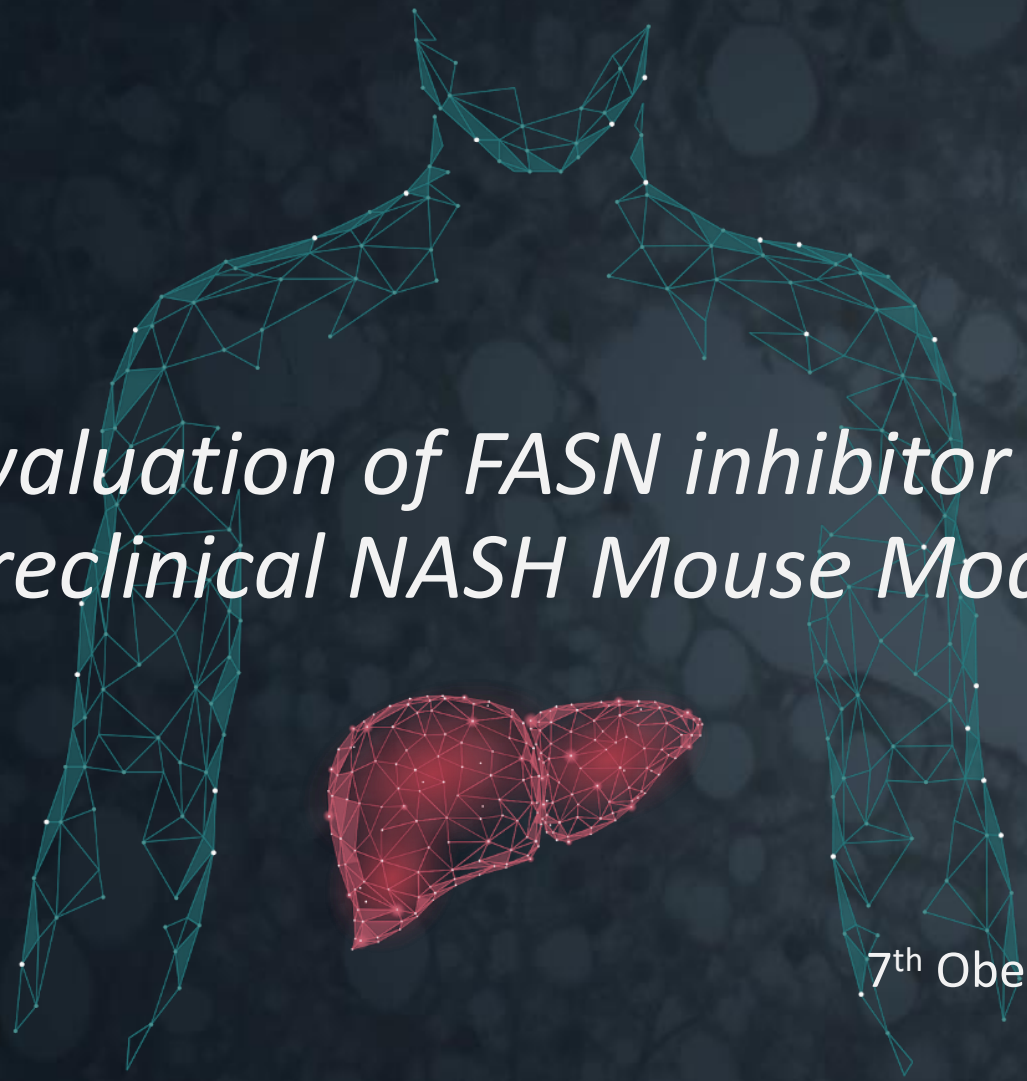

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Evaluation of FASN inhibitor & GLP-1 Combination in Preclinical NASH Mouse Model

Wen-Wei Tsai

Director, R&D

Nov. 28, 2023

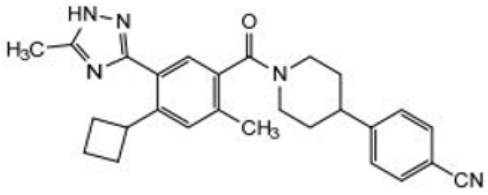
7th Obesity and NASH Drug Development Summit

Outline

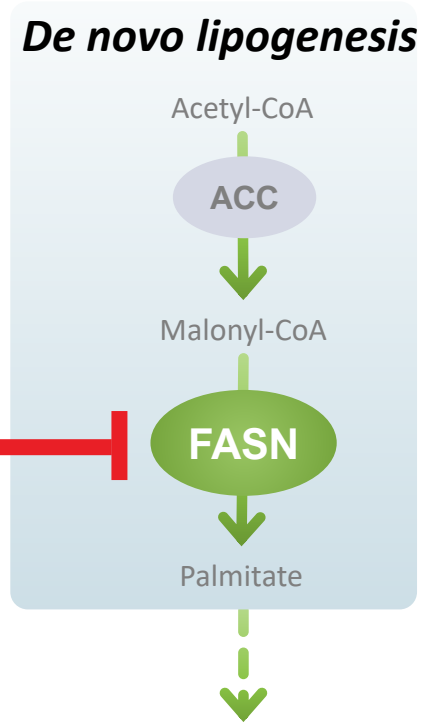
- Background of fatty acid synthase (FASN) and GLP-1 in NASH
- Evaluation of FASN inhibitor and GLP-1 combination in preclinical NASH model
  - Model introduction, study design and efficacy
  - AI-based digital pathology assessment of fibrosis endpoints
  - Transcriptomic profiling
- Summary

Denifanstat (TVB-2640) reduces DNL and inhibits key drivers of NASH

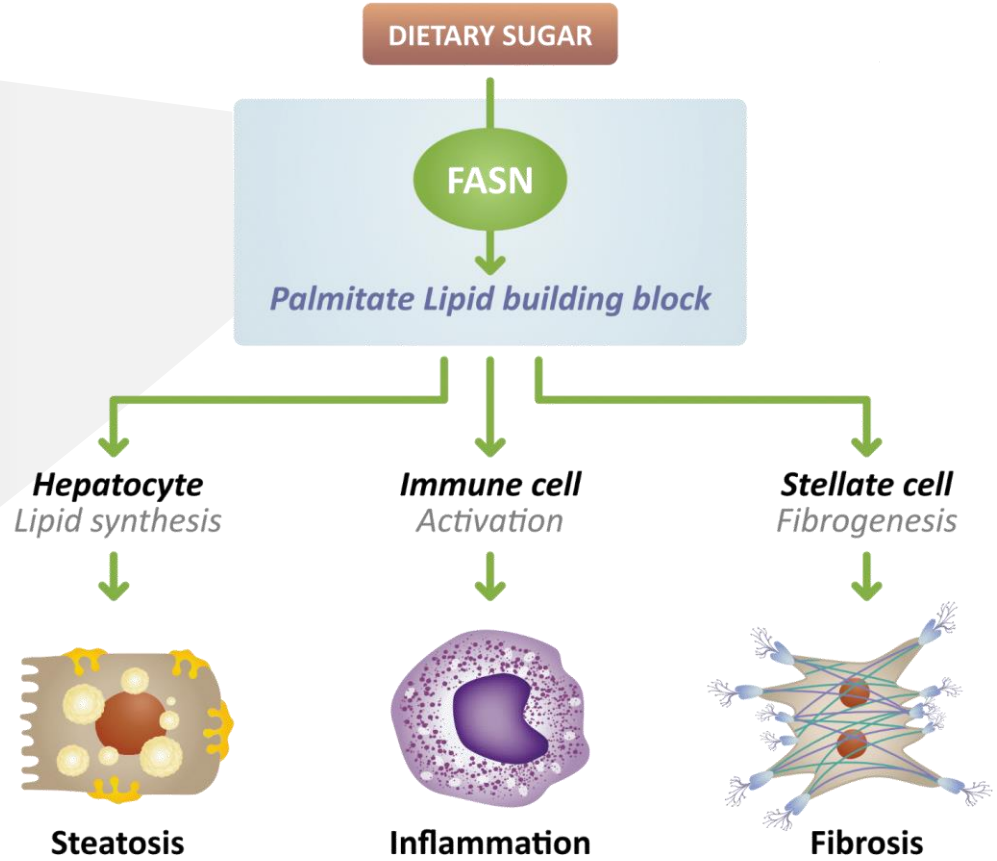
De novo lipogenesis (DNL) is increased in NAFLD and NASH



Denifanstat (TVB-2640)



Lipid synthesis
- Free fatty acids
- Triglycerides
- Lipotoxins



O'Farrell et al., Scientific Reports, 2022

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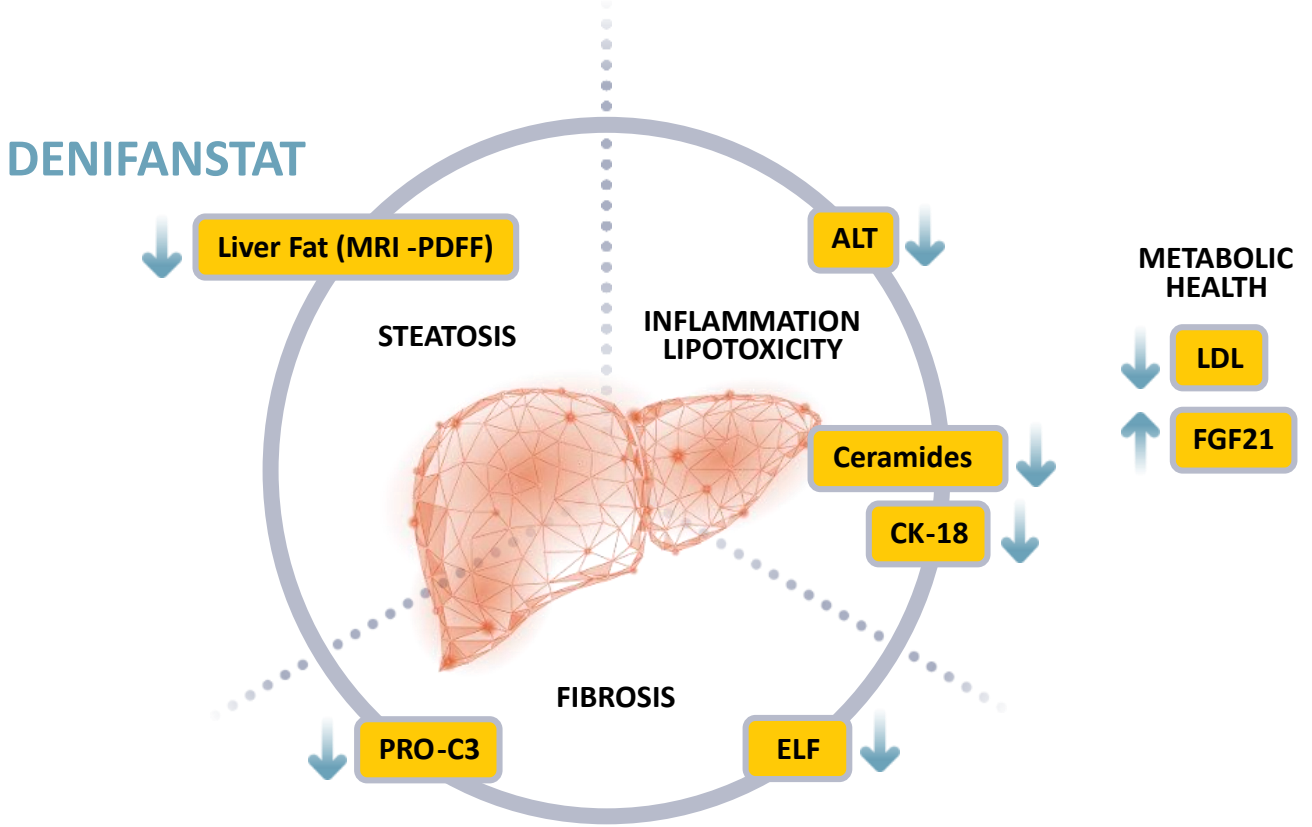
Denifanstat reduced several biomarkers associated with NASH

