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APOE*3Leiden(.CETP) mice as translational animal models for cardiovascular and metabolic diseases. Application in pharma

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Hans will give a short introduction on the background and specific characteristics of the E3L.(CETP) mice, address their predictive value with respect to outcome of clinical studies and show examples of the application of the mice in pharmacological studies towards mechanism of action in lipid metabolism and atherosclerosis.

The APOE*3-Leiden mouse model is the platform that we use most often in our scientific group Vascular and Metabolic Diseases.

A further developed model is the APOE*3-Leiden.huCETP double transgenic mouse which has proven to be very suitable for testing the effects of drugs and nutritional factors on plasma HDL and triglyceride levels, atherosclerosis and metabolic syndrome. The new model is based on TNO-Pharma's proprietary mouse model, the Apolipoprotein E*3-Leiden (APOE*3-Leiden) transgenic mouse, an established and well-recognized model for hyperlipidemia and the development of atherosclerosis. In this newly generated mouse, human cholesterol ester transfer protein (huCETP) under control of its natural flanking regions was introduced into the APOE*3-Leiden mouse resulting in a more human-like lipoprotein metabolism with transfer of cholesterol ester from HDL to the apoB-containing lipoproteins in exchange for triglycerides. As a result of this adverse lipoprotein distribution and the higher amount of atherogenic apoB-containing lipoproteins, the E3L.CETP transgenic mice develop increased atherosclerosis on a Western-type diet as compared to E3L transgenic mice.

The new model has the same favorable characteristics as the APOE*3-Leiden mouse, such as (i) responsiveness to all hypolipidemic drugs currently used in the clinic, such as statins, fibrates, ezetimibe and niacin, at similar dosages and in a similar way to humans, (ii) the ability to titrate cholesterol and triglycerides to any desired level and (iii) to conduct atherosclerosis studies in a progression (prevention) design or a regression (therapeutic) design. Moreover, the APOE*3-Leiden / huCETP mouse is very well suited to testing the effect of drugs that modulate HDL levels. The mice demonstrate reduced apoB-containing lipoproteins and increased HDL levels upon treatment with the registered drugs atorvastatin, fenofibrate and niacin and with CETP-inhibitors. PCSK9 inhibition demonstrated a significant additional effect on top of a statin with respect to lipid-lowering and atherosclerosis.

APOE*3-Leiden/huCETP is a model for mixed dyslipidemia, a condition comparable with diabetic dyslipidemia and it is a predictive animal model: Drugs and nutritional factors that failed in clinical studies, such as the GPR109a agonist MK-0354, the CETP-inhibitor torcetrapib, an experimental RCT-inducer, plant sterol derivative and policosanols, also failed in this mouse model (see publication list). With respect to biologicals, studies have been performed with mAbs and vaccines against PCSK9, CETP, ox-LDL, Endothelial Lipase, IL-6, and with rec.HDL, GLP-1 and PYY analogues and an EPO-receptor agonist.

The mouse models have been used extensively in studies for pharma and food industry in testing efficacy and increasingly safety of small molecules and protein-based therapies and work towards the mechanism of action (> 150 studies).

Short CV

Hans Princen studied chemistry with major in biochemistry at the University of Nijmegen, where he also completed his PhD. In 1983 he joint TNO, where he is involved in preclinical and clinical research into the following areas: Hepatic and intestinal lipid metabolism (since 1984), apolipoprotein synthesis (since 1988), LDL oxidation (since 1990), atherosclerosis (since 1997), insulin resistance (since 2004). From 1996 on he focussed on in vivo physiology and pharmacology of cardiovascular disease using TNO's proprietary mouse models, the E3L and E3L.CETP mice, and their validation and commercialization as translational mouse models for hyperlipidemia, atherosclerosis and insulin resistance.

From 1991 to 2005 he was head of the sector Lipids and Atherosclerosis and subsequently of the department of Vascular and Metabolic Diseases. Currently, he is senior scientist in the department of Metabolic Health Research. He has published 176 papers, among which 167 papers in peer-reviewed journals and 9 chapters in books, and supervised 14 PhD students during their thesis work. Current H-index 47 (Google Scholar); 43 (WoS). He supervised over 130 TNO-studies mainly in E3L.(CETP) mice for the pharmaceutical and food industry.