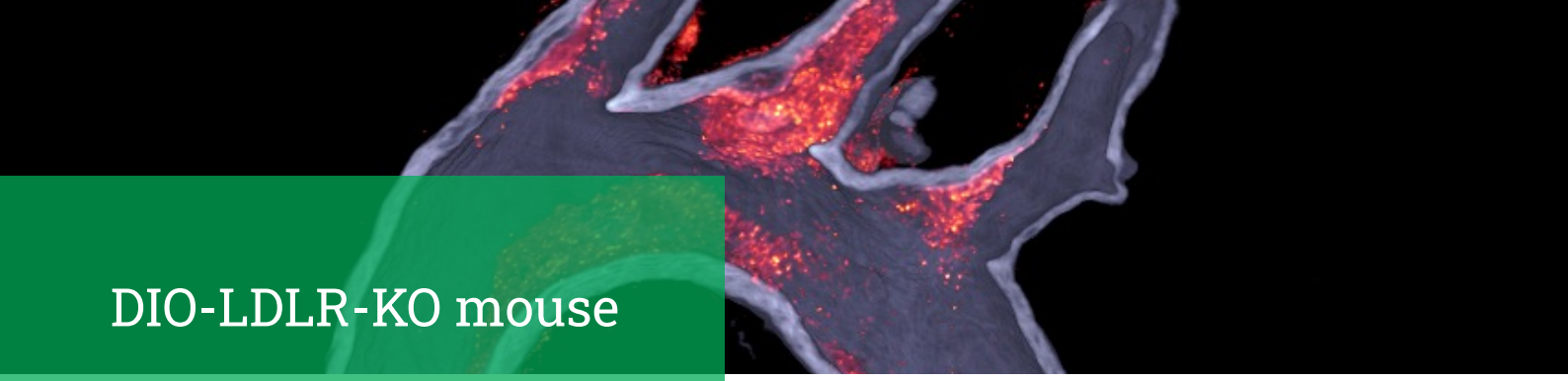


DIO-LDLR-KO mouse

Mouse model of atherogenic dyslipidemia

Diet-induced obese mouse model of dyslipidemia and atherosclerosis

The low-density lipoprotein receptor knockout mouse model (LDLR-KO) fed western diet develop obesity (DIO), elevated plasma total cholesterol, LDL and triglyceride levels, and extensive atherosclerotic plaque. Uniquely, light sheet 3D imaging of isolated vasculature combined with deep learning assisted image analysis enables precise and unbiased analysis of plaque volume and vascular wall inflammation.
The DIO-LDLR-KO mouse model allows for prophylactic and therapeutic drug efficacy testing.

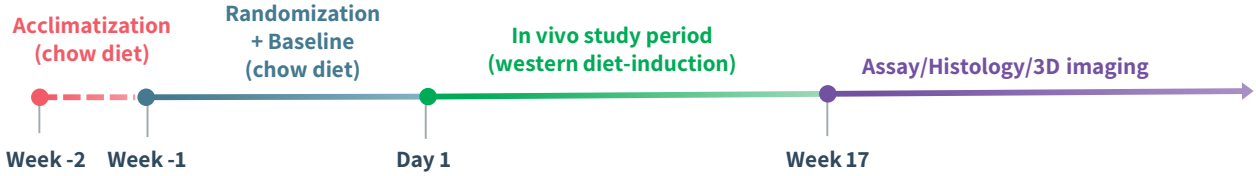
Key model traits

- Male LDLR-/- mice on western diet.
- Dyslipidemia with hypercholesterolemia (LDL).
- Widespread atherosclerotic plaque formation.
- 3D imaging pipeline for detailed characterizing of plaque volume and vascular wall inflammation in specific anatomical regions of vasculature.
- Prophylactic and therapeutic intervention.

Model induction	Western diet (D12079B) for 17 weeks.
Strain	LDLR-KO (B6.129S7-Ldlrtm1Her/J)

Study outline

Drug dosing: SC, QD
Food intake: QW (24h)