- **Ph2a FASCINATE-1 and Ph2b FASCINATE-2 interim results to date show:**
  - Significant reduction in liver fat by MRI-PDFF
  - Improvements in multiple biomarkers
    - Inflammation
    - Fibrosis
    - Cardio metabolic health

- **FASCINATE-2 biopsy study is ongoing with denifanstat in F2/F3 NASH**
  - Results expected in Q1 2024

Consistent with mechanism of FASN inhibition:
Denifanstat targets steatosis, inflammation and fibrosis



Loomba et al., Gastroenterology, 2021

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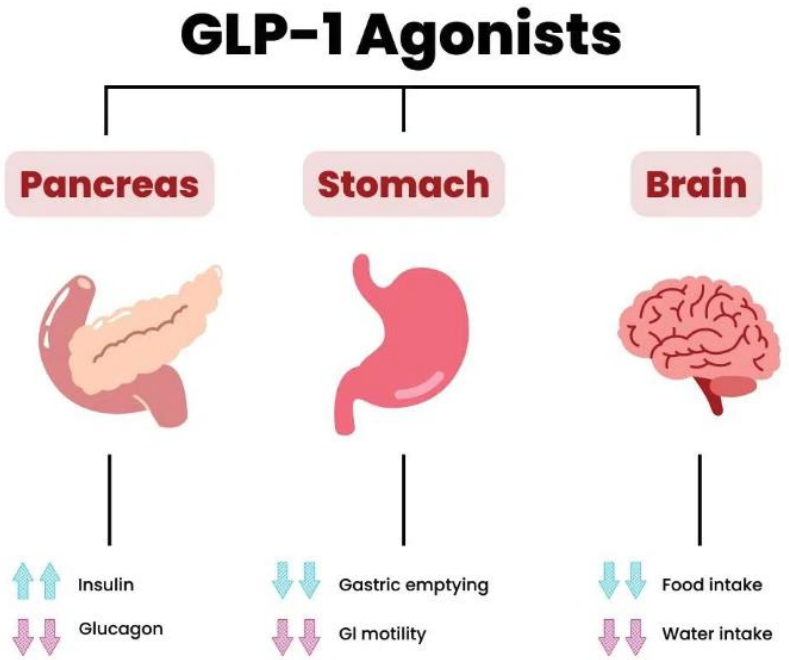
GLP-1/semaglutide reduces body weight which is associated with NASH resolution but not fibrosis improvement

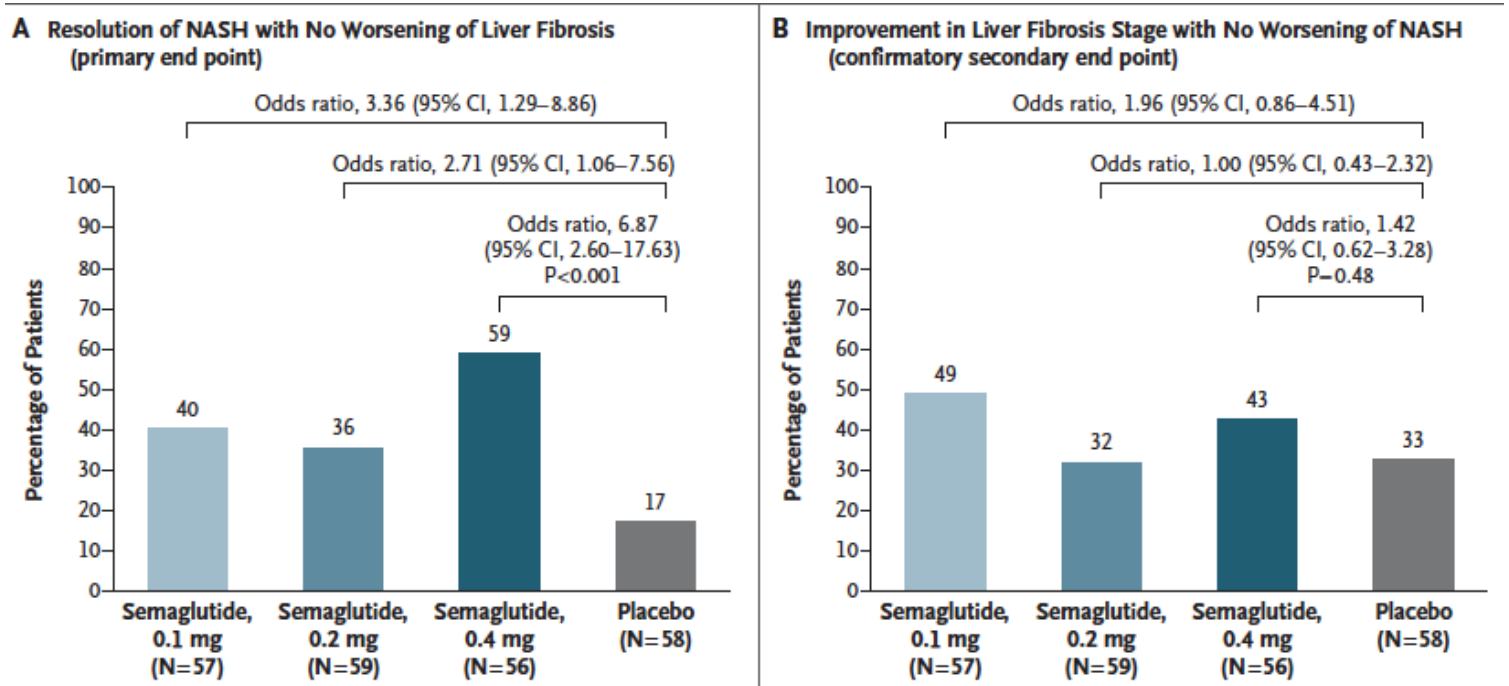
GLP-1 agonists reduce body weight and glucose, and provide metabolic benefits



Adapted from xcode.life

Semaglutide improved NASH resolution, but not fibrosis

NASH patients with biopsy confirmed F2-F3 fibrosis and NAS ≥4 were enrolled for 72 weeks semaglutide treatment



Body weight changes from baseline to week 72: -4.8% -8.9% **-12.5%** -0.6%

Newsome et al. NEJM 2021

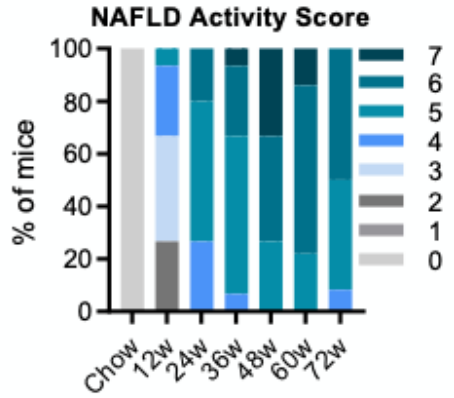
Hypothesis

- FASN inhibition has a direct anti-fibrotic effect in hepatic stellate cells
- FASN inhibitor alone or in combination with GLP-1 analog would decrease liver fibrosis in NASH
- Complementary MOAs of FASN inhibitor (liver centered DNL inhibition) and GLP-1 (weight loss and peripheral effect) combination could provide added benefits for NASH

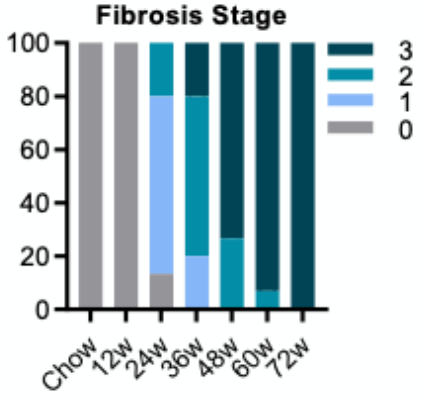
Introduction of Gubra GAN DIO-NASH mouse

Gubra-Amylin-NASH (GAN) diet induced obesity (DIO) mouse model:

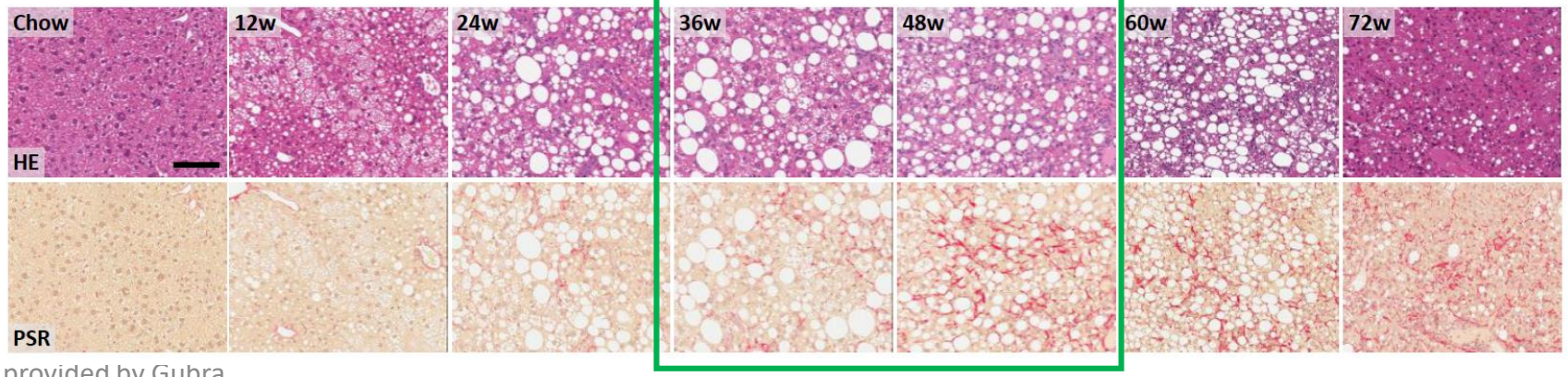
- C57BL/6JRj mice fed with GAN diet (40% fat, 22% fructose, 2% cholesterol)
- Mice develop obesity and insulin resistance – suitable for metabolic target evaluation
- Mice develop NASH features and fibrosis
- Paired biopsies allow pre & post treatment histological assessment



