The small molecule competitive inhibitor of ATP citrate lyase, EVT0185, reverses liver fibrosis in preclinical mouse models by targeting hepatic stellate cells

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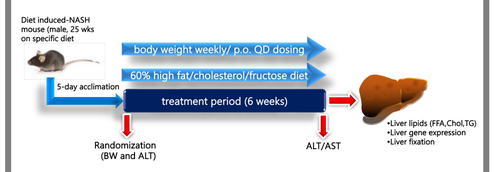
BACKGROUND

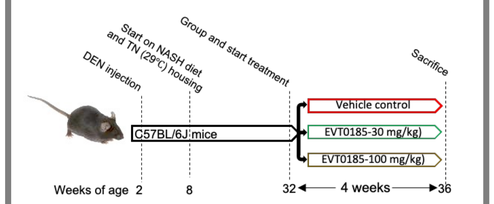
A key driver of liver fibrosis is activated hepatic stellate cells (HSCs). Like cancer cells, activation of HSC is linked to changes in aerobic glycolysis, de novo lipogenesis, and free cholesterol; metabolic pathways that are thought to support the HSC proliferation and secretion of extracellular matrix and cytokines. Phenotypic screening in primary mouse hepatocytes identified EVT0185 as a novel small molecule inhibitor of de novo lipogenesis in hepatocytes that competitively inhibits ACLY activity in cell-free assays. Using three distinct preclinical mouse models of Non-Alcoholic Steatohepatitis (NASH), oral delivery of EVT0185 dose-dependently reversed steatosis and ballooning but also effectively reversed fibrosis.

