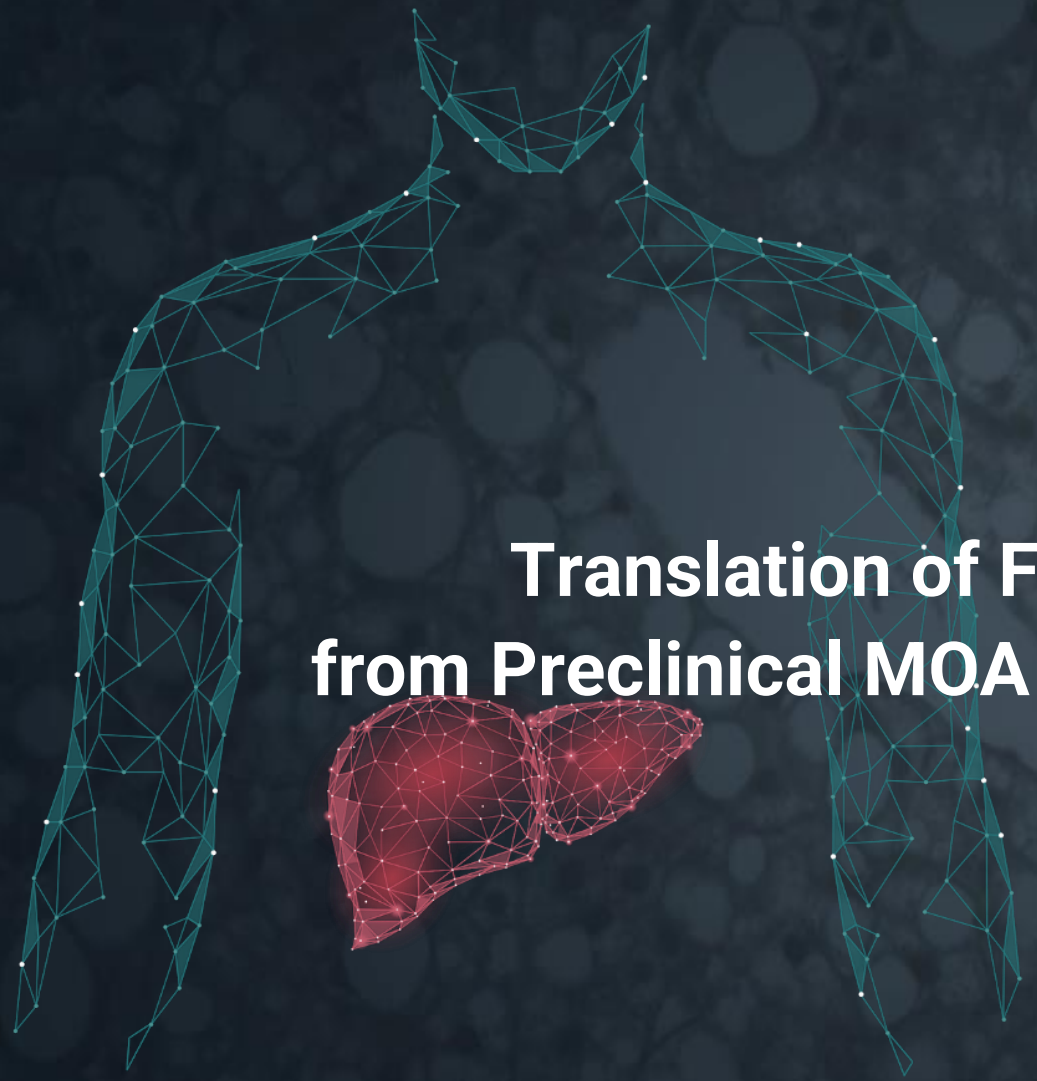

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Translation of FASN Inhibitor TVB-2640 from Preclinical MOA to Clinical POC in NASH

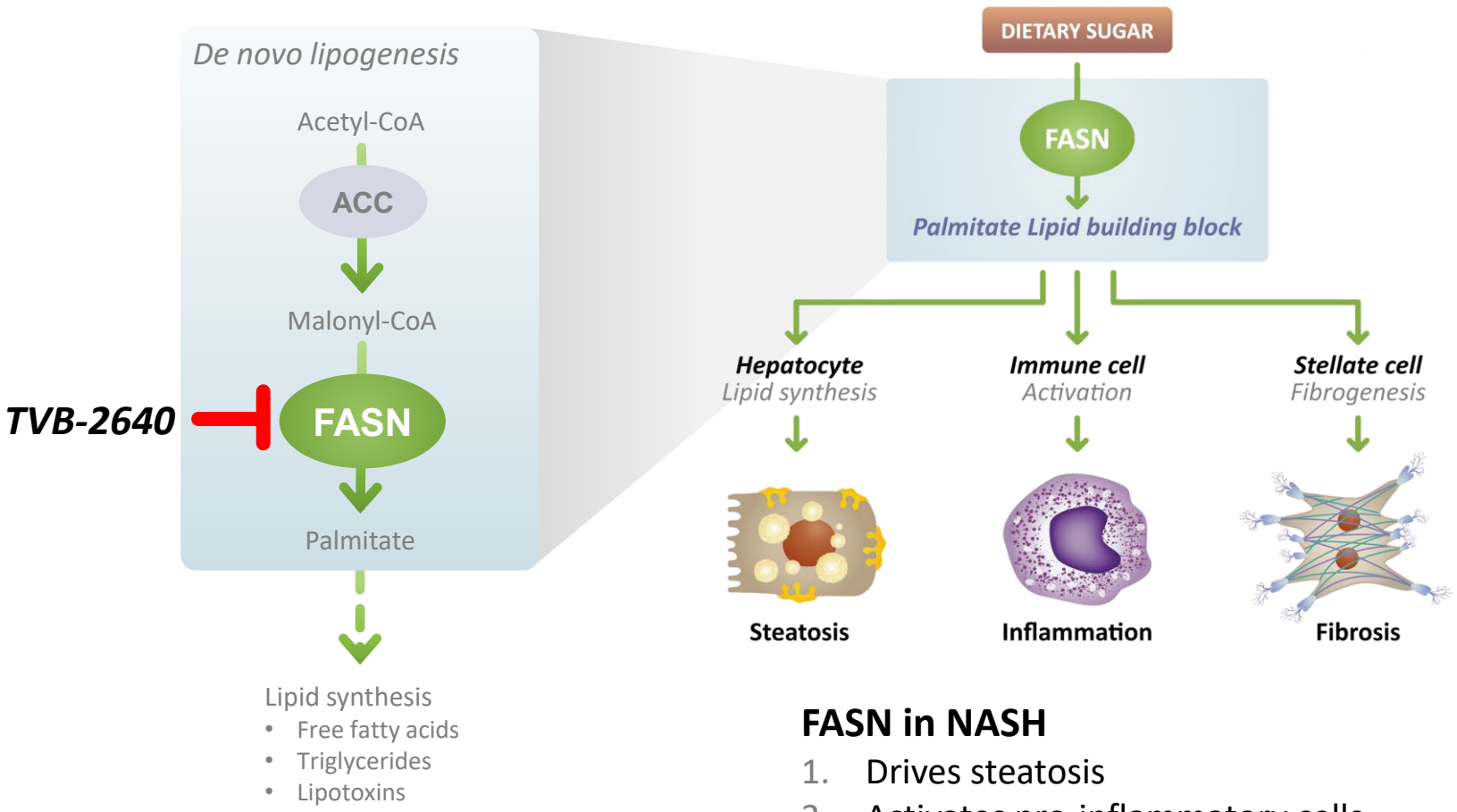
NASH and Fibrosis Conference

Sept 29-30 2021

Marie O'Farrell, PhD

VP, Research and Development, Sagimet

FASN is a compelling target in NASH: directly involved in 3 key drivers of the disease