Manifest MASH (NAS 4-5) is consistently observed at 24 weeks

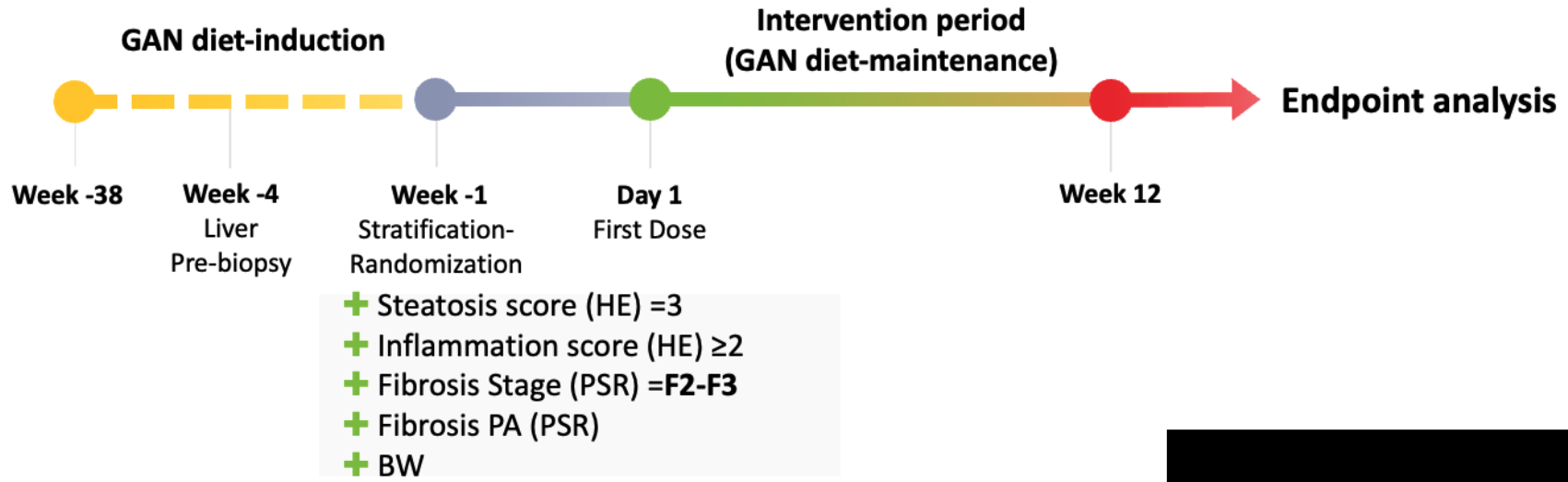


All mice develop advanced fibrosis at ≥48 weeks of GAN diet feeding



Modified from slides provided by Gubra

Study design to evaluate FASN inhibitor and GLP-1 combination



Treatment groups

NC: Normal chow diet control, n=8

VEH: NASH vehicle control, n=16

FASN: **TVB-3664** (FASN inhibitor), 10mg/kg, PO, QD, n=16

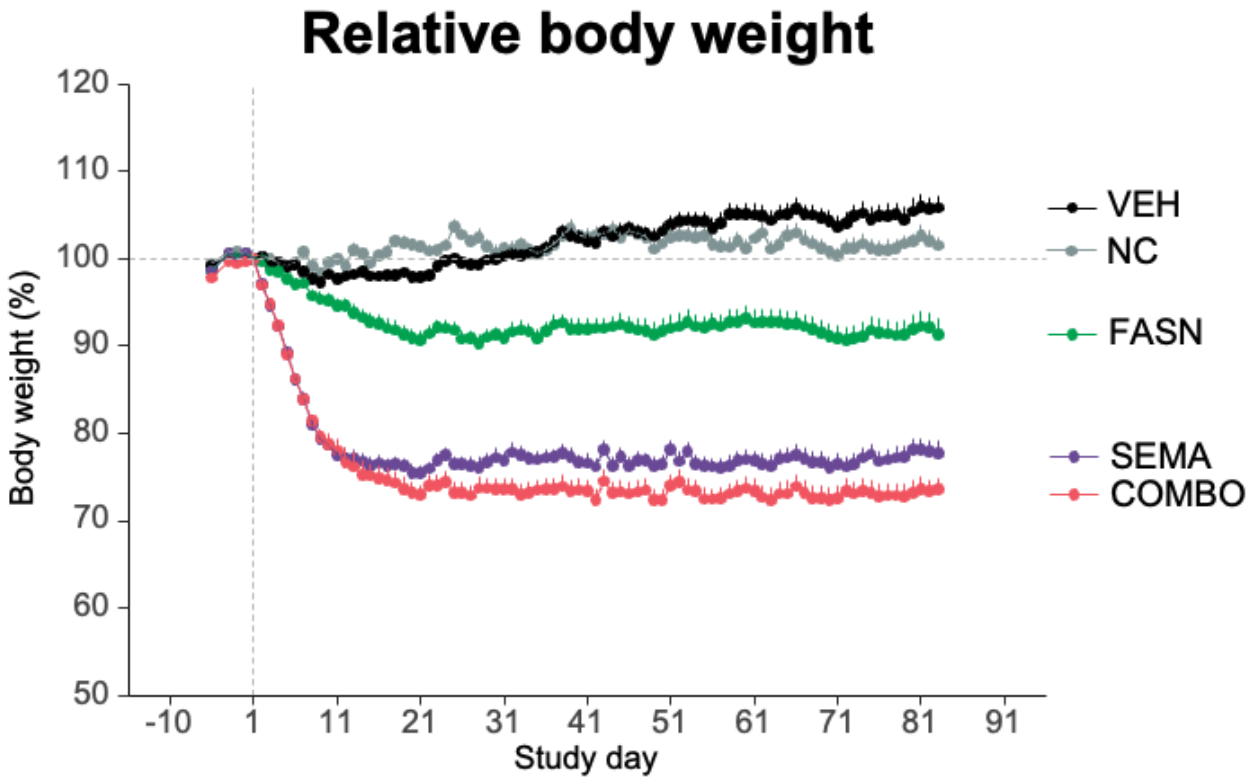
SEMA: Semaglutide (**weight loss dose**), **30 nmol/kg**, SC, QD n=16

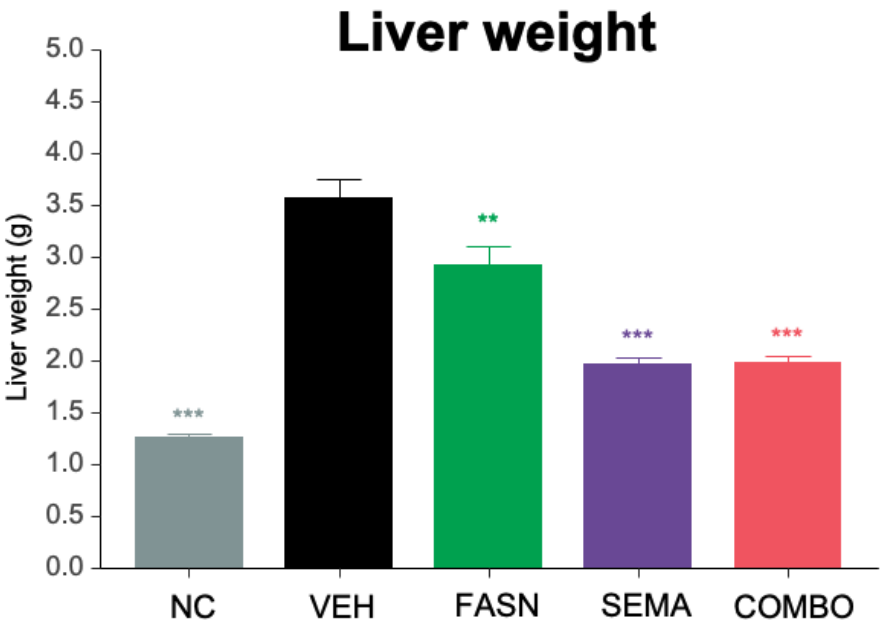
COMBO: TVB-3664/Semaglutide combo, n=16

	TVB-2640 (Denifanstat)	TVB-3664
Status	In clinical development	For preclinical evaluation
In vitro FASN biochemical inhibition: human IC50 (µM)	0.044	0.026
In vitro palmitate inhibition: human cells IC50 (µM)	0.030 Hela	0.018 Hela
In vitro palmitate inhibition: mouse cells IC50 (µM)	0.543 CT26	0.012 CT26
Mouse PK	Poor	Best

O'Farrell et al., Scientific Reports, 2022

Semaglutide reduced body weight by ~25% in NASH mice





Cumulative food intake was reduced in SEMA and COMBO groups

***p<0.01, ***p<0.001*

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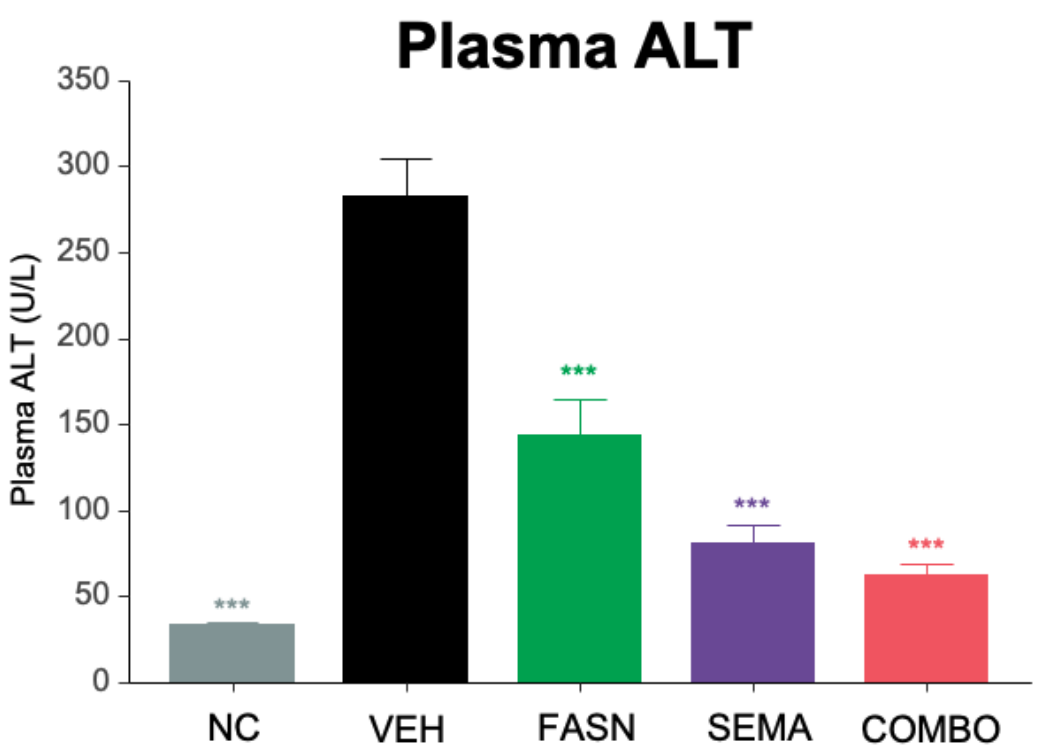
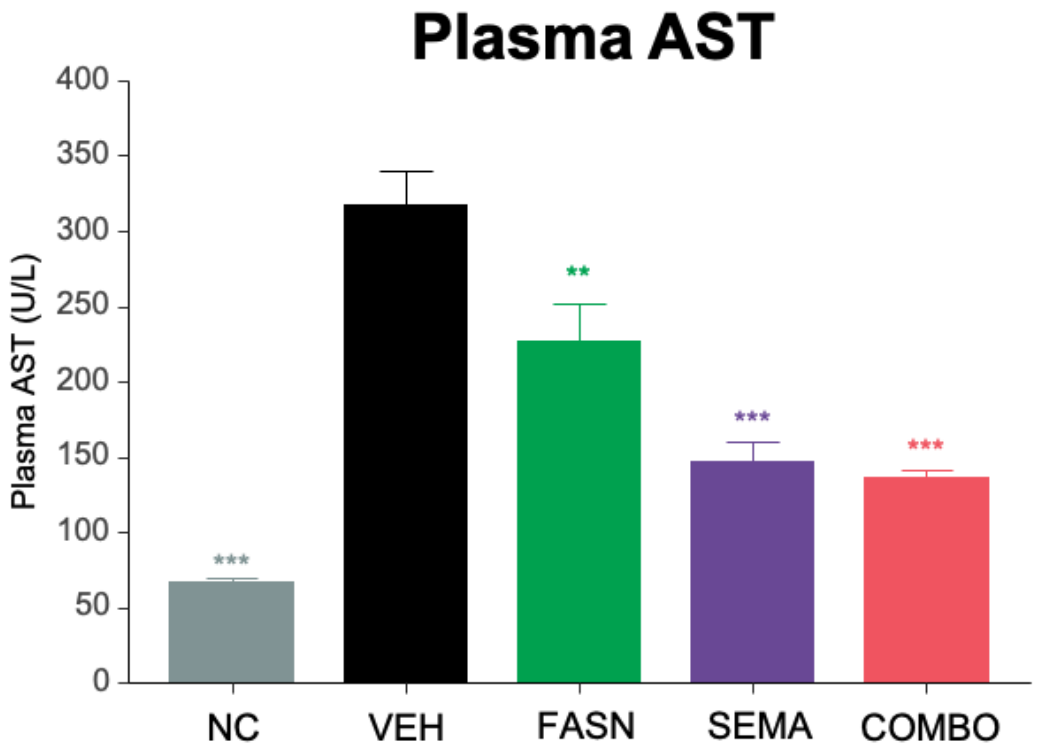
FASN inhibitor, semaglutide and combination reduced ALT and AST





