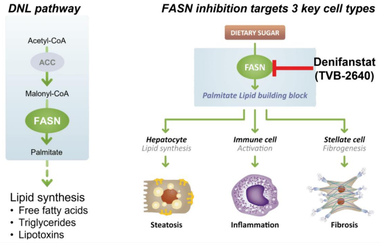
Fatty acid synthase (FASN) inhibitor reduces atherosclerosis development in diet-induced dyslipidaemia LDL receptor knockout mice with MASH

Wen-Wei Tsai[1], Eveline Gart[2], Martine C. Morrison[2], Eduardo Martins[1], George Kemble[1], Marie O'Farrell[1]

1. Sagimet Biosciences, San Mateo, United States, 2. TNO Metabolic Health Research, Leiden, Netherlands

Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH
- FASN inhibition targets 3 hallmarks of MASH: inhibits liver fat synthesis & accumulation (hepatocytes), inhibits fibrosis (hepatic stellate cells require DNL for activation) and decreases inflammation (inflammasome activation by palmitate)[1]
- Denifanstat has recently demonstrated statistically significant MASH resolution and fibrosis improvement in the Phase 2b MASH study, FASCINATE-2 (NCT04906421)[2]
- Denifanstat decreased LDL-cholesterol and increased polyunsaturated triglycerides in both Phase 2a FASCINATE-1[3] and Phase 2b FASCINATE-2[2] studies, suggesting potential cardiovascular benefits in addition to direct liver effects

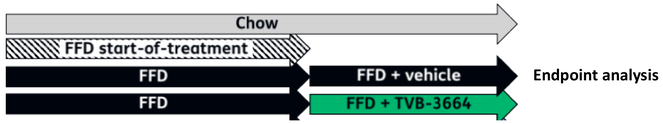


Hypothesis & Aims

- Hypothesis: FASN inhibitor would prevent atherosclerosis through reduction of circulating cholesterol in the context of MASH
- This study was to evaluate the effect of FASN inhibitor on plasma lipids and atherosclerosis in LDL receptor knockout (Ldlr-/-) mice with dyslipidaemia and MASH
- The effect of FASN inhibitor on circulating inflammatory factors and liver histology was also evaluated

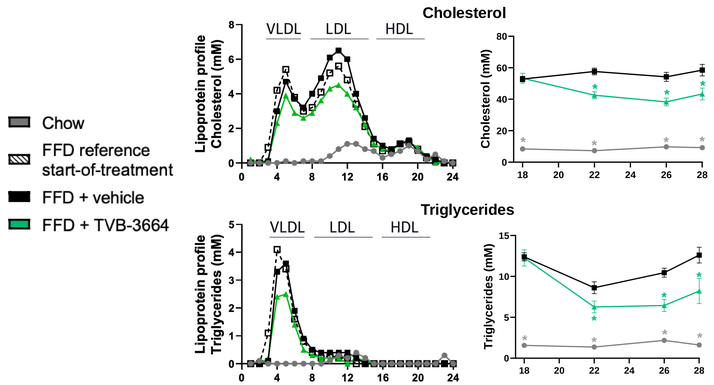
Methods

- Male Ldlr-/-.Leiden mice were fed with fast-food diet (FFD) for 18 weeks to induce dyslipidaemia, atherosclerosis and MASH features, and treated with TVB-3664 (a surrogate FASN inhibitor for denifanstat, 5 mg/kg, PO, QD) for 10 weeks. Endpoints included plasma lipids, lipoprotein profile, inflammatory marker profile, liver histology and histological analysis of atherosclerosis in the aortic root (lesion area and severity according to the AHA score in 4 cross sections, *TNO, Netherlands*).

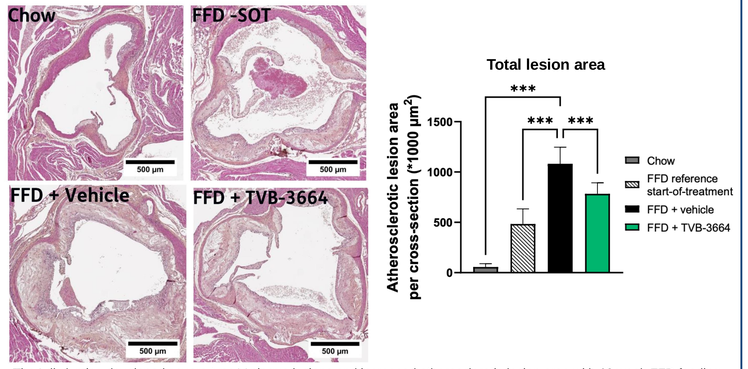


Results

FASN inhibitor rapidly reduced circulating cholesterol and triglycerides in Ldlr-/- MASH mice

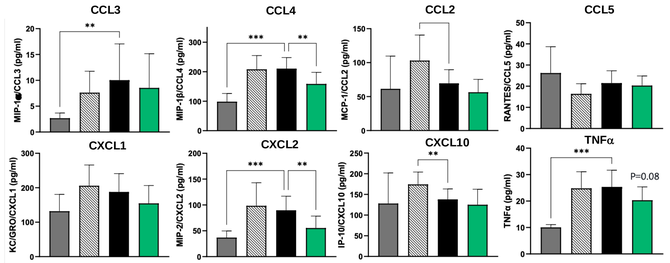


FASN inhibitor reduced total atherosclerotic lesion area per cross-section of aortic root

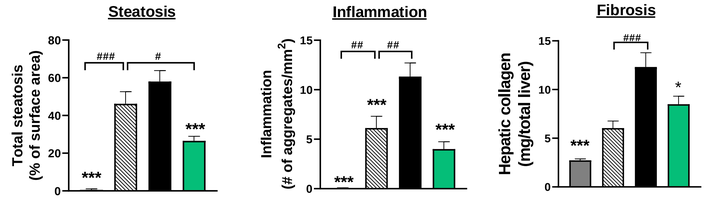


The Ldlr-/- mice developed severe type V plaque lesions and increased atherosclerotic lesion area with 28-week FFD feeding

FASN inhibitor reduced several inflammatory markers related to atherosclerosis in Ldlr-/- MASH mice



FASN inhibitor improved liver histology in Ldlr-/- MASH mice



All figures represent data mean + SD with *p<0.05, **p<0.01 and ***p<0.001 vs FFD-vehicle. *Chow n=8; vehicle, TVB-3664, n=14~15*

Conclusions

- Denifanstat has shown promise on LDL-C lowering and liver histological improvements in MASH patients in Phase 2b FASCINATE-2 study[2]
- FASN inhibitor not only reduced circulating cholesterol but also decreased the development of atherosclerosis and improved liver histology in a mouse model of dyslipidaemia and MASH
- FASN inhibitor also decreased inflammation by reducing several circulating inflammatory markers, such as CCL4 and CXCL2, in Ldlr-/- MASH mice
- These results suggest that a FASN inhibitor like denifanstat could provide benefit in cardiovascular as well as liver health, supporting clinical evaluation of denifanstat for long term outcomes in MASH patients

References

(1) O'Farrell et al., 2022. Scientific Reports. doi:10.1038/s41598-022-19459-z
(2) Loomba et al., 2024. The Lancet Gastroenterology & Hepatology. doi:10.1016/S2468-1253(24)00246-2
(3) Loomba et al. 2021. Gastroenterology. doi:10.1053/j.gastro.2021.07.025