Randomization
- BW

Pre-Termination
- Plasma TG/TC/LDL/HDL

Termination
- Dissection of aorta and arteries for 3D imaging
- Liver

Terminal Biochemistry:
- Plasma Serum Amyloid A
- Liver TG/TC

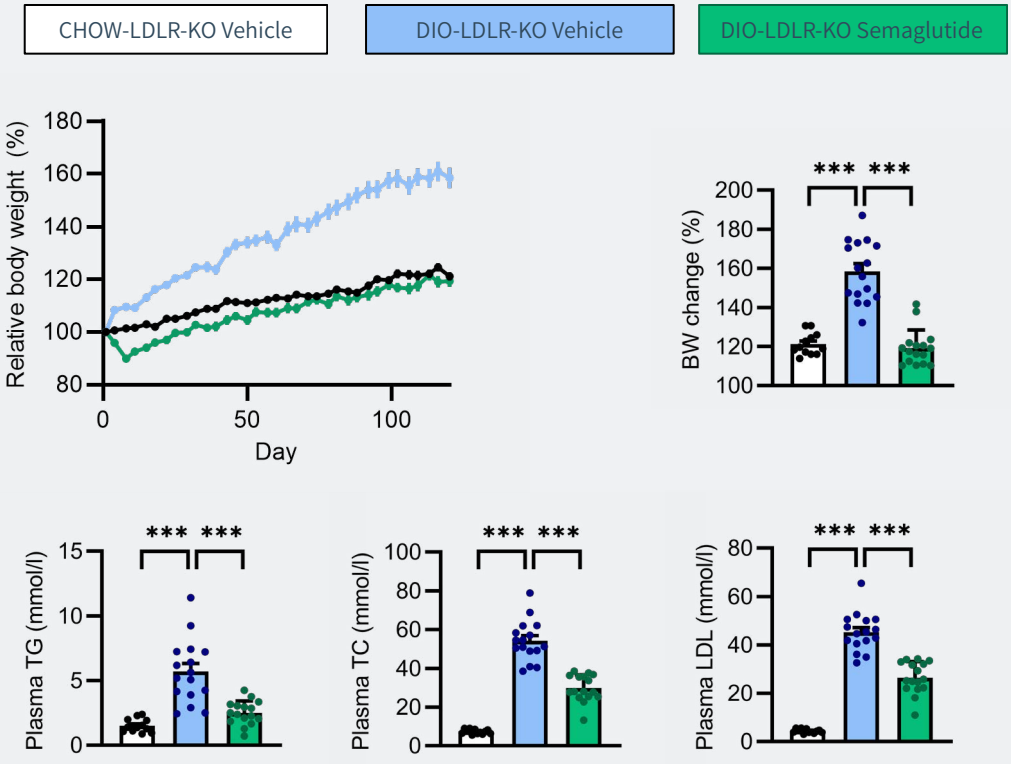
Terminal 3D quantitative imaging:
- Plaque volume and distribution
- Arterial wall inflammation (CD45)

Terminal tissue/blood samples for optional analysis:
- Aortic root – RNAseq/Histology
- Liver – RNAseq/Histology
- Plasma – Biochemistry

Dyslipidemia

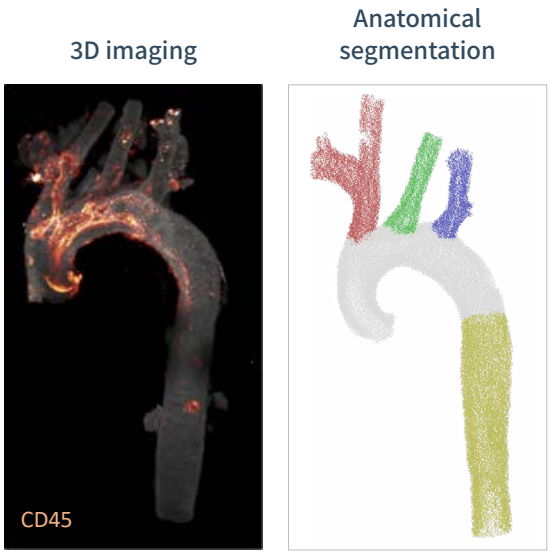
DIO-LDLR-KO mice demonstrate obesity in conjunction with dyslipidemia, as evident in increased plasma triglycerides (TG), total cholesterol (TC) and LDL.

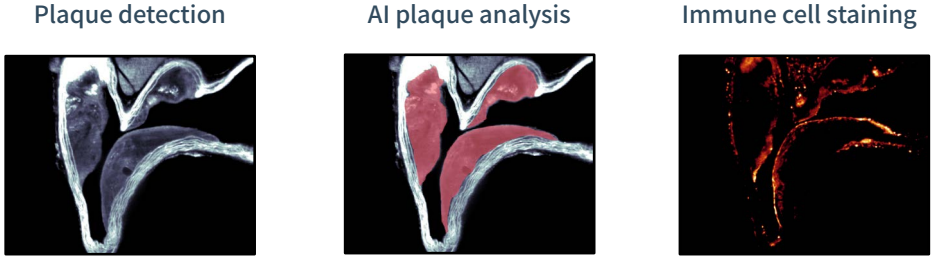
Prophylactic semaglutide treatment in DIO-LDLR-KO mouse model prevents obesity development and reduces plasma TG, TC and LDL levels.

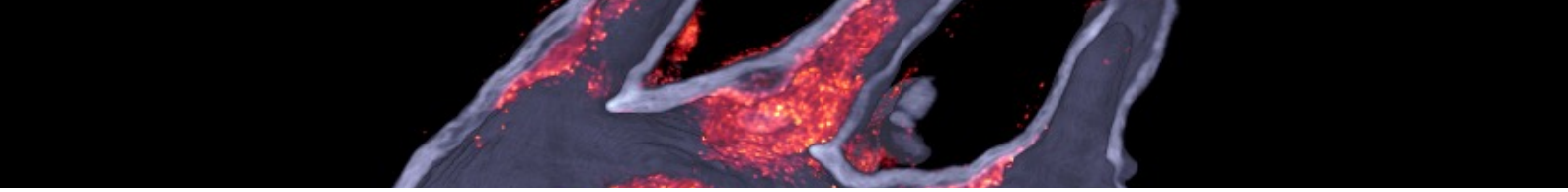


3D imaging for evaluation of atherosclerosis

Light sheet microscopy of optically transparent aorta and arteries enables accurate mapping of plaque volume in each anatomical region of the vasculature. Deep learning pipeline is established for rapid assessment of plaque distribution based on tissue autofluorescence. Immunohistochemistry for CD45 enables additional assessment of plaque immune cell burden.







Atherosclerosis

DIO-LDLR-KO mice demonstrate extensive plaque formation and plaque leukocyte infiltration in the aortic arch and branching sites of the major arteries.

Semaglutide prophylactic treatment reduces total plaque volume with anatomical region-specific differences and reduces vascular wall inflammation.