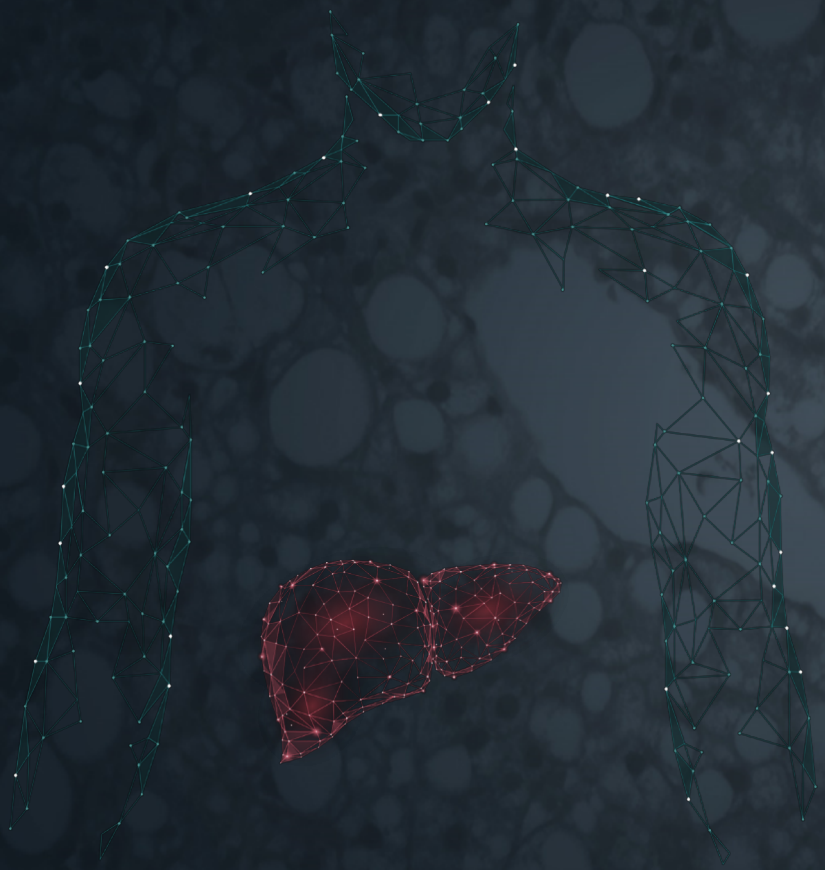

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FASN Inhibitor TVB-2640 in NASH