FASN in NASH

1. Drives steatosis
2. Activates pro-inflammatory cells
3. Activates stellate cells

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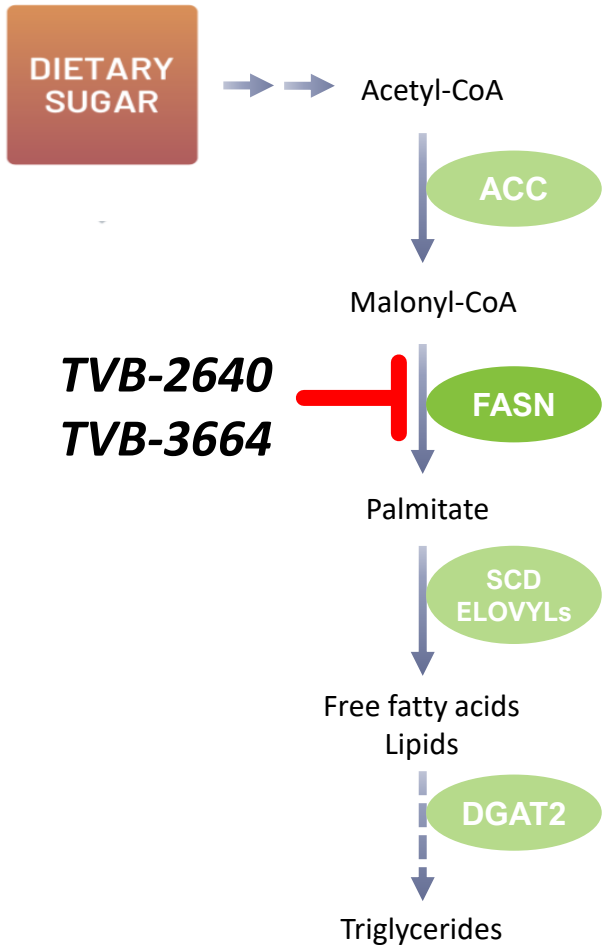
TVB-2640 is a potent FASN inhibitor in clinical development



TVB-2640: in clinical development for NASH

- Orally-available small molecule (MW=440)
- Once-daily dosing (10-12 hr half-life in blood)
- Potent (EC50~50 nM)
- Dose-dependent, predictable PK/PD
- Inhibits hepatic de novo lipogenesis, Phase 1b

TVB-3664: used for preclinical efficacy only

- A related FASN inhibitor with similar human FASN potency[1]
- Superior properties for mouse studies than TVB-2640
  - Better mouse PK and higher potency against murine FASN

[1]*Heuer et al. EBioMedicine 16 (2017) 51–62*

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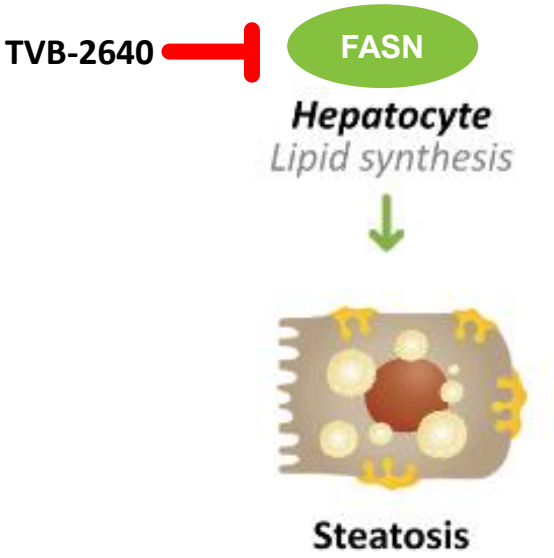
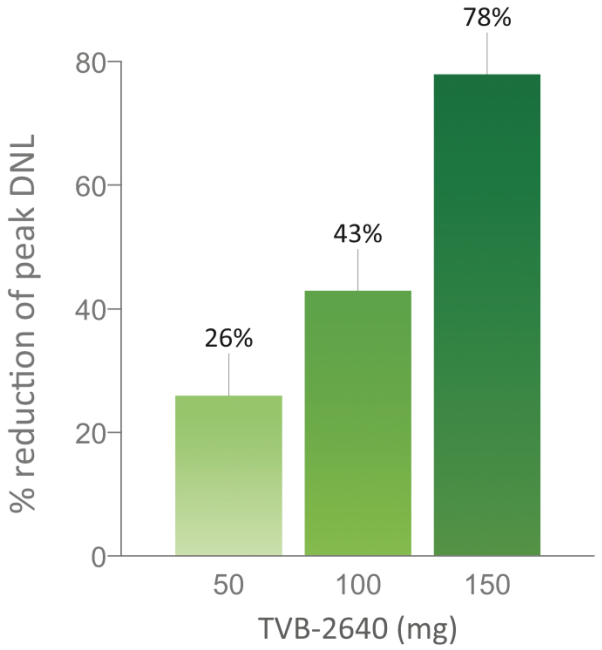
The role for FASN in liver fat synthesis is well documented and proven

TVB-2640 reduces de novo lipogenesis and liver fat in clinical studies



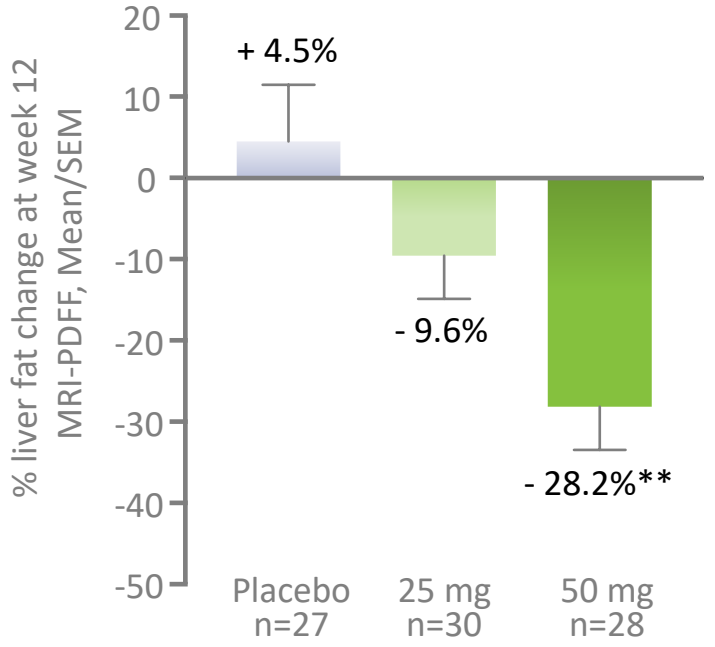
Reduces hepatic DNL in human

- Phase 1b ^{13}C-acetate tracer study[1]
- 10 days of TVB-2640 treatment



Reduces liver fat in NASH patients

- Phase 2 FASCINATE-1 MRI-PDFF study
- 12 weeks TVB-2640 treatment



[1]Syed-Abdul et al, 2020 Hepatology, 72; 103-118. (Fructose challenge initiated 12 hr after the last dose of TVB-2640)
[2]Loomba et al., Gastroenterology, 2021, Jul 23, doi: 10.1053/j.gastro.2021.07.025.
Liver fat reduction is independent of T2D, baseline MRE and baseline liver fat. **p<0.005, ***p<0.001. LSM difference versus placebo. Mean/SEM.