***p<0.01, ***p<0.001*

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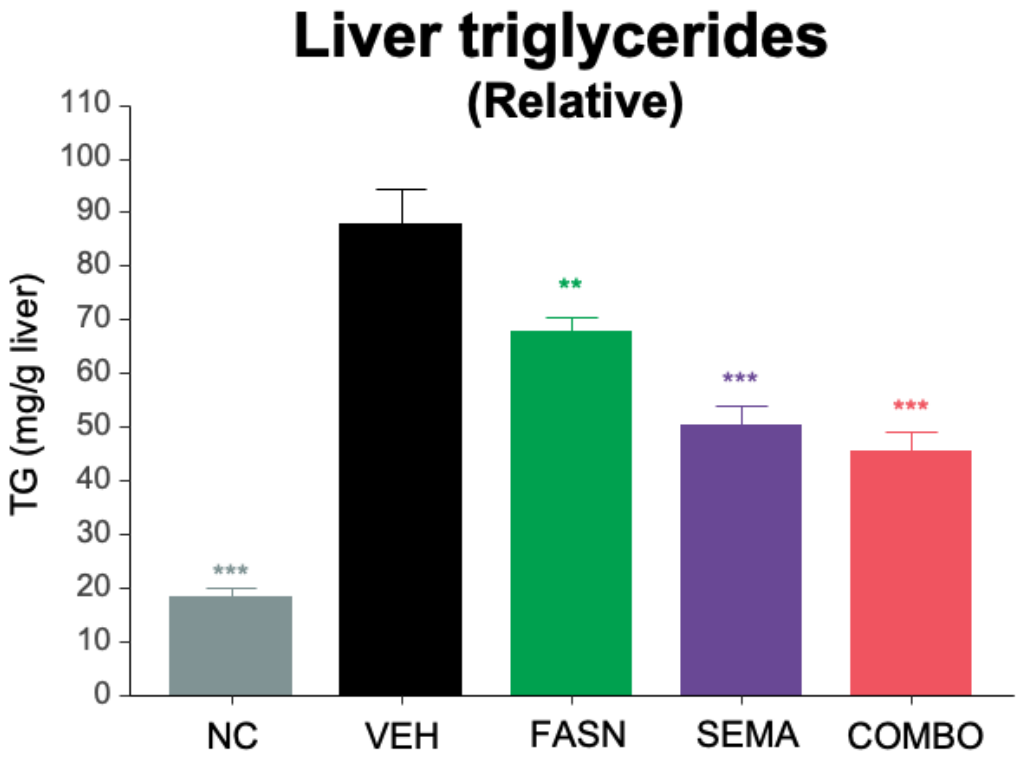
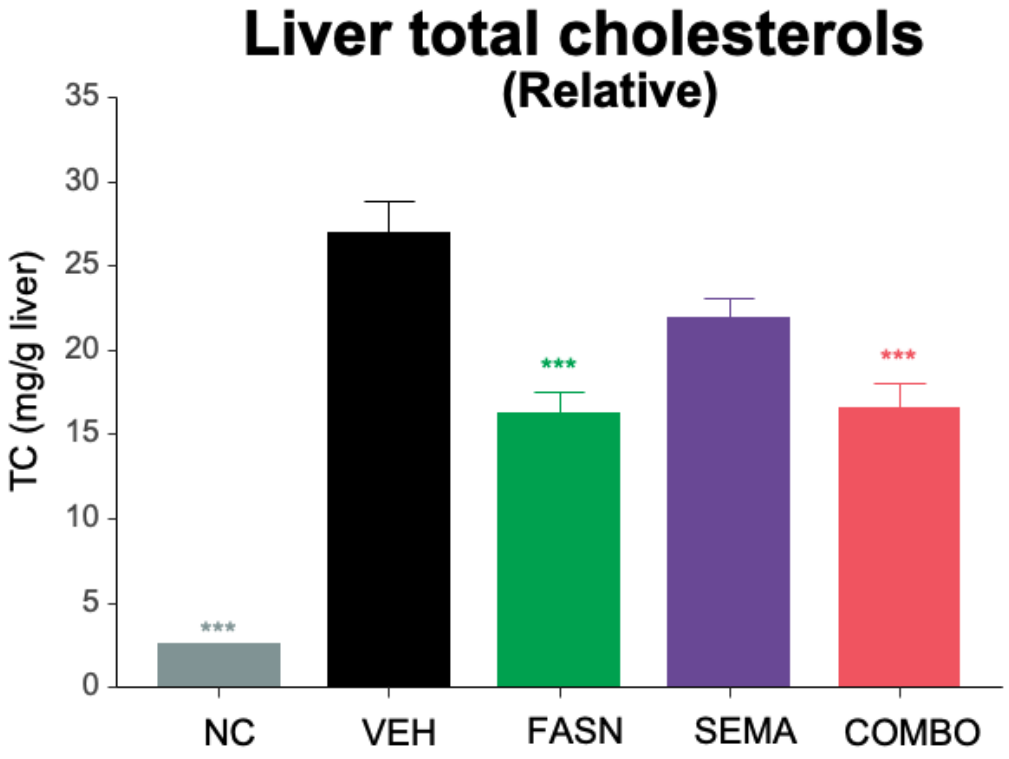
FASN inhibitor, semaglutide and combination reduced liver triglycerides and total cholesterols





***p<0.01, ***p<0.001*

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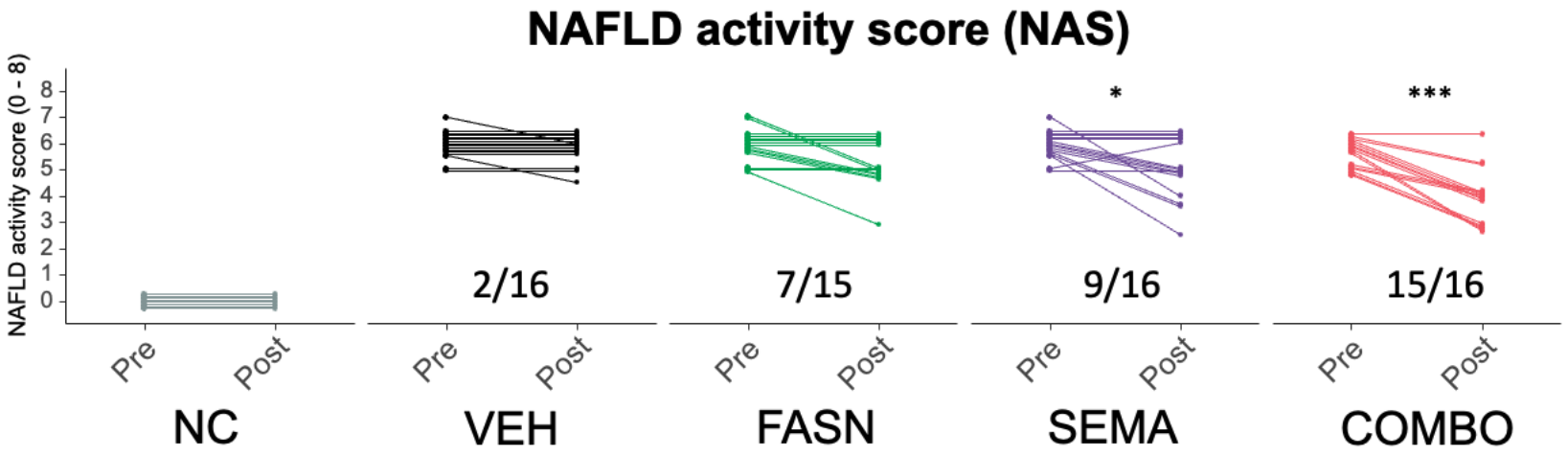
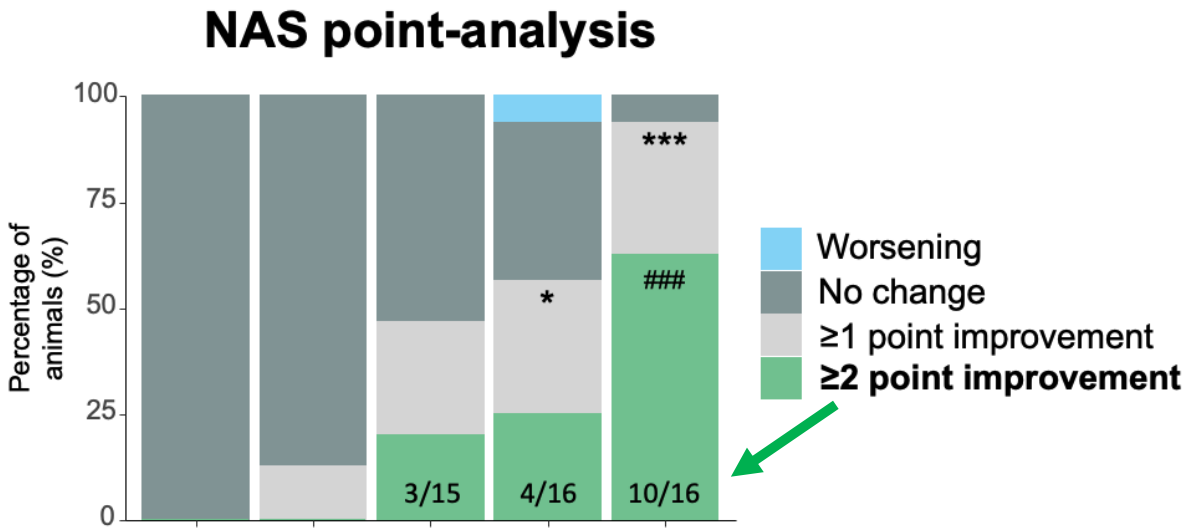
Combination of FASN inhibitor and semaglutide showed a synergistic effect on NAS reduction





