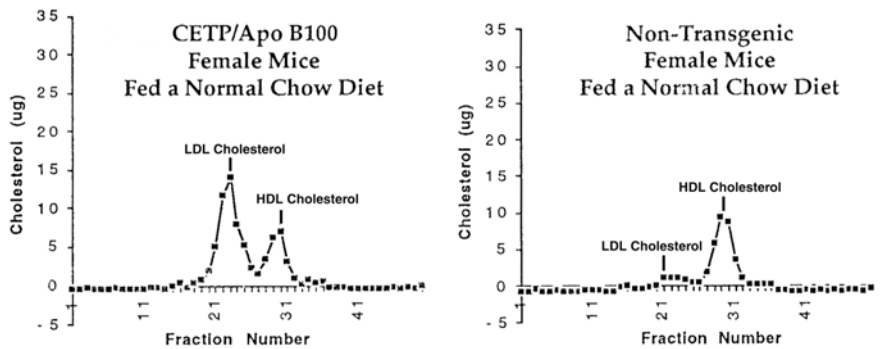
CETP-ApoB100 Double Microinjected Mouse (model 001007)

- These mice express both cholesteryl ester transfer protein and apolipoprotein B100 resulting in an animal model with a human-like serum HDL/LDL distribution.
- The LDL-cholesterol is increased three to four fold and the HDL-cholesterol is reduced approximately 60 percent as compared to non-transgenic controls.¹
- This model is useful for identifying and evaluating compounds to treat hypercholesterolemia or HDL/LDL-cholesterol imbalance to reduce the risk of developing atherosclerosis.

Analysis of study data indicate the development of atherosclerosis pathology in CETP-ApoB100 Double Microinjected Mice after administration of either a high-fat/ high-cholesterol diet² or a normal mouse chow for six months.

Tissue sections from the heart and ascending aorta were evaluated by a pathologist and the extent of fat staining in each

Comparison of female CETP-ApoB100 Double Microinjected Mice with non-transgenic control mice fed a normal chow diet:



section was scored using an arbitrary scale from zero to five (zero being the least stained, and five being the most stained). The maximum total score possible for each animal was 200.

The average score obtained from eight female CETP-ApoB100 Double Microinjected Mice fed a high-fat/high-cholesterol diet was 132.5 compared with 47.7 for nine non-transgenic female mice fed the same diet.

On the high-fat/high-cholesterol diet, lesions in the CETP-ApoB100 Double Microinjected Mice consisted of extensive foam cell accumulations distorting the overlying endothelium and infiltrating the media, compared to the non-transgenic mice which had much less staining usually restricted to a fine rim of cells underlying some regions of the endothelium. Significantly more cholesterol crystals and fibrotic lesions were also observed.³

Taconic's CETP-ApoB100 Double Microinjected Mice are maintained on a (C57BL/6 x SJL) background and are hemizygous for both transgenes.

ApoB100 Microinjected Mouse (model 001004) and CETP Microinjected Mouse (model 001003)

The ApoB100 Microinjected Mice express high levels of human apolipoprotein B100 resulting in an animal model with elevated serum levels of both total and LDL-cholesterol.⁴ The ApoB100 mouse develops atherosclerosis on a high-fat, high-cholesterol diet in a manner similar to the CETP-ApoB100 Double Microinjected mouse.⁵

The CETP Microinjected Mice express the human plasma enzyme, cholesterol ester transfer protein, resulting in an animal model with a dramatic reduction in serum HDL-cholesterol.¹

Each of these models is hemizygous for the transgene. The ApoB100 Microinjected Mice and the CETP Microinjected Mice are each maintained on a C57BL/6 x SJL background. These mice are available either for controls or as independent research models.

sPLA₂ Microinjected Mouse (model 001005)

- These models carry the human Group II secretory phospholipase A₂ (sPLA₂) transgene.⁶ sPLA₂ has been found to be abundant in human atherosclerotic lesions supporting its role in atherosclerosis pathology. The mouse expresses sPLA₂ in the serum at a level eight times greater than in non-transgenic control mice.
- The sPLA₂ Microinjected Mice are highly susceptible to atherosclerosis when fed high a fat, high cholesterol diet. Surprisingly these mice also develop significant atherosclerotic lesions when fed a normal chow diet.⁷
- In addition HDL from the sPLA₂ Microinjected Mice fails to protect against the inflammatory effects of oxidized LDL in a co-culture model of an artery wall.⁷
- sPLA₂ Microinjected Mice have significant increases of biologically active phospholipids. Oxidized phospholipids are known to be involved in atherosclerotic lesion development.⁸

Taconic's sPLA₂ Microinjected Mice are available as hemizygotes and are maintained on a C57BL/6 background. This model has been cryopreserved and is no longer in live production. Cryorecovery is available – contact your Taconic for more information.

Origin of Models

CETP - The CETP mouse was developed in the laboratory of David Grass at Xenogen Biosciences (now Caliper Life Sciences). The model was created by microinjecting the human *CETP* gene into (C57BL/6J x SJL) F2 zygotes. Taconic received stock in April 1996 at the second backcross from the founder line. The mice were then backcrossed one generation to C57BL/6 prior to

intercrossing for homozygosity. A homozygous colony is maintained for the production of hemizygotes through mating to C57BL/6NTac.

ApoB100 - The ApoB100 Microinjected Mouse was developed by MacRae F. Linton *et al.* of the Gladstone Institute of Cardiovascular Disease. The model was created by microinjecting the human apolipoprotein B100 gene into C57BL/6J x SJL zygotes. The resultant mice were backcrossed to C57BL/6 for 4 generations (N4). Taconic received stock from Xenogen Biosciences (now Caliper Life Sciences) in May 1996. The mice are maintained by backcrossing hemizygous ApoB100 mice with C57BL/6NTac inbred mice.

CETP-ApoB100 – The CETP-ApoB100 microinjected model was developed in the laboratory of David Grass at Xenogen Biosciences (now Caliper Life Sciences) by crossing the ApoB100 microinjected model with the CETP microinjected model. At Taconic, the CETP-ApoB100 model is produced by mating the hemizygous ApoB100 transgenic model (001004-T) with the homozygous CETP transgenic model.

sPLA₂ – This model was developed at Xenogen Biosciences (now Caliper Life Sciences) by microinjecting the *PLA2G2A* gene into C57BL/6 x SJL zygotes. Taconic received stock in April 1996 from founder line 703. The mice are maintained by backcrossing hemizygous sPLA₂ mice to C57BL/6NTac inbred mice

Ready For Your Experiments

Taconic's Lipoprotein/Atherosclerosis Microinjected Models are produced in Isolator Barrier Unit (IBU™) facilities under Murine Pathogen Free (MPF™) conditions and shipped in Taconic Transit Cages (TTC™) with an up-to-date health report. Barrier housing conditions are recommended for maintenance of each line.

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4. Linton et al. 1993 *Journal of Clinical Investigation*, 92:3209-3037
5. Purcell-Huynh et al. 1995 *Journal of Clinical Investigation*, 95:2246-2257
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7. Ivandic et al. 1999 *Arteriosclerosis, Thrombosis, and Vascular Biology*, 19:1284-1290
8. Leitinger et al. 1999 *Arteriosclerosis, Thrombosis, and Vascular Biology*, 19:1291-1298

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