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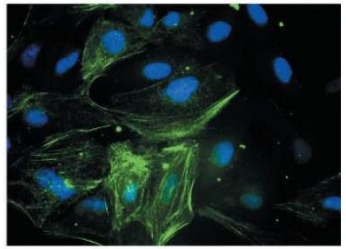
FASN inhibitor decreases fibrogenic gene expression in human hepatic stellate cell line

Direct effect on stellate cell line

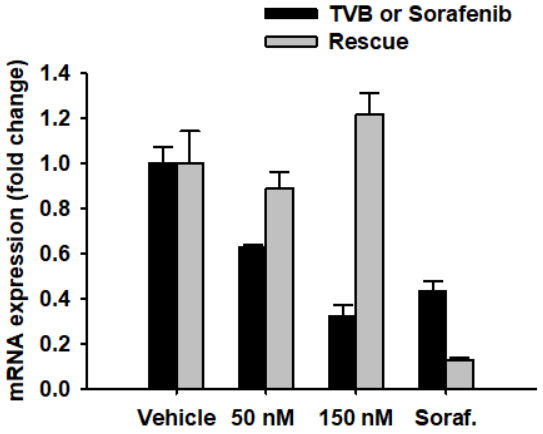
LX-2



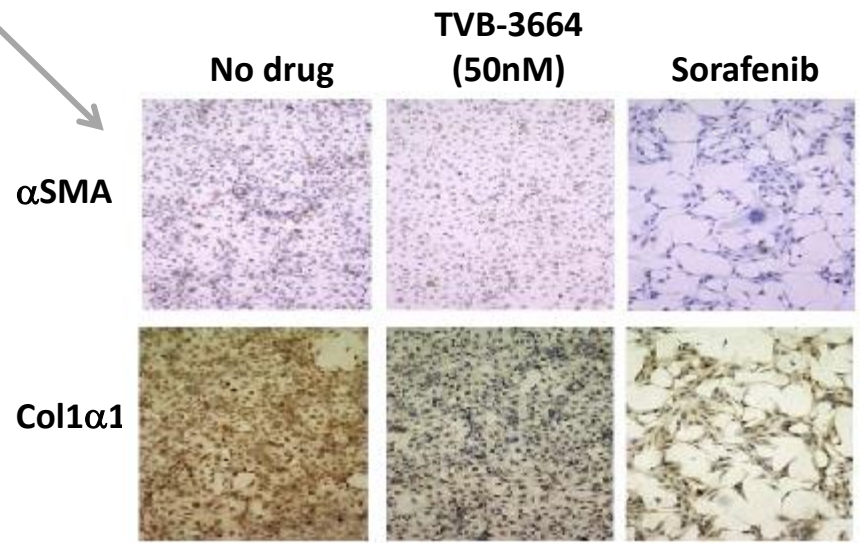
Human hepatic stellate cell line – activated

1.Treat 48 hr
2. RT-qPCR
3. No drug "rescue" 48 hr
4. RT-qPCR

Col1α1



1.Treat 48 hr
2. IHC



TVB-3664

- Dose dependent
- Rescuable
- Not cytotoxic

Fibrogenic Gene	Human Hepatic Stellate Cells % downregulation,	
	50 nM TVB-3664	150 nM TVB-3664
Col1a1	37%	68%
aSMA	37%	60%
bPDGF-R	0%	53%
TFGb-R1	0%	54%
TIMP1	19%	8%
TIMP2	12%	24%
MMP2	0%	50%

Collaboration with Scott Friedman

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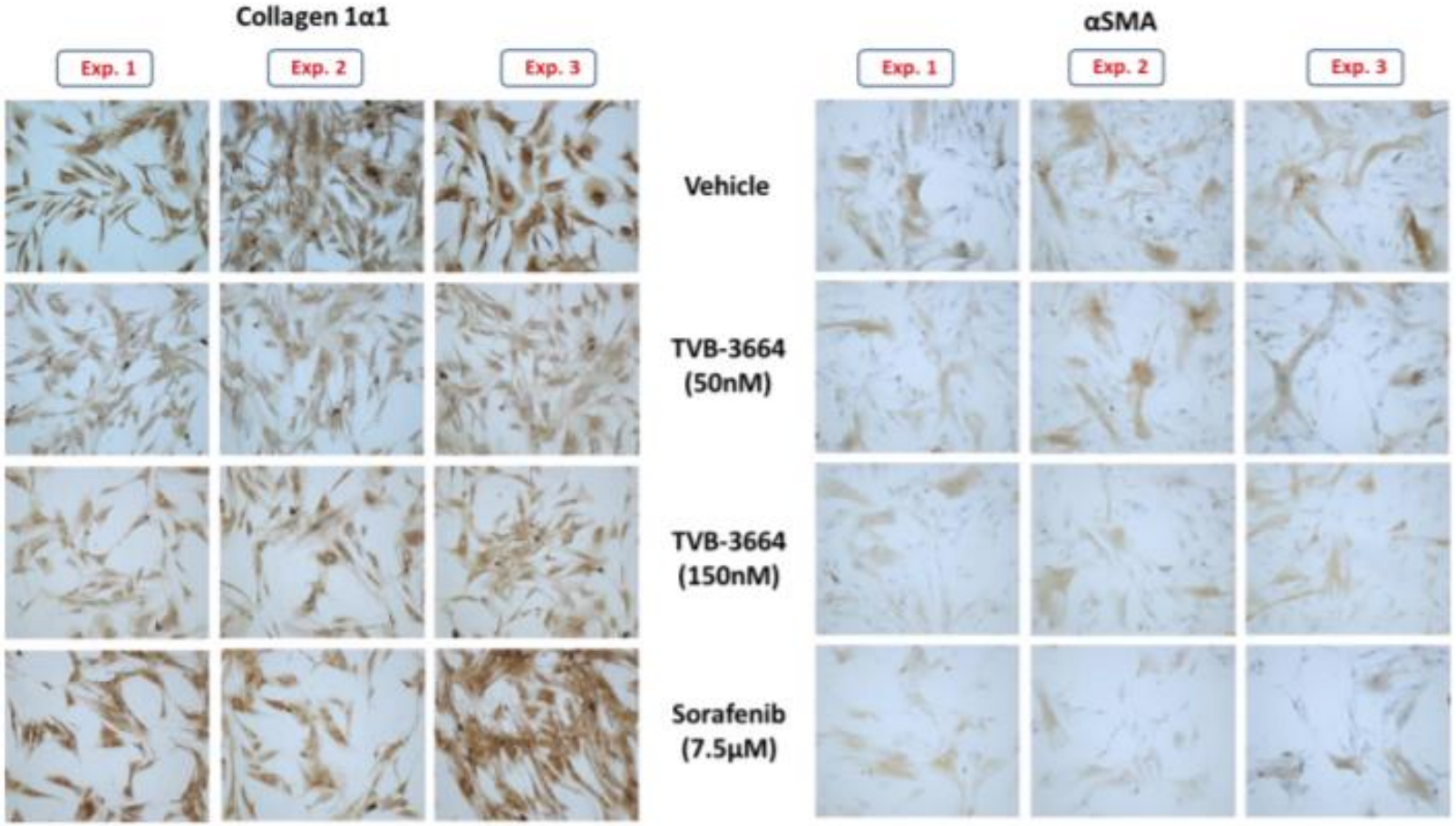
Decreased collagen and smooth muscle actin expression in primary human hepatic stellate cells



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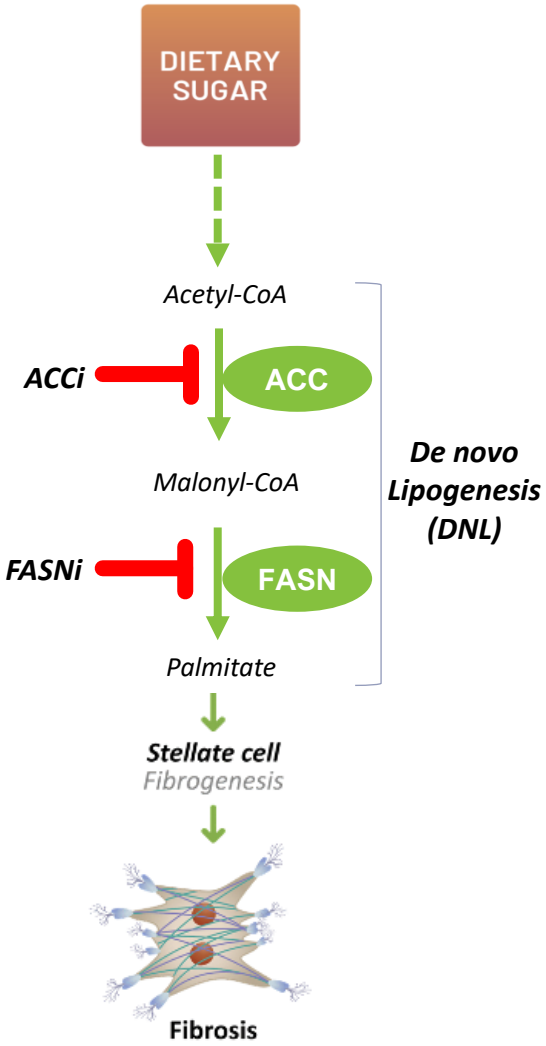
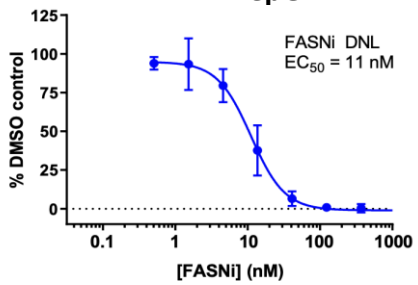
DNL pathway is required for stellate cell activation, production of collagen and fibrogenic activity

