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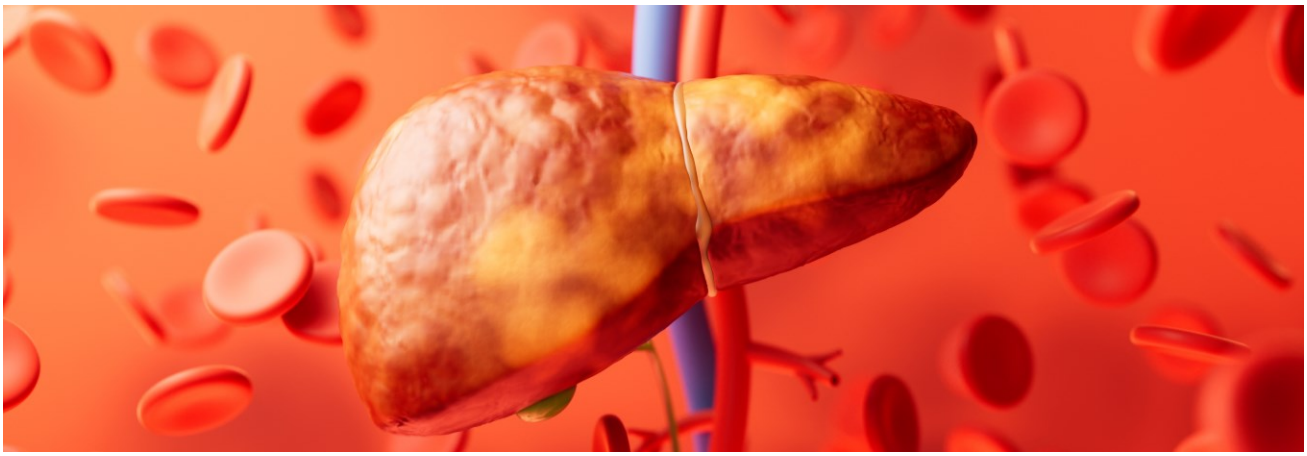
Licensing Opportunity

PI4KB inhibitors for the treatment of fatty liver disease



Application

PI4Kβ inhibitors (e.g. UCB9608) reduce triglyceride levels in fatty livers and prevent the progression of inflammation and fibrosis. Moreover, PI4Kβ inhibitors defatten steatotic liver grafts in ex-vivo perfusion machines so that the grafts become eligible for transplantation.

Features & Benefits

- Second medical use of PI4Kβ inhibitors in the treatment of fatty liver disease (e.g. UCB9608 was previously used as immunosuppressive agent)
- Independent of insulin signalling
- Mouse experiments validate in-vitro findings

Publication

- Ding, L., Huwyler, F., Long, F. et al. “Glucose controls lipolysis through Golgi PtdIns4P-mediated regulation of ATGL”, Nat Cell Biol 26, 552–566 (2024) https://doi.org/10.1038/s41556-024-01386-y
- Patent pending

transfer

ETH transfer
transfer@sl.ethz.ch
www.ethz.ch/transfer
Reference 2023-118

Invented by D-BIOL: Christian Wolfrum, Lianggong Ding

Technology Readiness Level

1 2 3 **4** 5 6 7 8 9

Background

The body stores fatty acids as triglyceride esters in lipid droplets in adipose tissue. Excess fat building up in the liver can lead to inflammation and fibrosis. Most common interventions involve change of lifestyle, change of diet and increased physical workout. There are no effective pharmaceutical approaches that treat fatty liver disease. In pathological situations a liver transplantation is the only way to prevent a fatal outcome.

Invention

The present invention relates to PI4KB inhibitors for the treatment of fatty liver disease, particularly non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

A cell-intrinsic mechanism senses glucose availability and drives lipolysis via adipose triglyceride lipase (ATGL). When glucose levels are low, the ATGL level increases. The ATGL enzyme releases the lipid droplets from the tissue. PI4KB (phosphatidylinositol 4-kinase beta) inhibitors simulate low glucose levels in the signaling pathway, which triggers the activity of ATGL. This cell-intrinsic pathway is independent from insulin signaling, probably providing the cell with means to meet complex physiological demands.

Tests in a mouse model confirm the mechanism. The inventors tested the defattening effect of UCB9608 ex vivo on a steatotic human liver graft, which was connected to a perfusion system.