EXPERIMENTAL MODELS

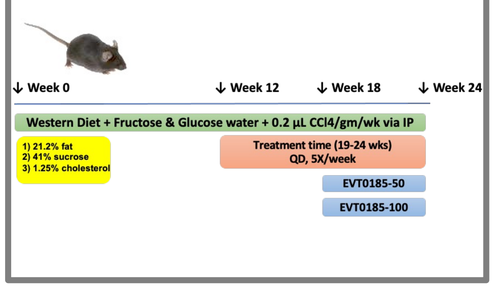
DIN-TAC MOUSE MODEL



NASH-DEN MOUSE MODEL

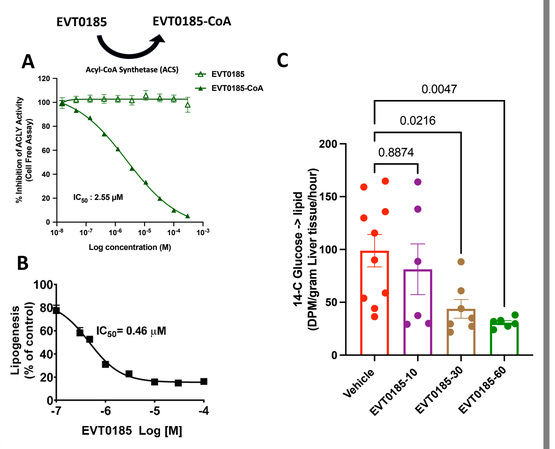


FAT NASH (HFD-CCL4) MOUSE MODEL



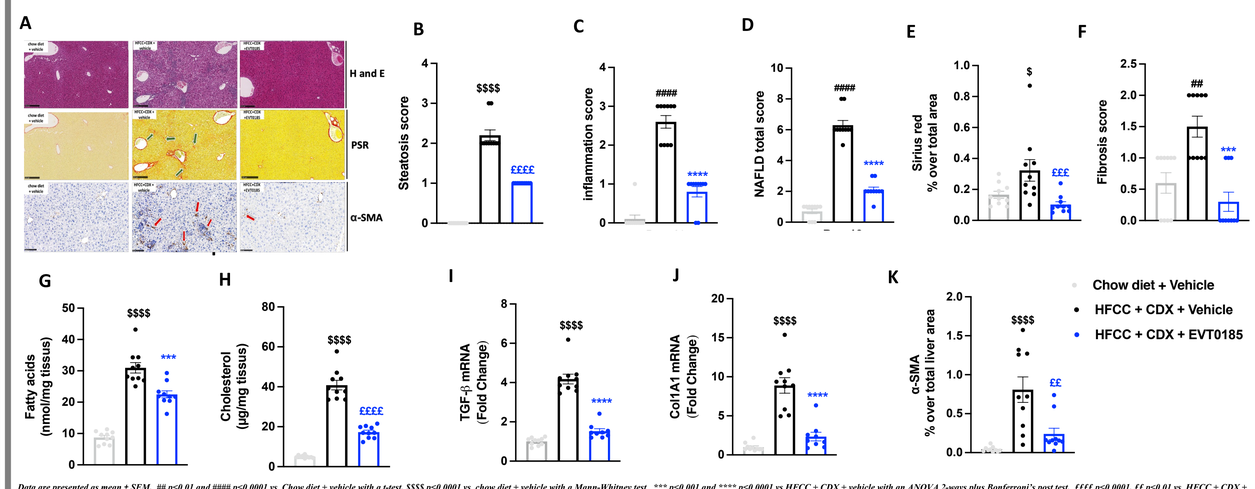
RESULTS

1) EVT0185-CoA inhibits ACLY and suppresses hepatic de novo lipogenesis (DNL) in vitro and in vivo



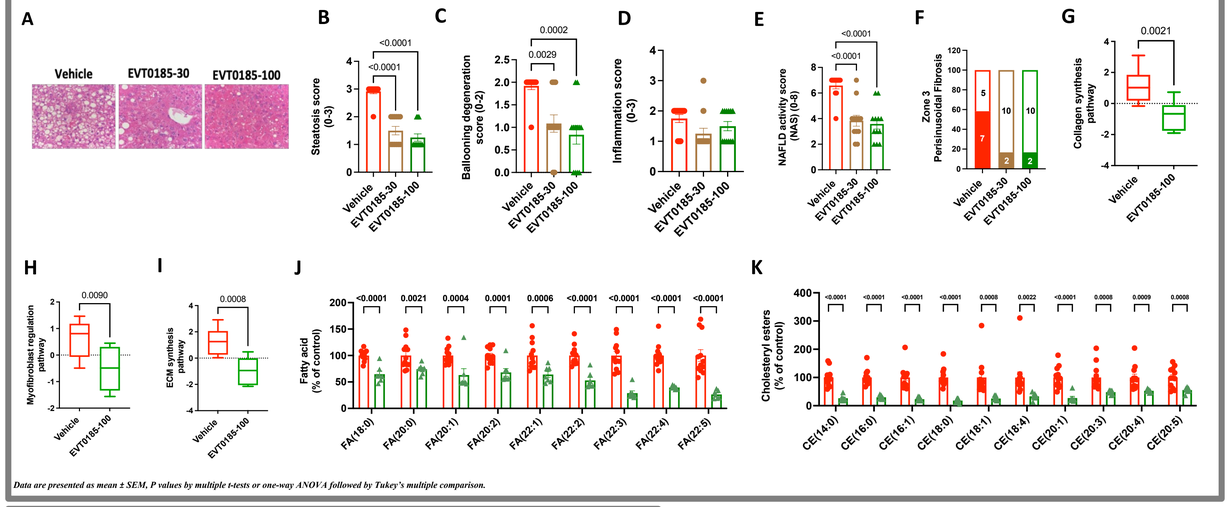
Data are presented as mean ± SEM, P values by one-way ANOVA followed by Tukey's multiple comparison.

2) EVT0185 decreases NAS and fibrosis in DIN-Tac model



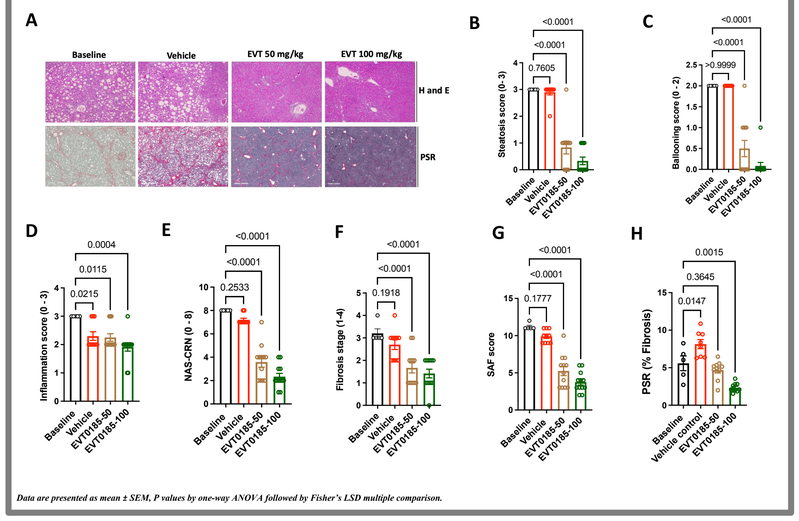
*Data are presented as mean ± SEM, ## p<0.01 and #### p<0.0001 vs. Chow diet + vehicle with a t-test, $$$$ p<0.0001 vs. chow diet + vehicle with a Munn-Whitney test. *** p<0.001 and **** p<0.0001 vs HFCC + CDX + vehicle with an ANOVA 2-ways plus Bonferroni's post test, ££££ p<0.0001, ££ p<0.01 vs. HFCC + CDX + vehicle with a Kruskal-Wallis plus Dunns post test.*