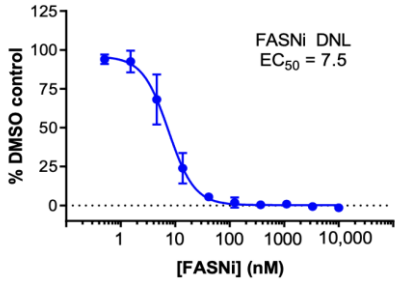


FASN inhibitor decreased DNL and procollagen in stellate cells

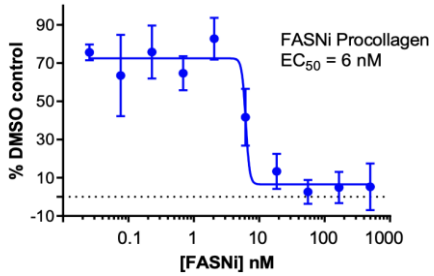
DNL in HepG2



DNL in LX2

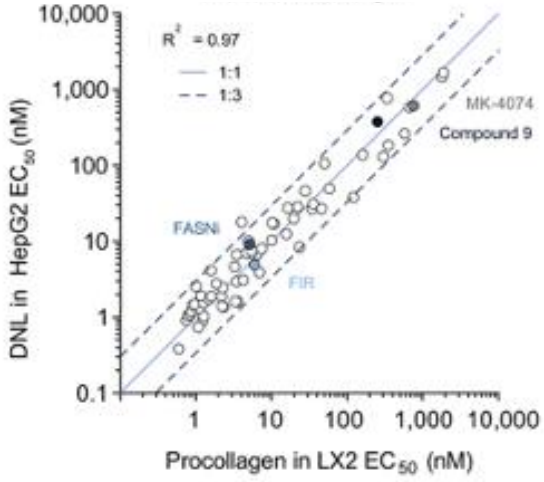


Procollagen in LX2



Strong correlation across large panel of FASN & ACC inhibitors

DNL vs Procollagen



HSCs became quiescent with suppressed glycolysis and mitochondrial oxidation

Data from Bates et al., 2020. J Hepatol, 20;30281-6

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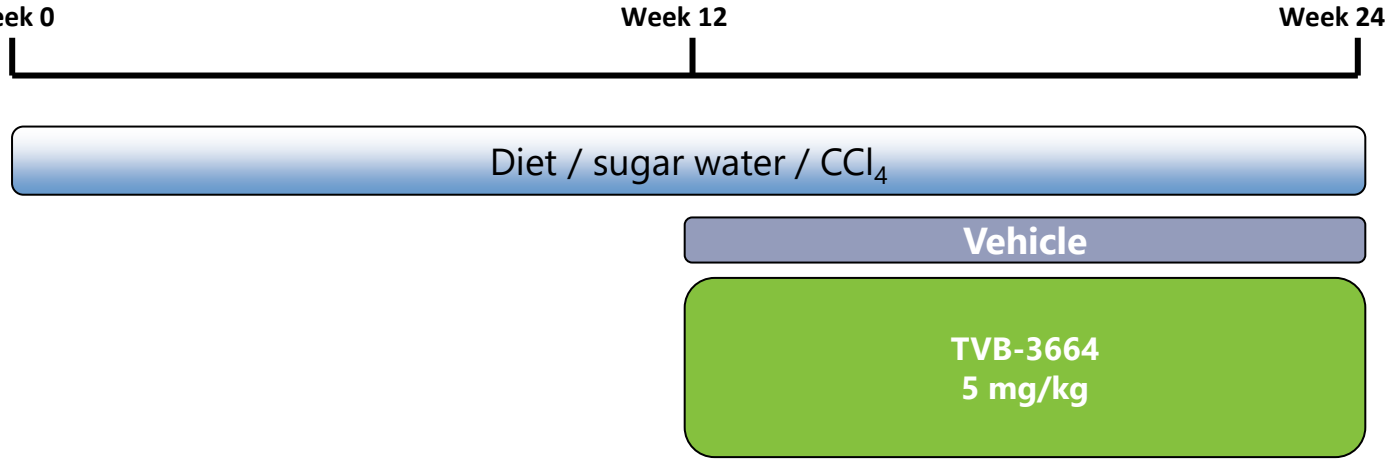
FASN inhibitor TVB-3664 tested in the CCl4 liver fibrosis model

Murine model developed by Dr. Scott Friedman

- Western diet, sugar water, weekly CCl_4 injection
- Initiate treatment after 12 weeks
- At 24 weeks, control animals have developed cirrhosis & hepatocellular carcinoma

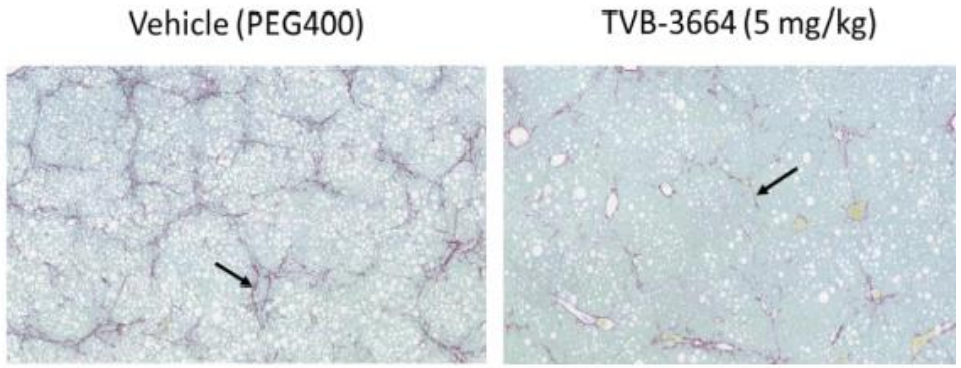


Liver – histology: conventional and AI
Liver – fibrogenic gene/protein expression
Serum markers
Tumor formation

Collaboration with Scott Friedman

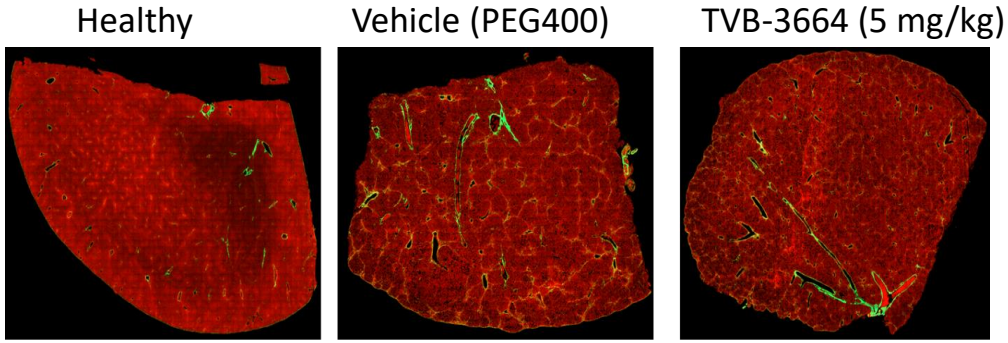
TVB-3664 reduces established fibrosis and HCC in the CCl4 liver fibrosis model