*p<0.05, **p<0.01, ***p<0.001

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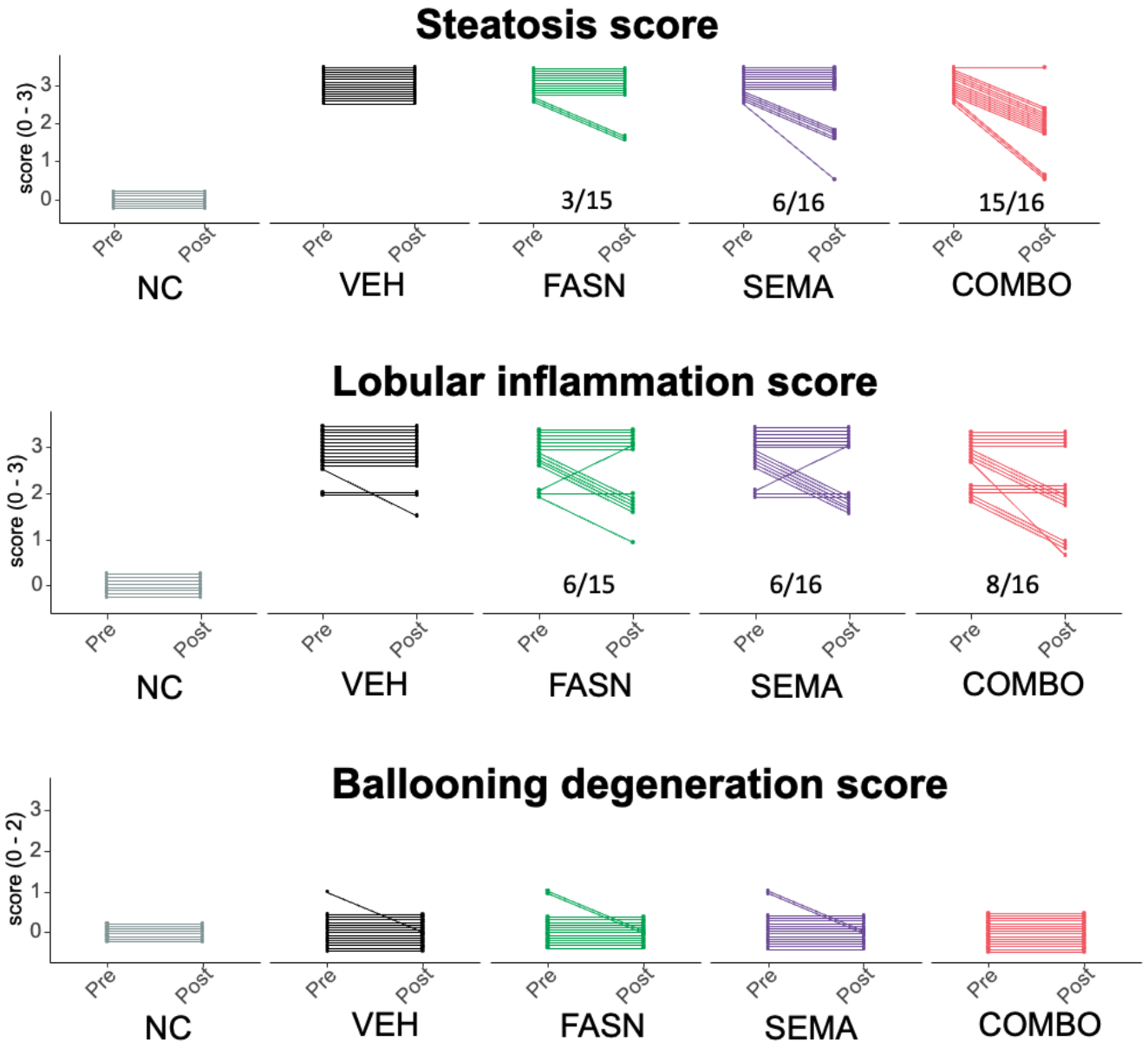
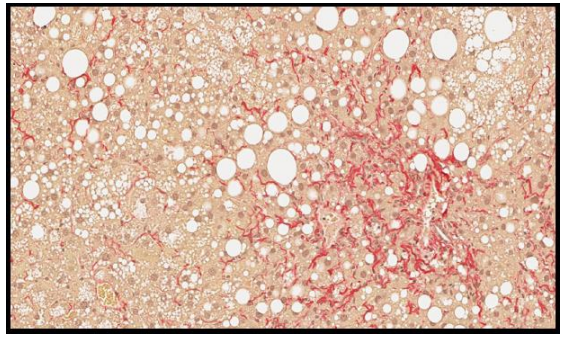
Combination of FASN inhibitor and semaglutide showed a synergistic effect on steatosis and inflammation reduction

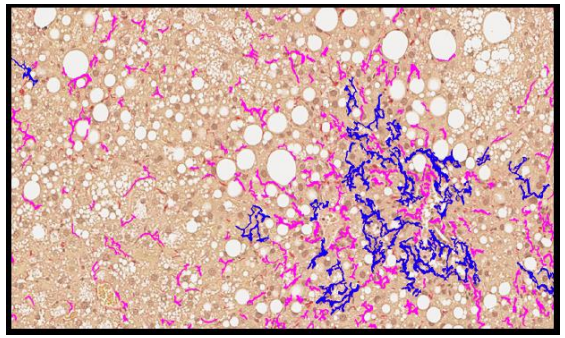


Introduction of FibroNest AI-based digital pathology platform

PSR image

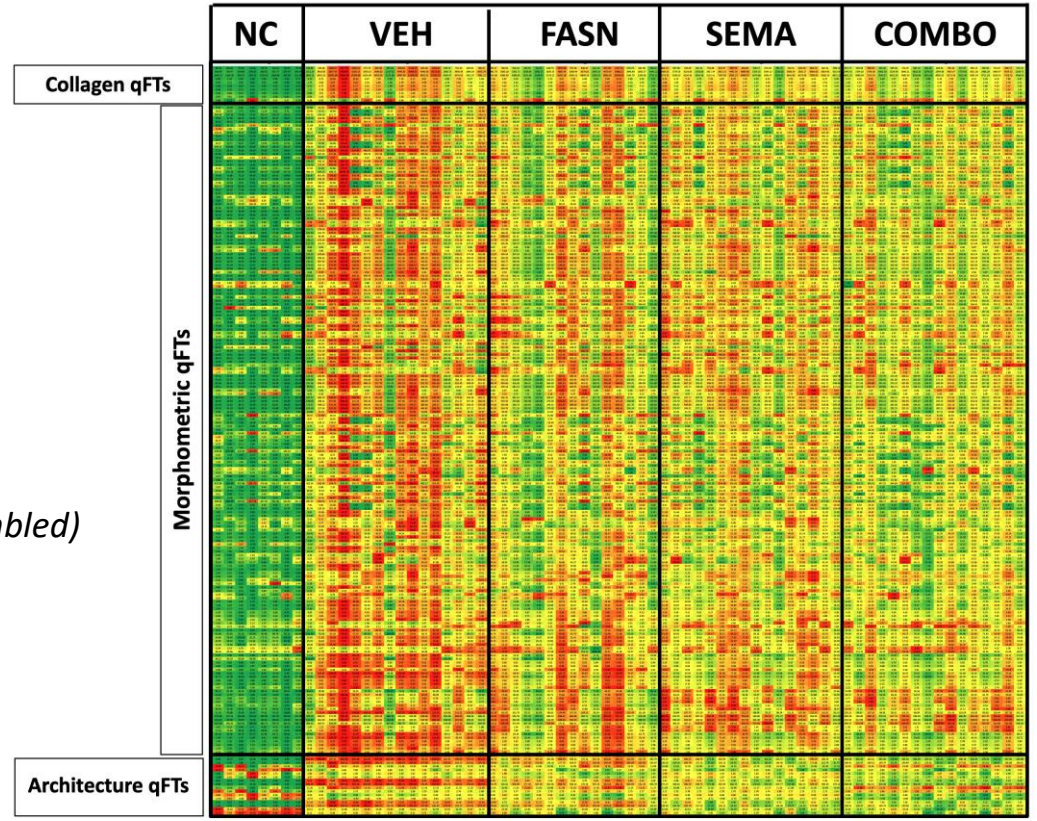


Collagen deconvolution matrix



Phenotypic Fibrosis Composite Score

- **Collagen Composite Score**
  - Collagen Area Ratio
  - Fine/Assembled Ratio
- **Morphometric Composite Score (All)**
  - Length, Width, Perimeter
    - *Morphometric Composite Score (Fine)*
    - *Morphometric Composite Score (Assembled)*
- **Architectural Composite Score**
  - Computational windows
  - How fibers are organized amongst each other



PHARMANEST

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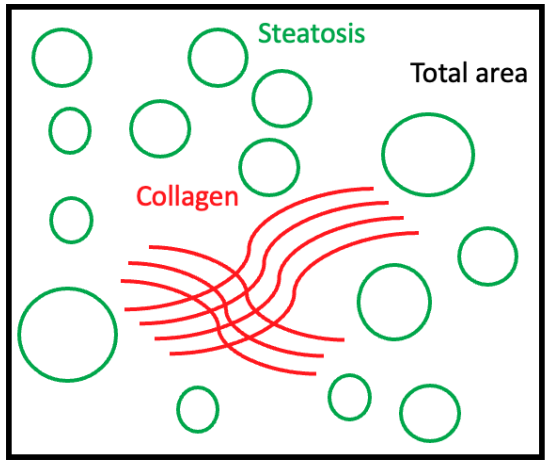
Fibrosis scores with parenchymal correction