3) EVT0185 decreases NAS and fibrosis in the NASH-DEN mouse model



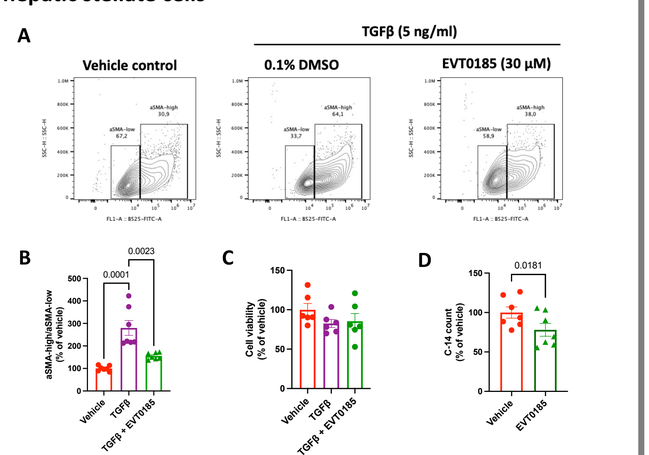
Data are presented as mean ± SEM, P values by multiple t-tests or one-way ANOVA followed by Tukey's multiple comparison.

4) EVT0185 decreases NAS and reverses fibrosis in the FAT NASH (HFD-CCl4) mouse model



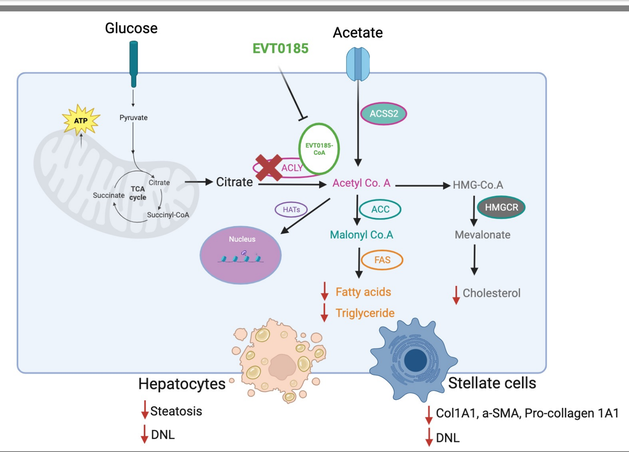
Data are presented as mean ± SEM, P values by one-way ANOVA followed by Fisher's LSD multiple comparison.

5) EVT0185 reduces DNL and inhibits the activation of human hepatic stellate cells



Data are presented as mean ± SEM, P values by unpaired t-test or one-way ANOVA followed by Tukey's multiple comparisons

GRAPHICAL ABSTRACT



METHODS

- Cell-free based assays were used to measure the effects of compound on human ACLY.
- Quantitation of fatty acid and cholesteryl esters was carried using ultra high-performance liquid chromatography/mass spectrometry method.
- NASH scoring and PSR quantification were performed blindly using Qupath and Image J software.
- Nanostring analysis in liver tissues were performed using a ncounter fibrosis panel.

SUMMARY

EVT0185 directly inhibits HSC activation and effectively reduces steatosis and ballooning while reversing fibrosis without ensuing hypertriglyceridemia supporting potential evaluation in clinical populations.

FUNDING

Espervita THERAPEUTICS

MITACS Accelerate