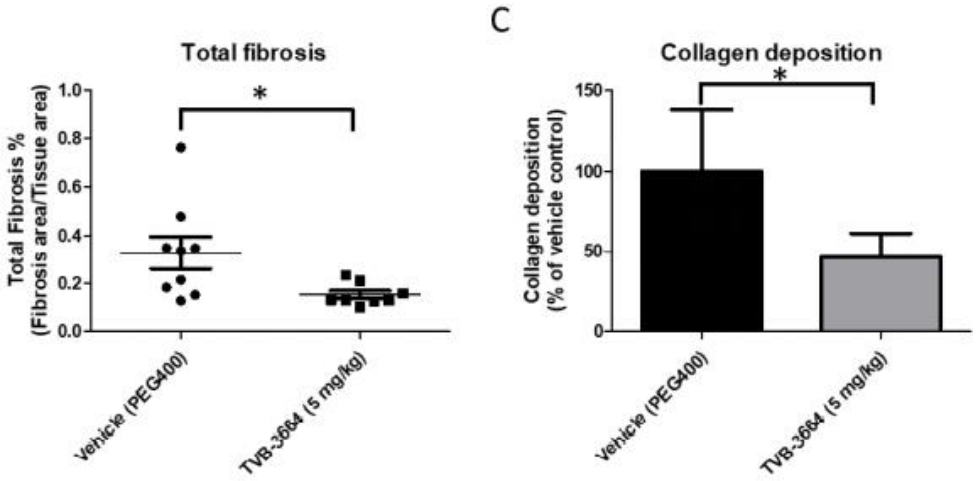
Reduces fibrosis: Conventional histology

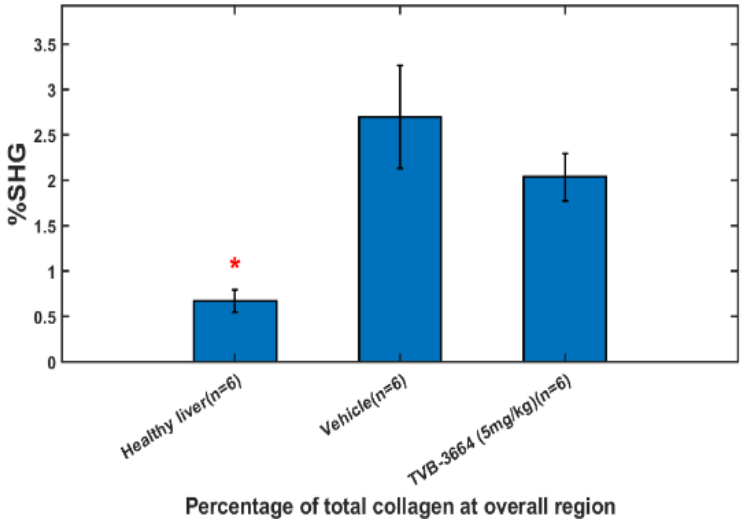


Sirius red

Reduces fibrosis: AI-based SHG analysis (HistoIndex)







Collaboration with Scott Friedman

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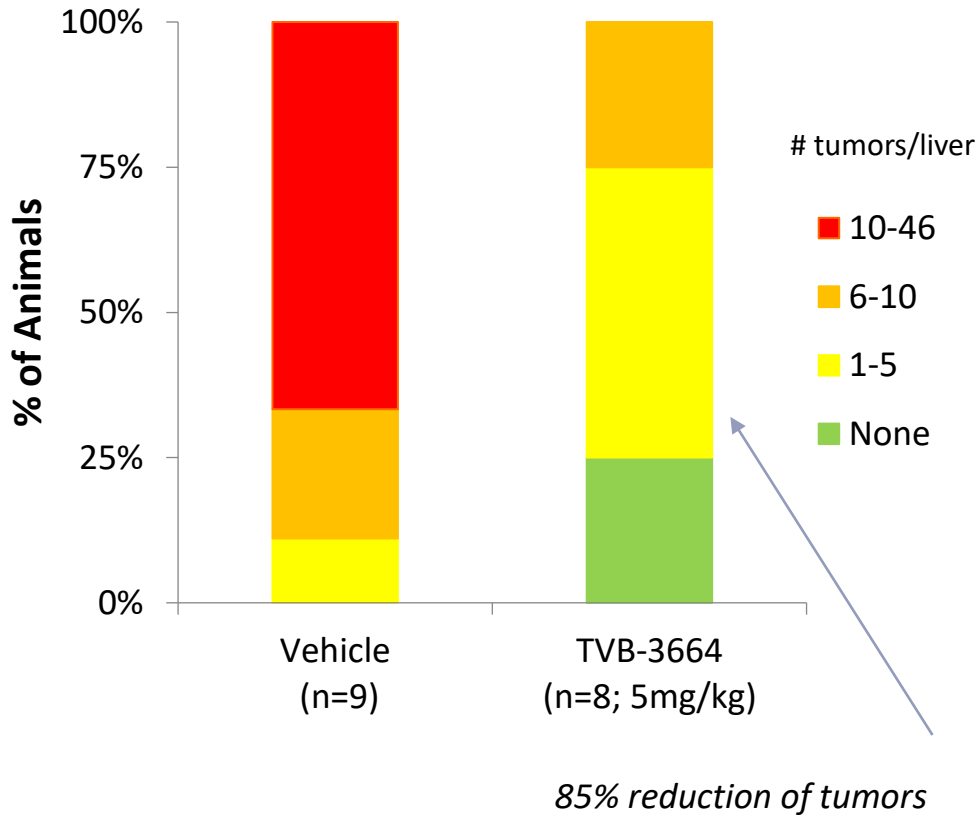
TVB-3664 reduced hepatic fibrosis and formation of liver tumors

Decreased fibrogenic gene expression, ALT and TGs

Assay	Parameter	Vehicle	TVB-3664 5mg/kg
mRNA expression (fold-change)	**Col1α1**	1 ± 0.1	0.3 ± 0.05*
	αSMA	1 ± 0.09	0.5 ± 0.02*
	βPDGFR	1 ± 0.1	0.3 ± 0.03*
	TGFβR1	1 ± 0.2	0.5 ± 0.04
	TIMP1	1 ± 0.2	0.3 ± 0.02*
	TIMP2	1 ± 0.2	0.3 ± 0.02*
	MMP2	1 ± 0.2	0.2 ± 0.03*
Protein expression (fold-change)	**Col1α1**	100.0 ± 18.3	50.6 ± 11.4*
	αSMA	100.0 ± 20.8	63.6 ± 9.64
Liver enzyme & lipid panel (fold-change)	**AST**	100.0 ± 12.9	79.5 ± 16.2
	ALT	100.0 ± 12.01	50.8 ± 5.9*
	Chol	100.0 ± 10.6	89.6 ± 8.6
	TriG	100.0 ± 11.9	68.6 ± 5.1*

Blocked tumor formation



85% reduction of tumors

Collaboration with Scott Friedman

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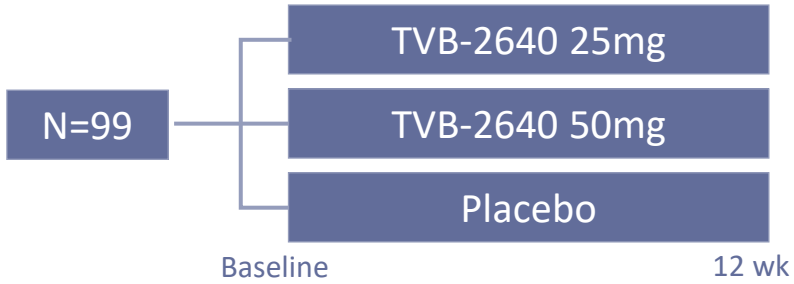
Ph2a study FASCINATE-1

FASN inhibitor TVB-2640 showed potent, dose-dependent reduction of liver fat, with high responder rate