- FASN inhibitor, semaglutide and combination reduced steatosis area

Pre-treatment



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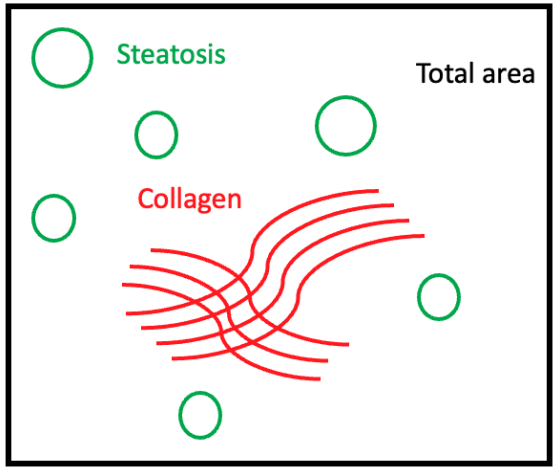
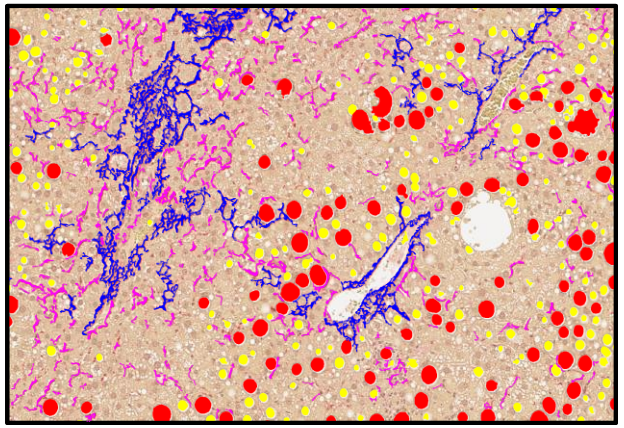
Post-treatment

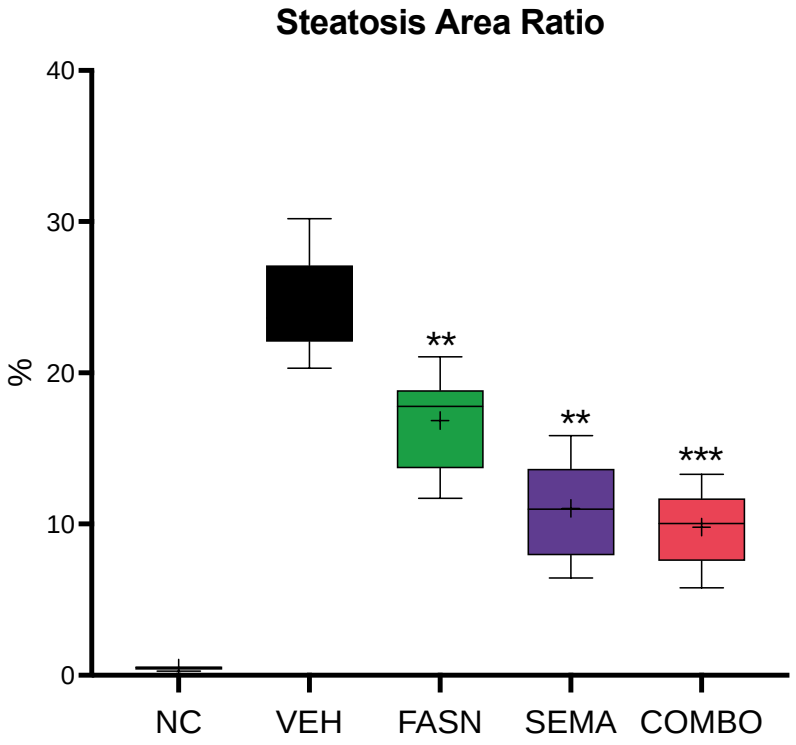


Lipid droplet/steatosis identification



$$\text{Collagen Area Ratio} = \frac{\text{Collagen Area}}{\text{Total Area}}$$

$$\text{Parenchymal corrected CAR} = \frac{\text{Collagen Area}}{\text{Total Area} - \text{Steatosis Area}}$$



***p<0.01, ***p<0.001*

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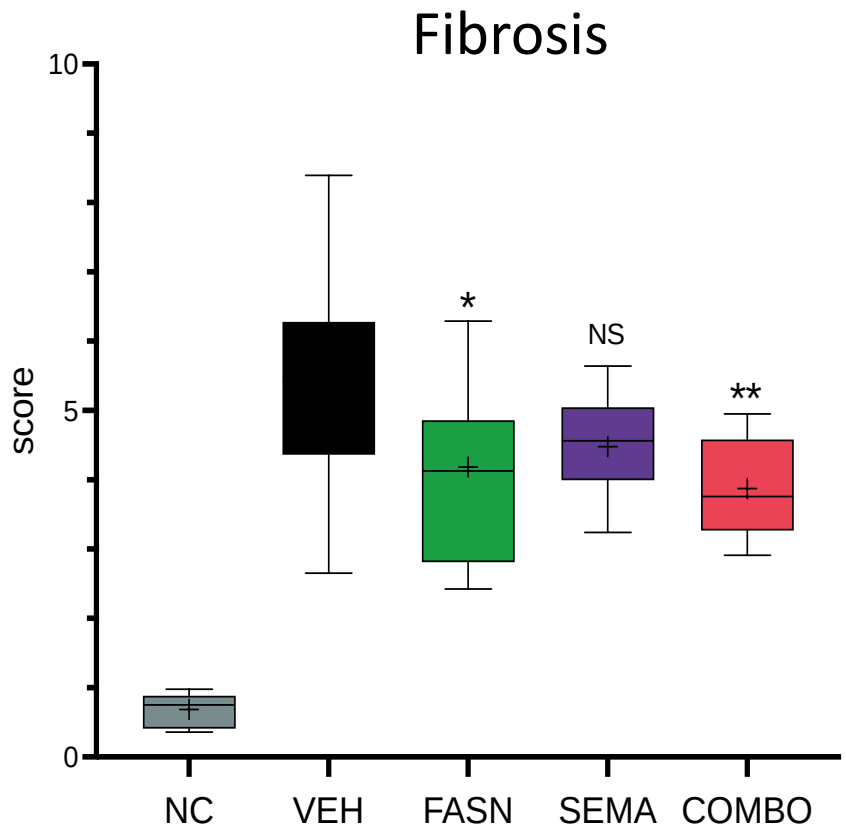
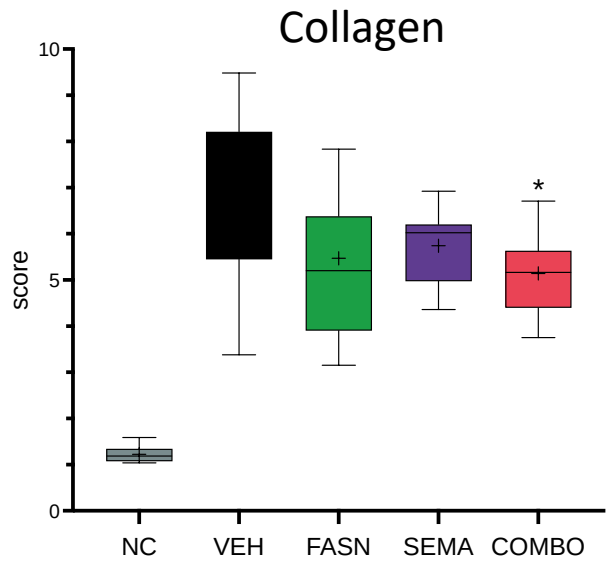
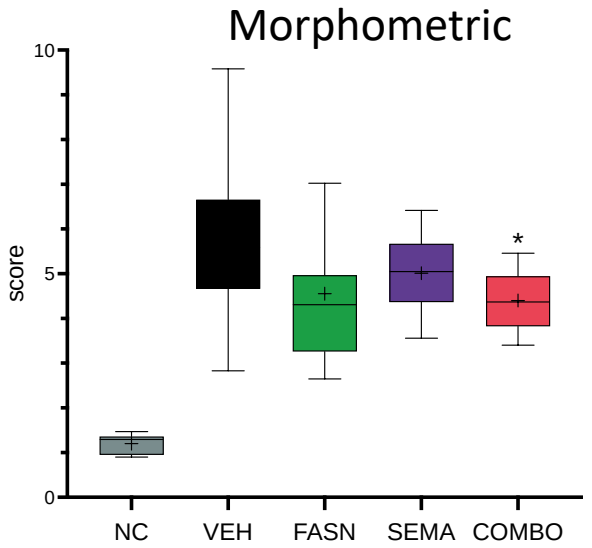
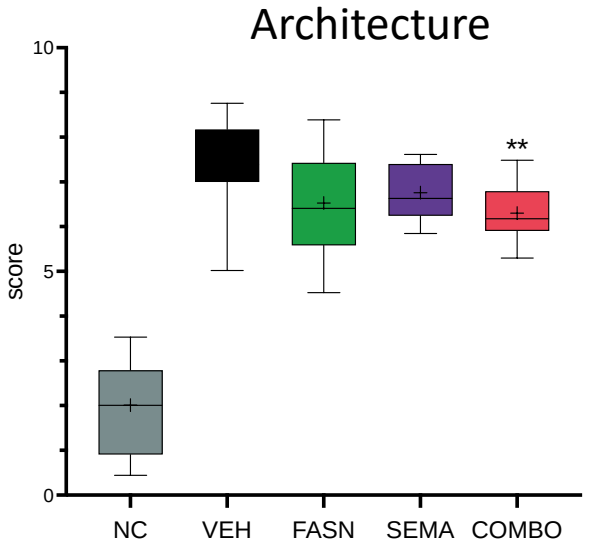
Combination of FASN inhibitor and semaglutide showed an additive effect on fibrosis reduction by AI-based FibroNest analysis

Distinct variables of fibrosis composite scores show consistent trends









 FibroNest analysis performed by PharmaNest; All scores shown with parenchymal correction; **p<0.05, **p<0.01*

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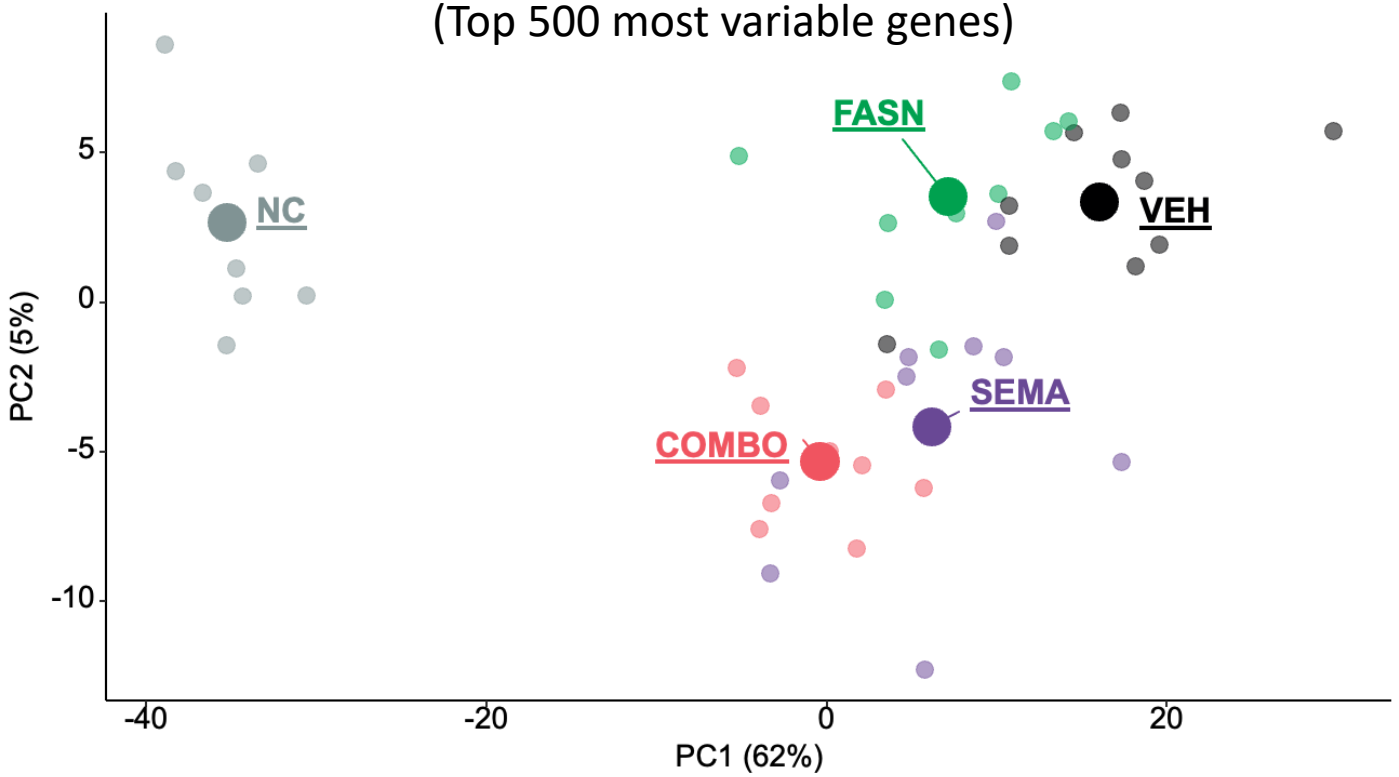
FASN inhibitor, semaglutide and combination resulted in different transcriptomic profiles

