Transcriptomic analysis revealed distinct mechanisms underlying the synergistic effect of a fatty acid synthase (FASN) inhibitor and resmetirom combination in LDL receptor knockout MASH mice

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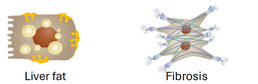
Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor. Denifanstat demonstrated MASH resolution and fibrosis improvement in the Phase 2b MASH trial, FASCINATE-2 (NCT04906421)[1]
- In preclinical models, FASN inhibitors improved 3 hallmarks of MASH: inhibited liver fat synthesis & accumulation (hepatocytes), inhibited fibrosis (hepatic stellate cells require DNL for activation) and decreased inflammation (inflammasome activation by palmitate)[2]
- Thyroid hormone receptor-beta (THR-β) agonists increase lipid oxidation which decreases liver fat; resmetirom demonstrated MASH resolution and fibrosis improvement in Phase 3 trial[3]



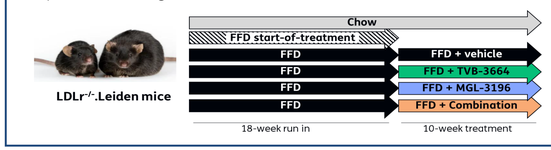
Denifanstat Reduces de novo Lipogenesis	Sugar → FASN → Fatty acids	**Direct** - decreases de novo lipogenesis	**Direct** – decreases fibrogenesis in stellate cells, liver fat and lipotoxicity
Resmetirom Increases mitochondrial beta-oxidation	Fatty acids → THR-β → Metabolized	**Direct** - increases fatty acid oxidation and improves mitochondrial function	**Indirect** – decreases fibrosis due to decreased liver fat and lipotoxicity

Aim

- In previous mouse studies, the combination of a FASN inhibitor and resmetirom showed an increased improvement of liver histology and lipid lowering versus monotreatment in diet-induced MASH
- This transcriptomic profiling study aimed to identify molecular mechanisms by which a FASN inhibitor and resmetirom contributed to disease improvement

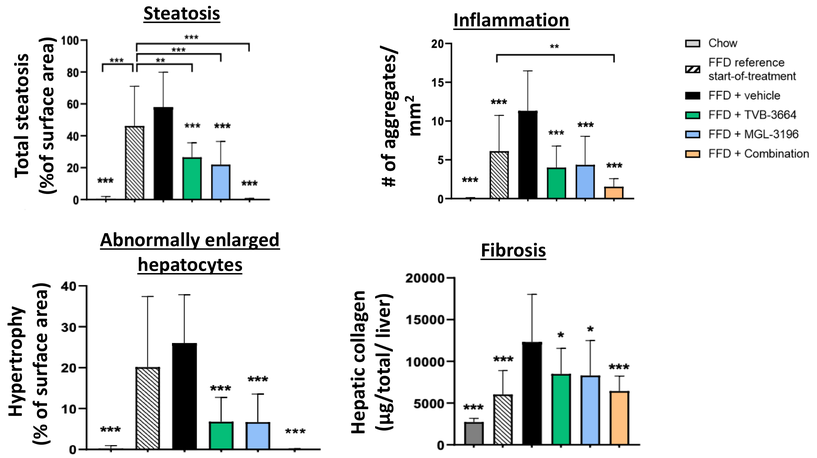
Methods

- Male Ldlr-/- mice were fed a fast-food diet (FFD) for 18 weeks to induce MASH features and treated with TVB-3664 (a FASN inhibitor surrogate for denifanstat, 5 mg/kg, PO, QD) or resmetirom (MGL-3196, 3 mg/kg, PO, QD) alone or in combination for 10 weeks. RNA-sequencing was performed using liver tissues



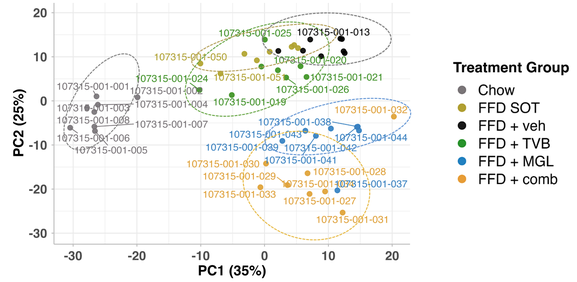
Results

Combination of a FASN inhibitor and resmetirom improved liver histology in Ldlr-/- MASH mice