NASH-TAG 2020

Marie O'Farrell, PhD
VP, Research and Development

Disclosures

Employee of Sagimet Biosciences Inc

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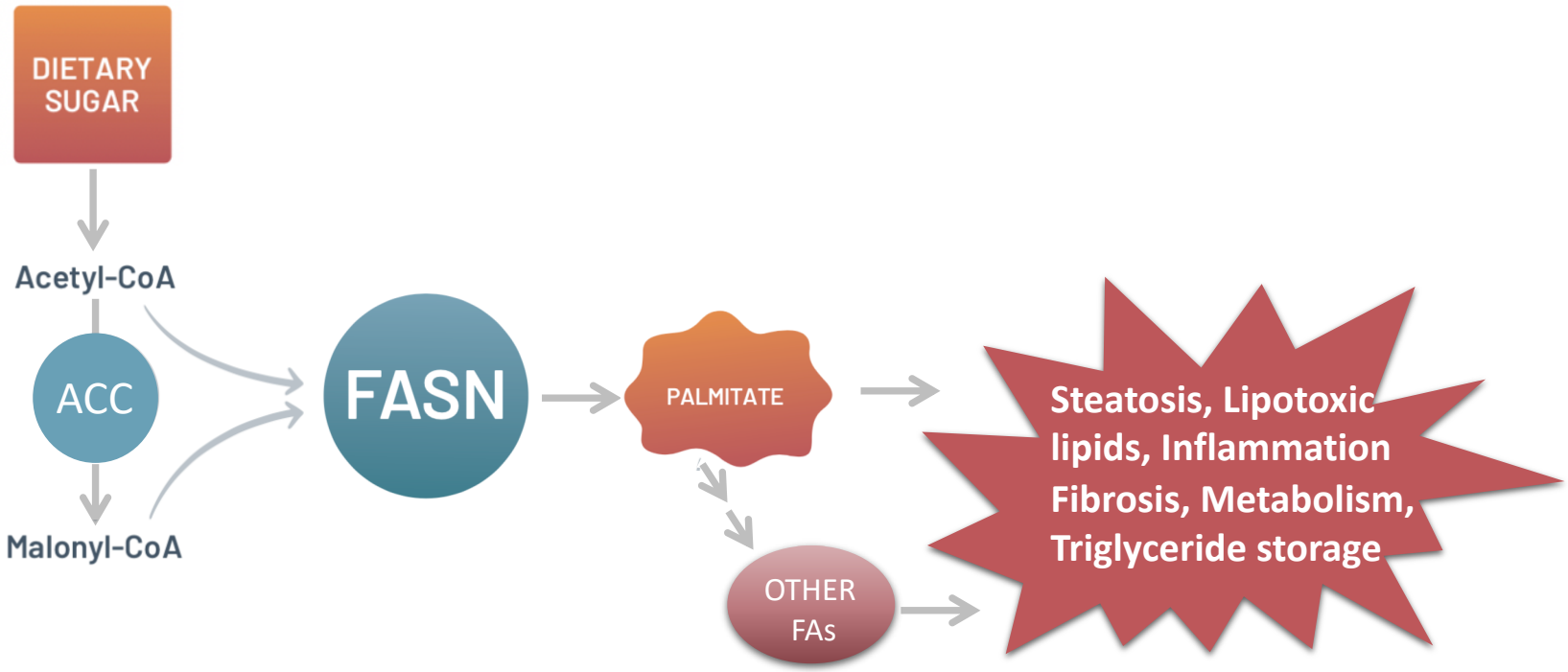
FASN is the last committed step in De Novo Lipogenesis (DNL)



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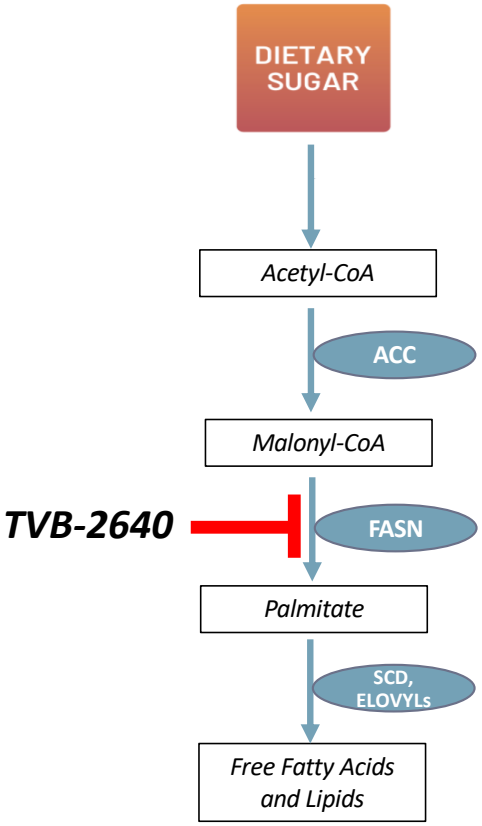
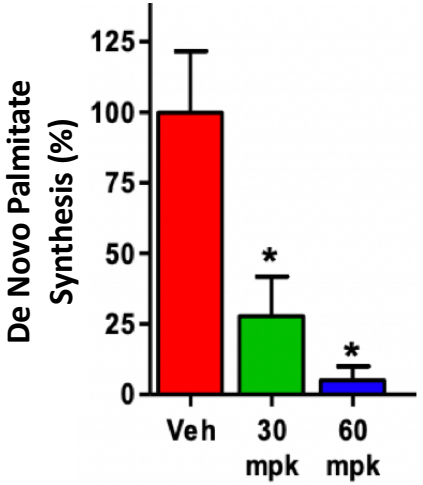
TVB-2640 is a potent and selective first-in-human FASN inhibitor