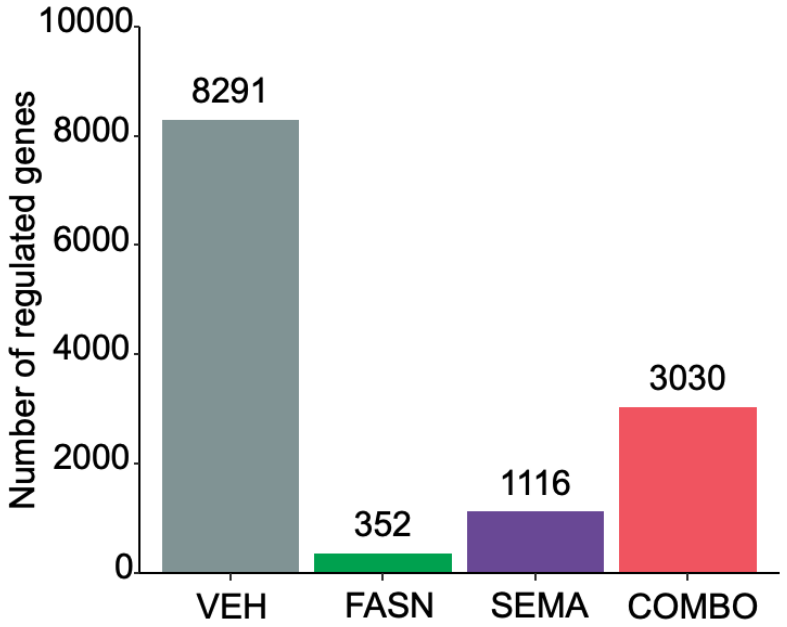
Principal component analysis

(Top 500 most variable genes)



Differential expression analysis

(VEH compared to NC group,
FASN, SEMA, COMBO compared to VEH)



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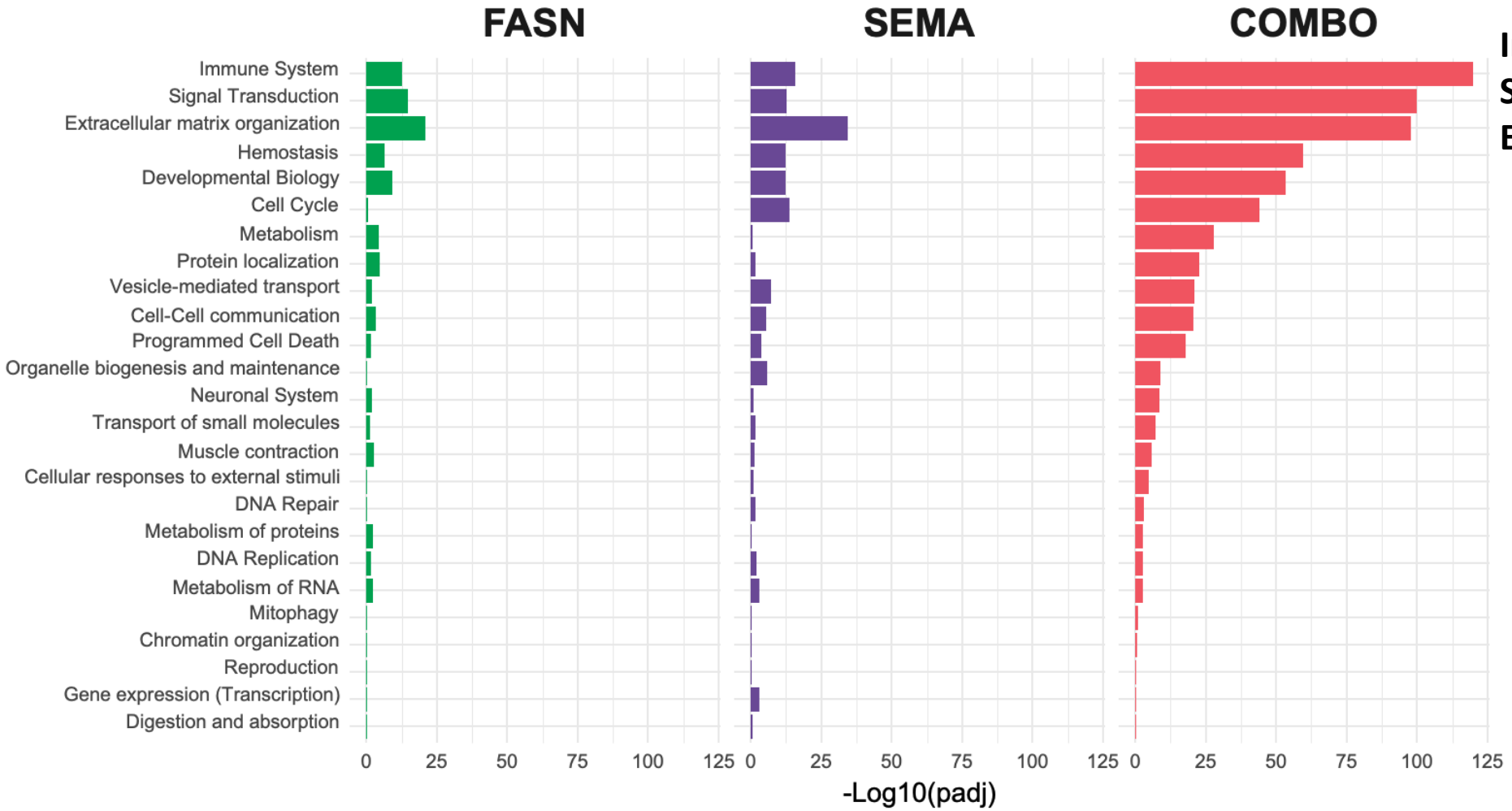
Combination of FASN inhibitor and semaglutide showed a synergistic effect on pathway regulation

Top reactome pathways for enriched genes compared to vehicle group



Immune system
Signal transduction
Extracellular matrix organization

Pathways with significance level $p < 0.05$ after correction for multiple testing were shown in the graphs

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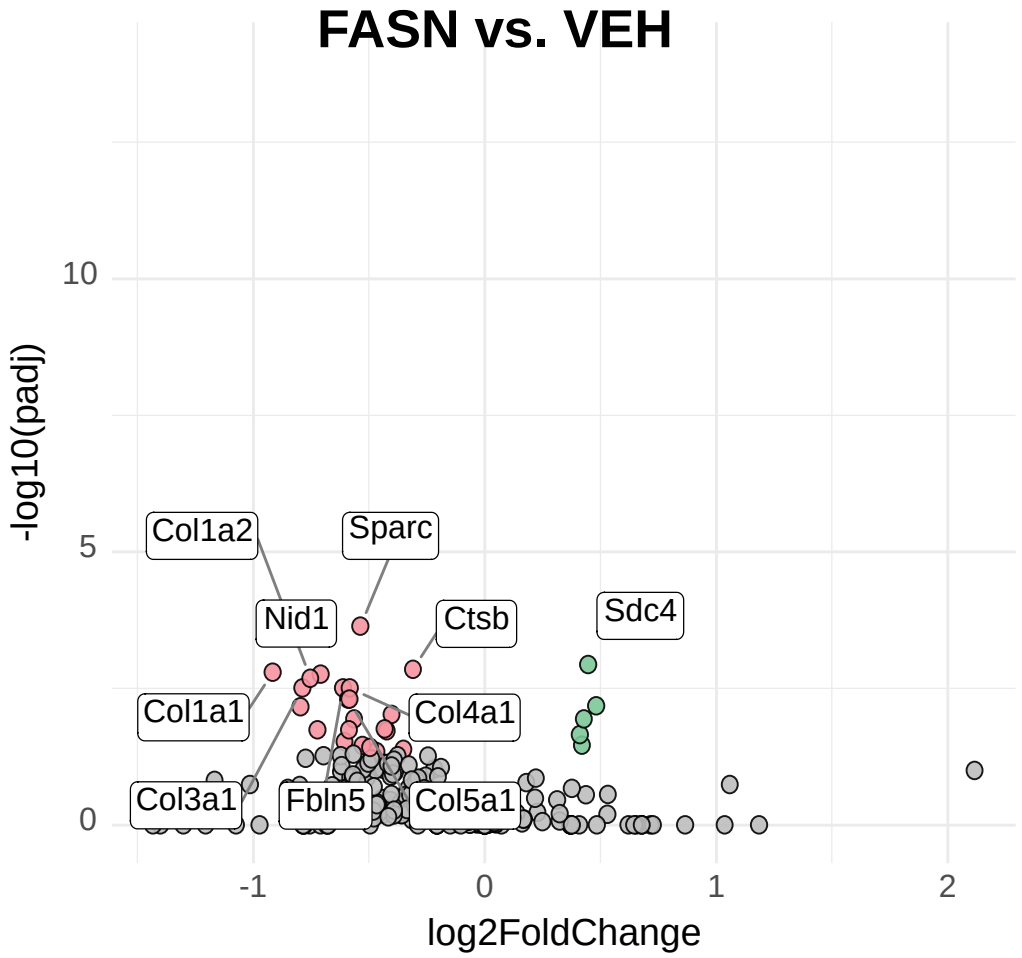
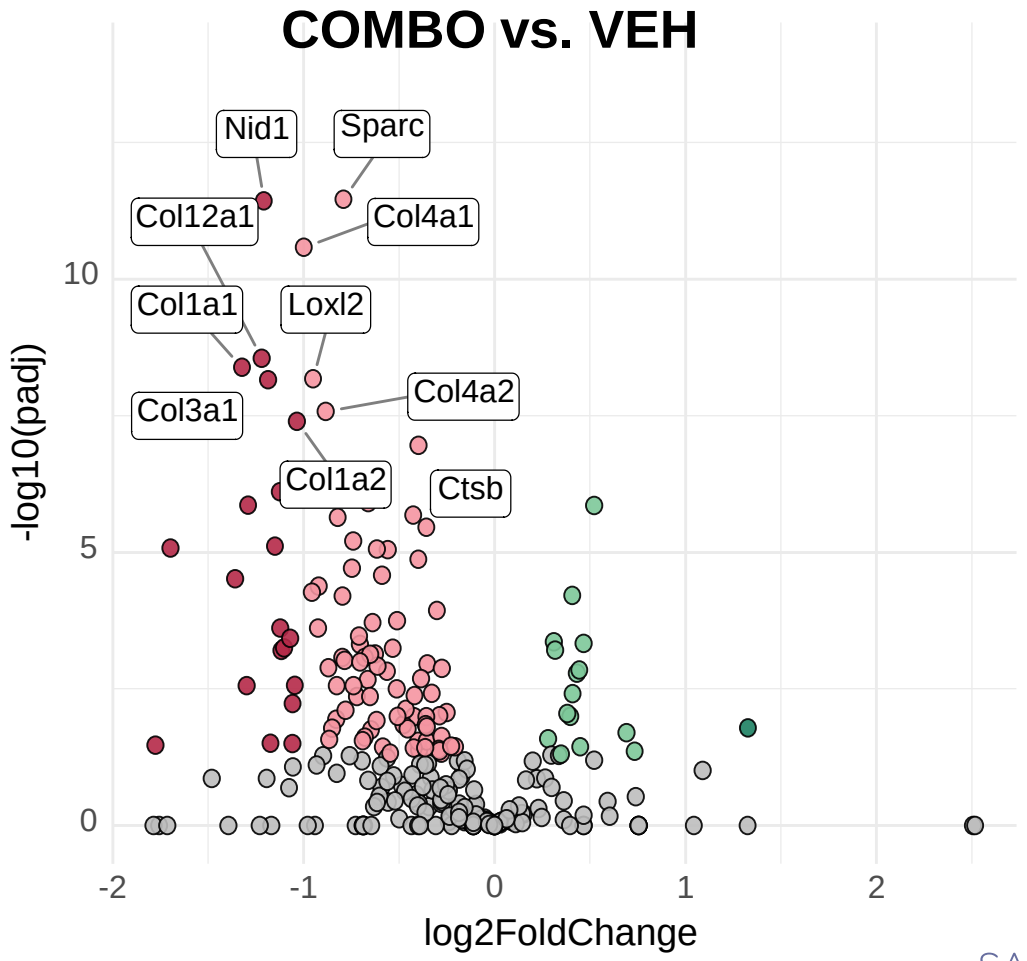
Combination of FASN inhibitor and semaglutide showed a synergistic effect to reduce expression of genes associated with extracellular matrix regulation