FASCINATE-1

A multi-center, randomized, placebo-controlled Phase 2 trial



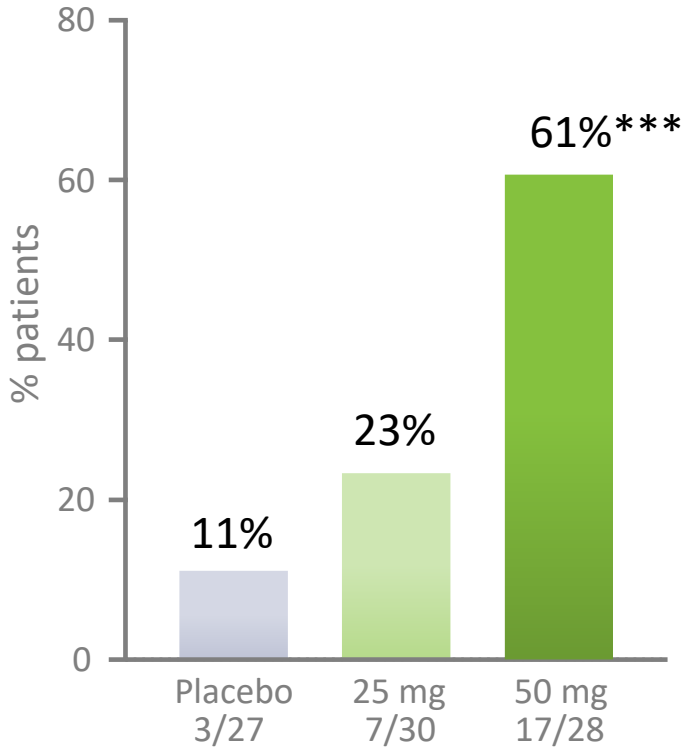
TVB-2640
- FASN inhibitor
- Once daily oral small molecule

Primary
- Liver fat reduction by MRI-PDFF
- Safety

Secondary
- % pts ≥30% reduction of liver fat
- ALT, AST
- Serum biomarkers

Liver fat responder frequency

≥30% relative reduction at week 12



Loomba et al., Gastroenterology, 2021, doi: 10.1053/j.gastro.2021.07.025.

Liver fat reduction is independent of T2D, baseline MRE and baseline liver fat. **p<0.005, ***p<0.001. LSM difference versus placebo. Mean/SEM.

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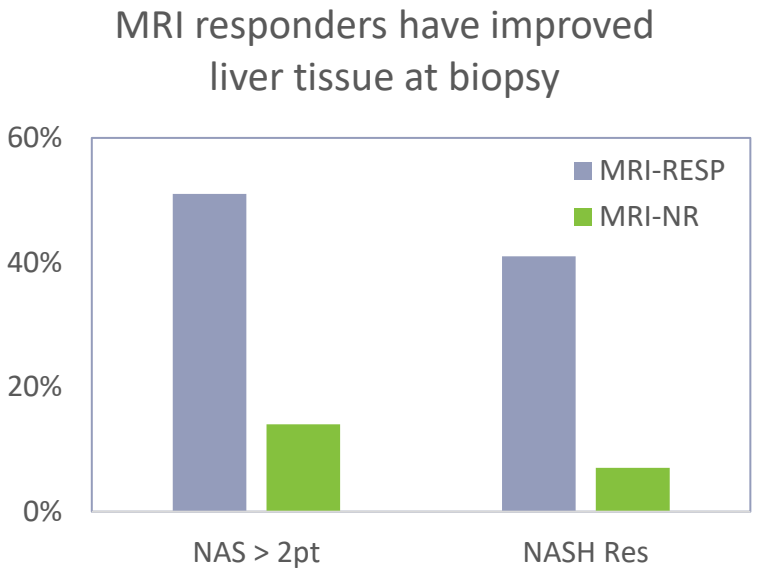
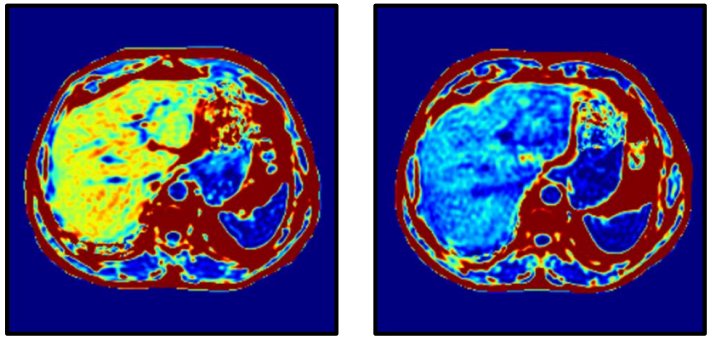
≥30% reduction of liver fat predicts critical biopsy endpoints





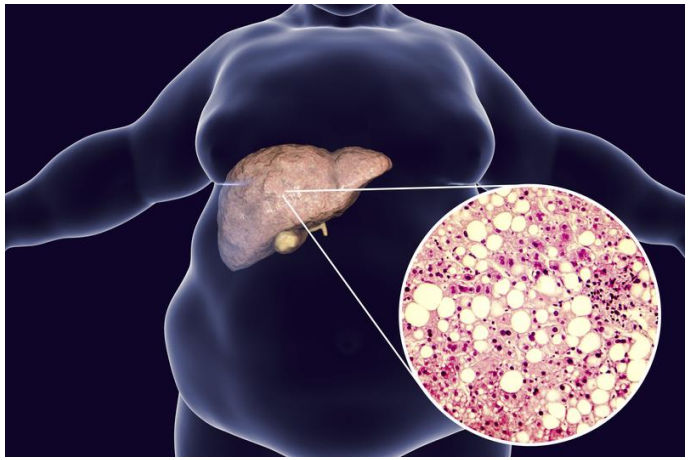
Screening Week 12

Biopsy endpoints correlated with MRI-PDFF response

- ≥2-point improvement in NAFLD Activity Score (NAS)
- NASH resolution
- Fibrosis improvement

} FDA accelerated approval

Correlation demonstrated across 7 studies



Stine et al., Clin Gastroenterology and Hepatology 2020. https://doi.org/10.1016/j.cgh.2020.08.061

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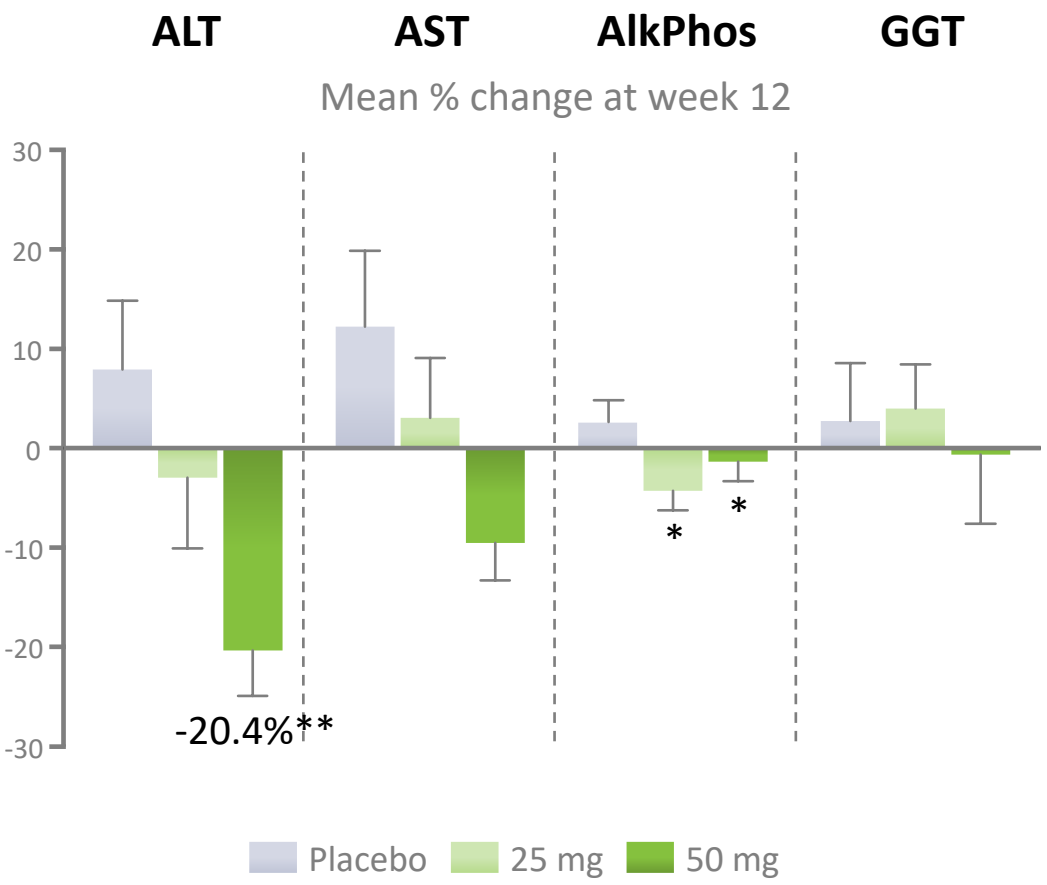
Dose-dependent improvement in liver health markers

