Leiden Metabolic Research Services (LMRS) provides a large contract research program on energy metabolism in relation to obesity, type 2 diabetes and atherosclerosis. Within this field of expertise we offer custom-made drug and dietary intervention studies in our unique APOE*3-Leiden.CETP mouse model, a well-established model for human-like lipid metabolism and atherosclerosis.

**Main advantage over other mouse models**

- Responds to lipid-lowering and HDL-increasing interventions similarly as humans:
  - Accomplished by its intact expression of apoE and the LDL receptor, and transgenic expression of human CETP.
  - Of note, apoE-deficient and LDL receptor-deficient mice do not respond to lipid-lowering interventions.

**Human-like pathologies**

- Dyslipidemia, with plasma lipid levels easily titrated to desired levels\(^1\)\(^-\)\(^1\)\(^4\).
- Insulin resistance, which develops on high-fat diets\(^8\)\(^-\)\(^1\)\(^2\).
- Non-alcoholic steatohepatitis (NASH), with hepatic accumulation of lipids and inflammatory cells\(^4\)\(^,\)\(^5\).
- Atherosclerosis, driven by both cholesterol and inflammation\(^1\)\(^-\)\(^4\)\(^,\)\(^1\)\(^0\)\(^,\)\(^1\)\(^3\)\(^-\)\(^1\)\(^6\).

**Validated intervention strategies**

- Lipid-lowering strategies, with reduction of atherosclerosis (e.g. statins\(^2\)\(^,\)\(^3\)\(^,\)\(^1\)\(^3\)\(^,\)\(^1\)\(^4\), PCSK9 inhibitors\(^3\), fibrates\(^8\)\(^,\)\(^1\)\(^1\)).
- HDL-raising strategies, with reduction of atherosclerosis (e.g. CETP inhibitors\(^2\)\(^,\)\(^1\)\(^3\), niacin\(^1\)\(^0\)).
- Anti-diabetic strategies, with improvement of insulin sensitivity (e.g. GLP1 analogs\(^4\)\(^,\)\(^8\)\(^,\)\(^1\)\(^2\), rosiglitazone\(^9\)).
**Dyslipidemia**

APOE*3-Leiden.CETP mice have a human-like plasma lipoprotein profile and plasma lipid levels. These mice respond to lipid-lowering strategies\(^1,3,7,10-15\) by virtue of a functional hepatic lipoprotein remnant clearance pathway involving apoE and LDLr. Moreover, as they express human CETP they also respond to HDL-increasing strategies\(^2,10,14\). This is thus an ideal model for pharmacological and dietary interventions for treatment of dyslipidemia.

Statins reduce plasma nonHDL-cholesterol\(^14\) (left) and CETP inhibitors increase HDL-cholesterol\(^2\) (right).

**Atherosclerosis**

APOE*3-Leiden.CETP mice develop diet-induced atherosclerotic lesions with all characteristics of human lesions. The various stages of atherosclerotic lesions (type I to V) can be distinguished\(^14\) and develop within 3-6 months, depending on the dietary cholesterol content.

Numerous pharmacological and dietary intervention studies have been performed in this model investigating the effect on atherosclerosis progression and regression\(^1,4,10,13,14\).

Atherosclerotic lesions upon Western-type diet feeding.

**Nonalcoholic steatohepatitis**

APOE*3-Leiden.CETP mice develop nonalcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) when fed a high-fat\(^5\) or Western-type\(^4\) diet. Typical characteristics resembling human NASH are observed, including macrophage and neutrophil infiltration and hypertrophy. This allows efficacy studies of compounds and dietary interventions aimed at reducing NASH in a representative, human-like setting.

NASH development upon high-fat diet feeding.
Obesity and insulin resistance

APOE*3-Leiden.CETP mice develop high-fat diet-induced obesity and insulin resistance\(^5,8,9,12\). **We offer custom-made drug and dietary intervention studies on all aspects of obesity and insulin resistance.** The hyperinsulinemic euglycemic clamp analysis\(^{12}\), the golden standard for insulin sensitivity, allows studying insulin sensitivity as well as glucose and fatty acid metabolism in various organs and tissues. Moreover, surrogate measures of insulin sensitivity such as glucose tolerance test are routinely performed. We additionally use genetic models of obesity, such as ob/ob and db/db mice.

Energy expenditure and brown fat activation

Novel strategies to reduce hyperlipidemia, obesity, insulin resistance and atherosclerosis include increasing brown fat activity. We offer a full set of in vivo and ex vivo techniques for investigation of energy expenditure, brown fat activity as well as mechanisms of action, including fully automated metabolic cages for determining glucose and fatty acid oxidation, and lipoprotein kinetics using tracers\(^1,6,7,9\).

In view of its intact apoE-LDLr-mediated remnant clearance pathway, the APOE*3-Leiden.CETP model is the preferred model as compared to other mouse models for studying the effect of brown fat modulation on hyperlipidemia and atherosclerosis\(^1\).

BAT activation using a β3-adrenergic receptor agonist reduces plasma triglycerides (TG), nonHDL-cholesterol and atherosclerosis\(^1\).
Selected references


5. Liang W et al. Metabolically induced liver inflammation leads to NASH and differs from LPS- or IL-1-induced chronic inflammation. Lab Invest 2014; 94(5): 491-502.


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