Differential expression analysis in reactome sub-pathway of extracellular matrix organization

(Top 10 most significantly regulated genes are highlighted)





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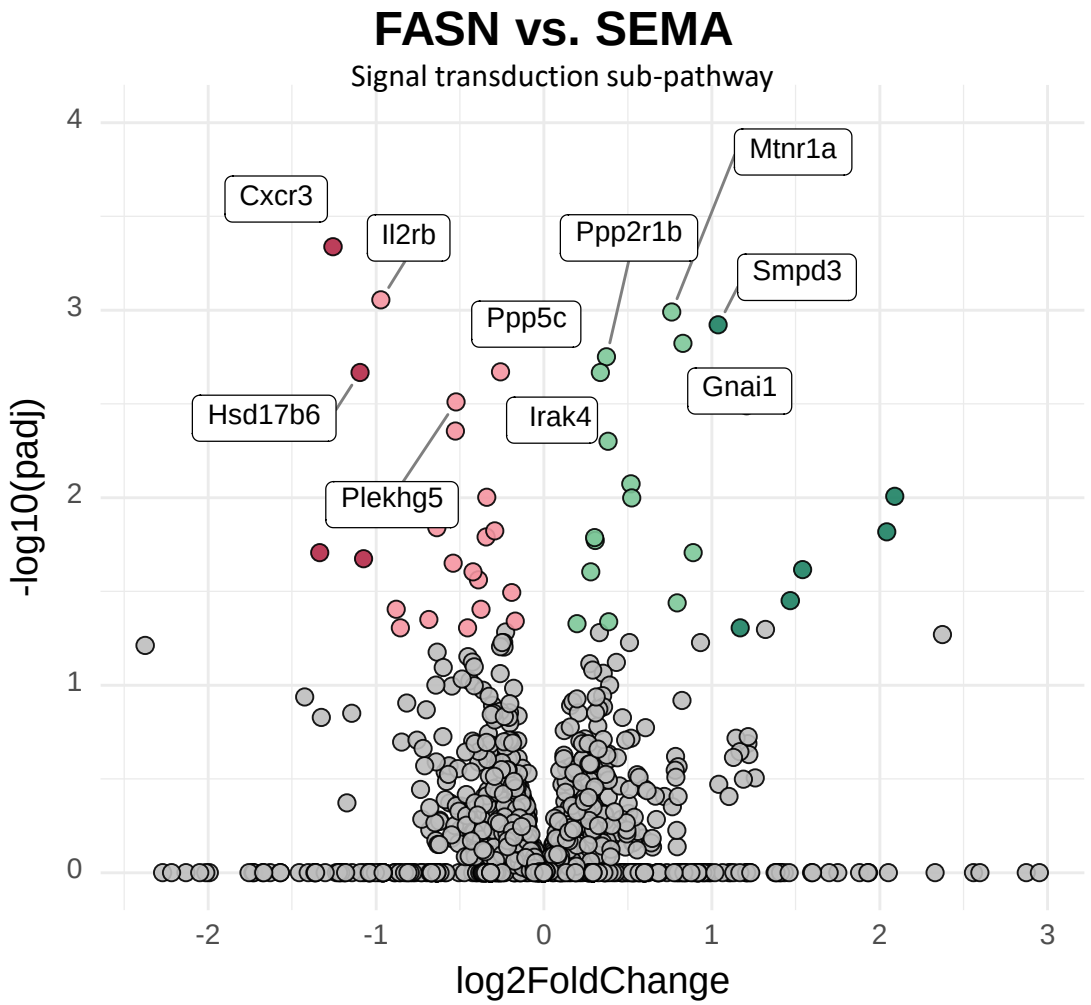
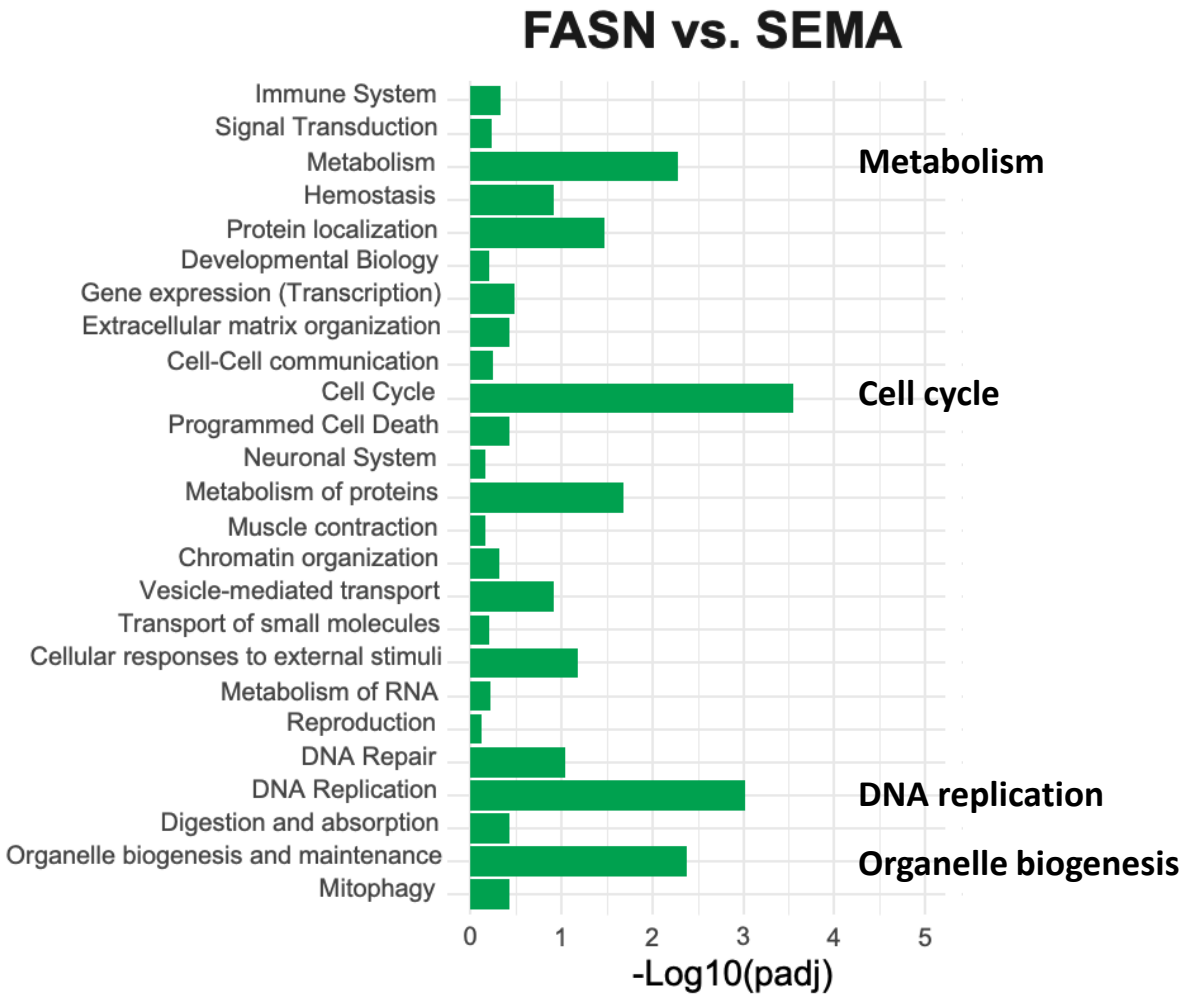
FASN inhibitor and semaglutide regulated not only overlapped but also distinct sets of genes





 Top 10 genes in signal transduction are highlighted in volcano plot

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Summary

- FASN inhibitor (TVB-3664) or semaglutide alone improved NAS and decreased several biomarkers associated with NASH
- Only the FASN inhibitor, but not semaglutide, showed significant reduction of liver fibrosis by digital AI pathology assessment
- FASN inhibitor and semaglutide combination showed further histological improvement of NAS and liver fibrosis compared to mono treatment
- Transcriptomic profiling suggested that FASN inhibitor and semaglutide combination not only has a synergistic effect but also provides distinct MOAs, as would be expected
- These preclinical data support clinical evaluation of denifanstat/GLP-1s combination therapy for NASH

Acknowledgements

- Sagimet team
- Mouse DIO-NASH study conducted by Gubra
- AI digital pathology conducted by PharmaNest