Normalization achieved in up to 58% of patients with ALT>ULN



Patients with baseline >ULN ALT only [1]

	Mean ALT change at week 12		≥17 U/L decrease at week 12		Normalization at week 12	
	n	%, absolute	N	% pts	n	% pts
placebo	11	+15%, +10 U/L[2]	2/11	18%	3/11	27%
25 mg	9	-16%, -6 U/L	3/9	30%	3/9	33%
50 mg	12	**-24% , -19U/L**	**6/12**	**50%**	**7/12**	**58%**

Patients with high baseline ALT show clear decrease with TVB-2640

Baseline median ALT 28 U/L (range 8-163)
***p<0.005, *p<0.05. Mean ±SEM. LSM difference versus placebo*

[1] ALT ULN: male 41 U/L, female 33 U/L
[2] median placebo change of -5% and +1U/L

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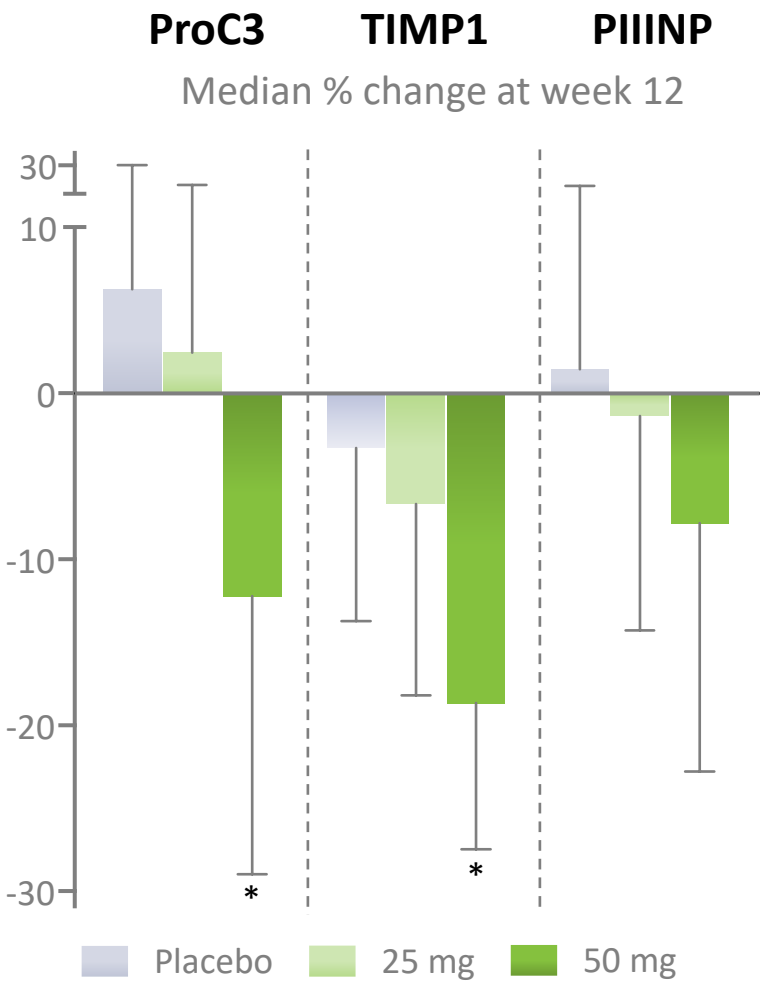
Decreased levels of fibrosis markers



ProC3 correlates with NASH fibrosis stage

- Marker of active type III collagen formation
- Baseline 17ng/mL (median) – F2-F3

Changes in fibrosis markers consistent with preclinical results

**p<0.05. Mann-Whitney U test versus placebo. n=27 (placebo), 28 (25 mg), 28 (50 mg). Median IQR.*

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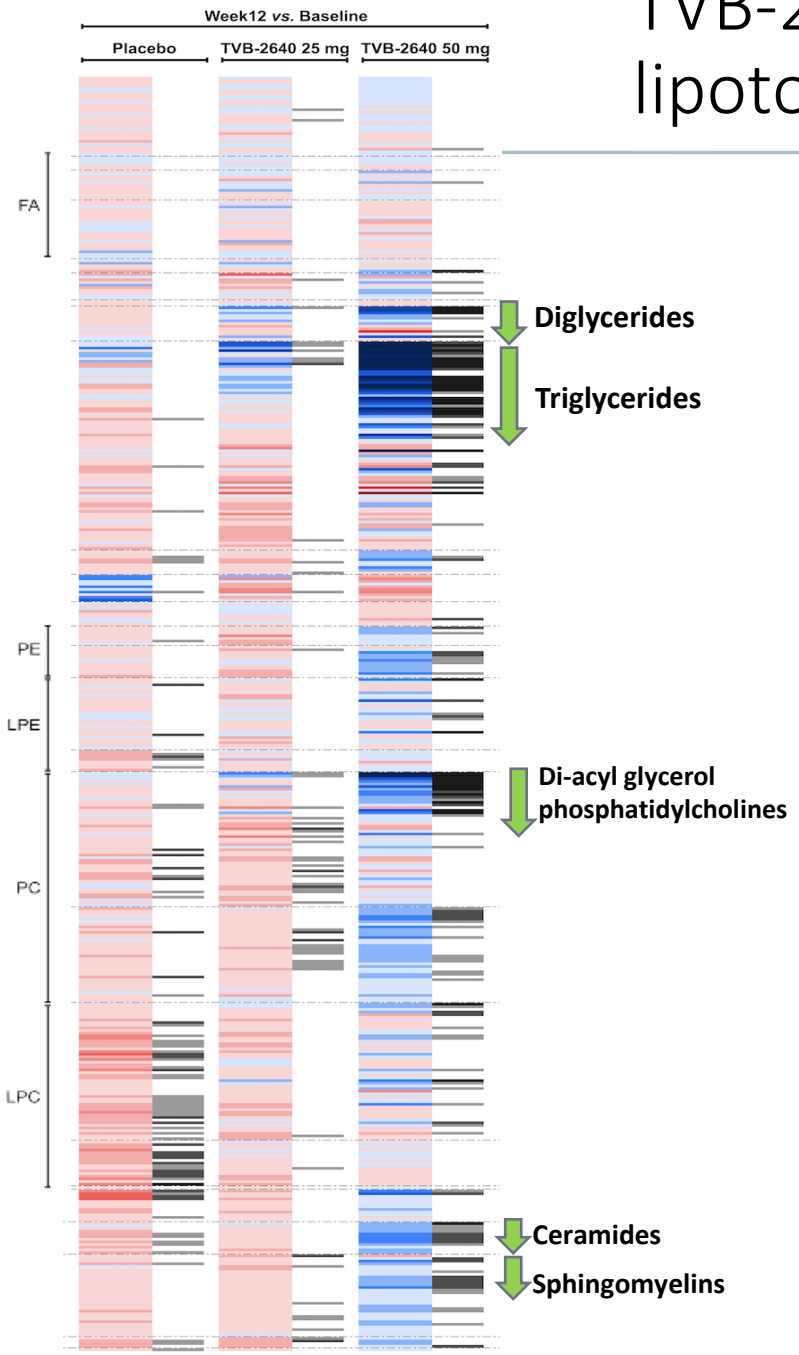
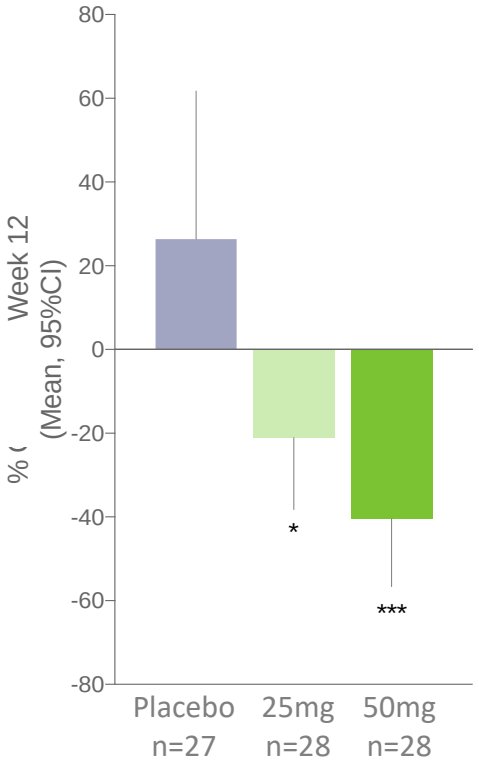
TVB-2640 reduces tripalmitin and significantly reduces lipotoxic ceramides