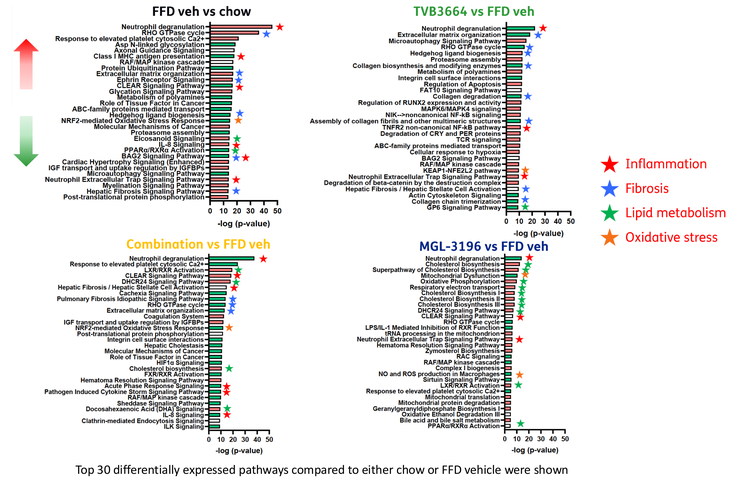
Figures represent data mean + SD with *p<0.05, **p<0.01 and ***p<0.001 vs FFD-vehicle. *Chow n=8; vehicle, TVB-3664, MGL-3196, combination n=14~15*

Principal component analysis revealed distinct transcriptional signature with each therapeutic intervention



Top 500 features by variance were used for Principal component analysis

Pathway analysis showed that FASN inhibitor modulated inflammatory, fibrotic pathways, resmetirom affected lipid metabolism, and combination therapy broadly impacted inflammatory and fibrotic pathways



Top 30 differentially expressed pathways compared to either chow or FFD vehicle were shown

Combination therapy showed greater reduction in expression of fibrosis-associated collagen genes compared to monotherapy

Treatment:	FFD+vehicle	FFD+vehicle	FFD+TVB	FFD+TVB	FFD+MGL	FFD+MGL	FFD+combi	FFD+combi	
Control:	chow	chow	FFD+vehicle	FFD+vehicle	FFD+vehicle	FFD+vehicle	FFD+vehicle	FFD+vehicle	
Param:	log2FC	pvalue	log2FC	pvalue	log2FC	pvalue	log2FC	pvalue	
Collagens (Major ECM Components in Liver Fibrosis)									
COL1A1	2.5	0.000	-1.5	0.000	-0.7	0.028	-1.8	0.000	Type I collagen (dominant in liver fibrosis)
COL1A2	2.4	0.000	-1.4	0.000	-0.6	0.016	-1.6	0.000	Type I collagen (dominant in liver fibrosis)
COL3A1	2.3	0.000	-1.4	0.000	-0.7	0.006	-1.8	0.000	Type III collagen (co-deposited with type I)
COL4A1	1.0	0.000	-0.8	0.000	-0.5	0.003	-1.3	0.000	Type IV collagen (basement membrane)
COL4A2	0.8	0.000	-0.7	0.000	-0.5	0.003	-1.1	0.000	Type IV collagen (basement membrane)
COL5A1	1.3	0.000	-0.7	0.000	-0.4	0.005	-0.8	0.000	Type V collagen (fibril assembly)
COL5A2	1.9	0.000	-1.3	0.000	-0.9	0.000	-1.4	0.000	Type V collagen (fibril assembly)
COL6A1	1.9	0.000	-1.1	0.000	-0.3	0.138	-0.9	0.000	Type VI collagen (ECM organization)
COL6A2	2.0	0.000	-1.2	0.000	-0.3	0.250	-1.0	0.000	Type VI collagen (ECM organization)

Differential gene expression analysis was performed using negative binomial generalized linear models implemented in DESeq2. Statistical significance was assessed using Wald test

Conclusions

- Transcriptomic analysis demonstrated that combination of a FASN inhibitor and resmetirom increased the anti-inflammatory and anti-fibrotic effects, and improved metabolic regulation including lipid and cholesterol synthesis in a mouse model of MASH and dyslipidemia
- These molecular changes provide a strong rationale for advancing this combination therapy into further clinical evaluation in MASH

References

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2. O'Farrell et al., 2022. Scientific Reports. doi.10.1038/s41598-022-19459-z
3. Harrison et al., 2024. N Engl J Med 2024;390:497-509