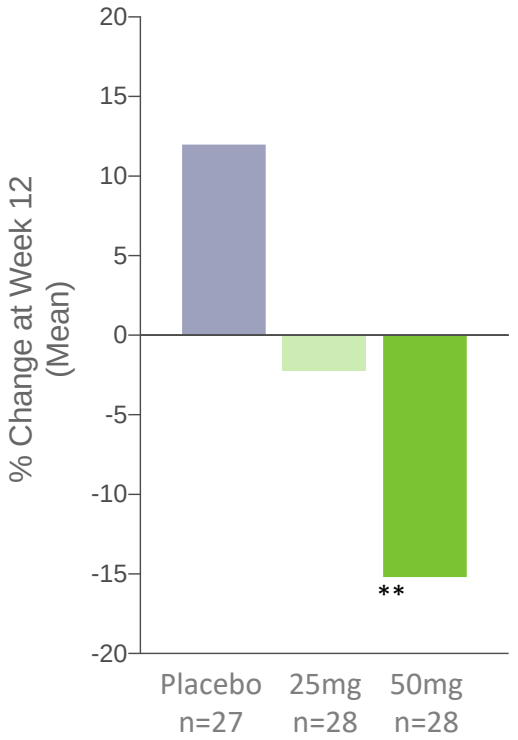


Tripalmitin

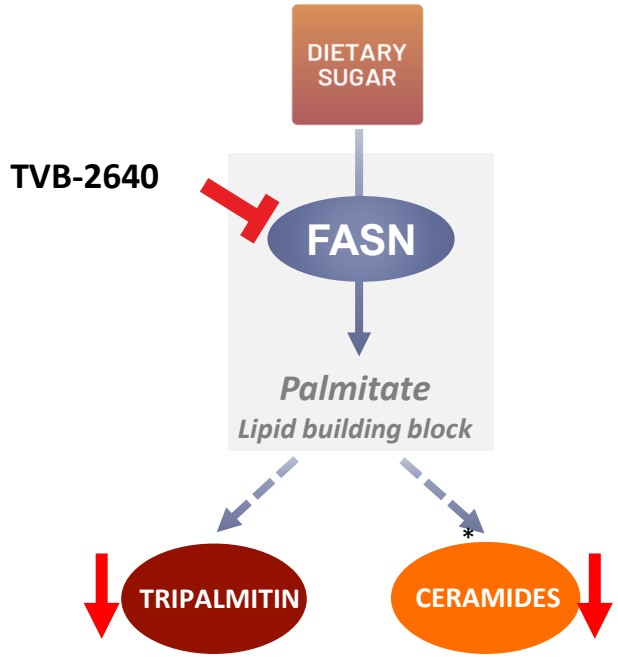
Proof of MOA



Ceramide C18:1/16:0



MOA model



*p<0.05, **p<0.005, ***p<0.001. Mann Whitney U test vs placebo for tripalmitin. Wilcoxon signed rank test for ceramide.

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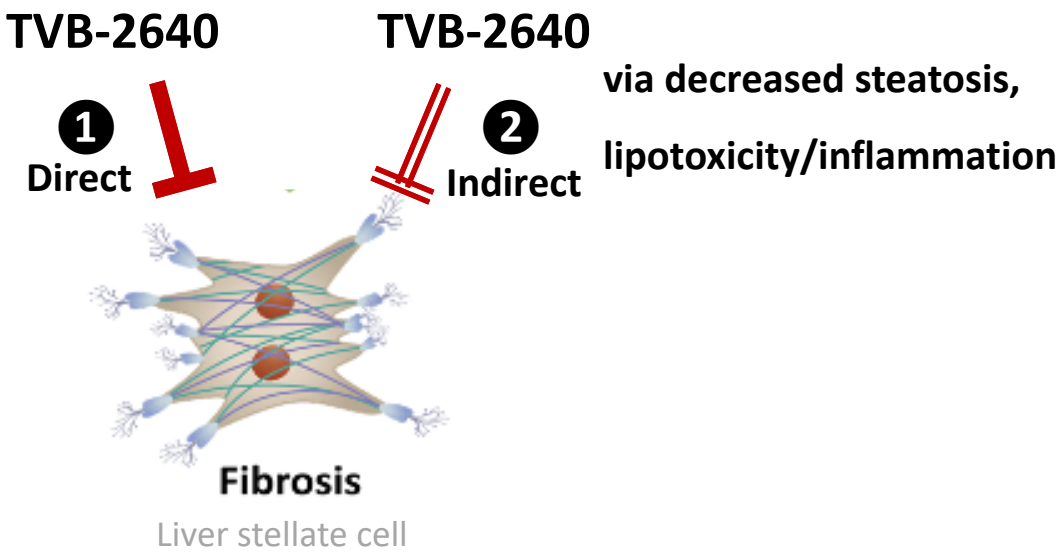
Preclinical and clinical results support FASN as a compelling target in NASH

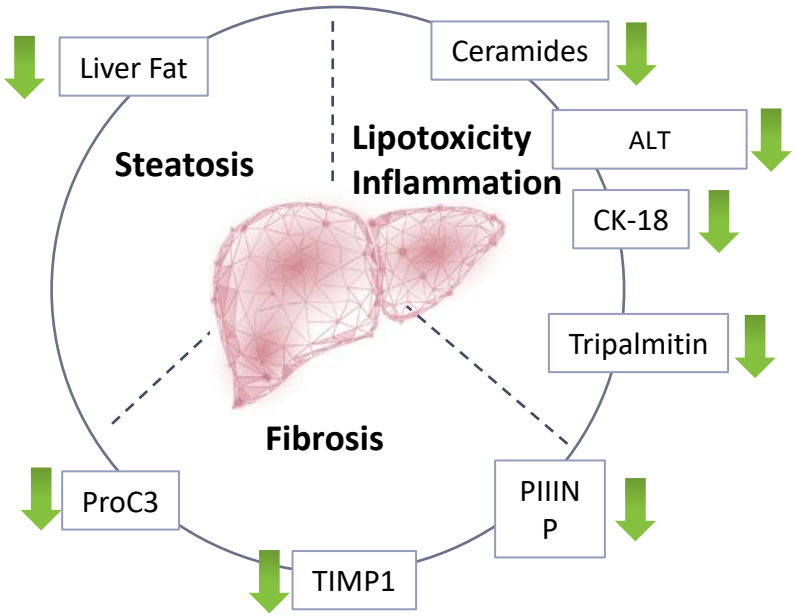
Mechanistic Studies

- Directly reduces hepatic de novo lipogenesis
- Direct inhibition of hepatic stellate cells and efficacy in mouse CCl4 NASH model with severe fibrosis
- Directly reduces inflammatory activity and Th17 cell development (earlier publications)



Ph2a FASCINATE-1 results

- FASNi therapy affects steatosis, markers of lipotoxicity/inflammation, fibrosis and metabolism



Acknowledgements

Sagimet Team

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- Hsin Chou

OWL

- Cristina Alonso

Sagimet Advisors

Investigators, sites and patients involved in FASCINATE-1

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