TVB-2640

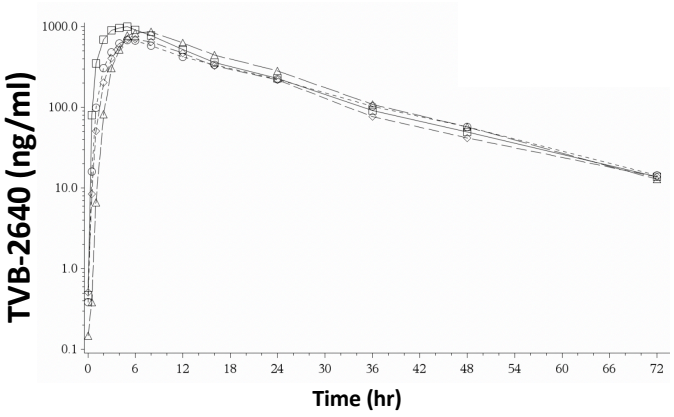
- Orally available small molecule
- Cellular EC50 approx. 50 nM

Rat single dose of TVB-2640 inhibits palmitate synthesis



*p<0.05

Human Pharmacokinetics Half-life of 10-12 hr



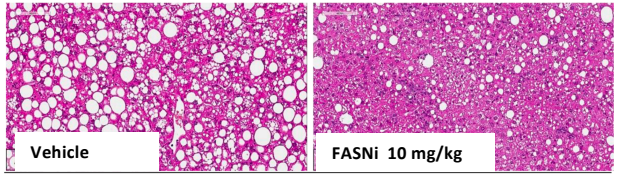
50 mg dose level
N~80

TVB2640 analog reversed steatosis in mouse DIO model, and reduced hepatic fibrosis and formation of liver tumors

HFHSD for 48 weeks
Vehicle or FASNi TVB-3664 for last 8 weeks

NASH-DIO model
40% AMLN diet
Gubra

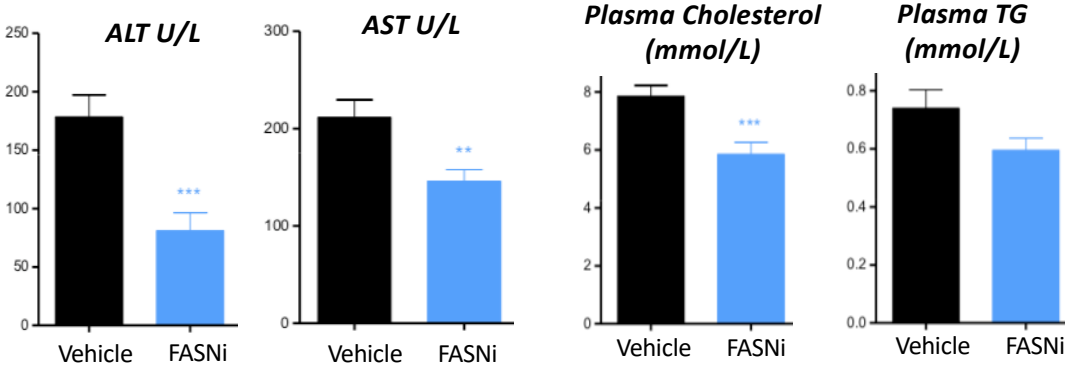
Treats steatosis



Liver H&E representative, 20x

- Steatosis score in all animals
- NAS score in all animals
- Ballooning and inflammation

Improves markers of liver metabolic health

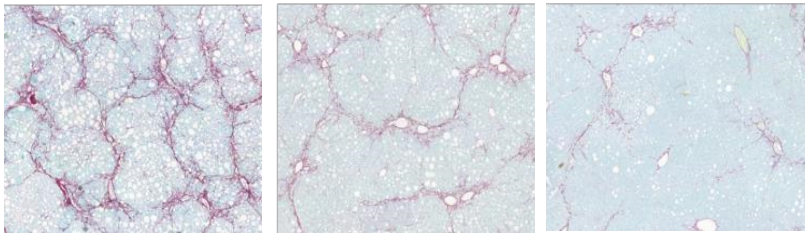


Gubra. Mean ± SEM, n=11-12, **p<0.01, ***p<0.001 vs. Vehicle

HFHSD, plus CCl4 1x/week for 6 months
Vehicle or FASNi TVB-3664 for last 3 months

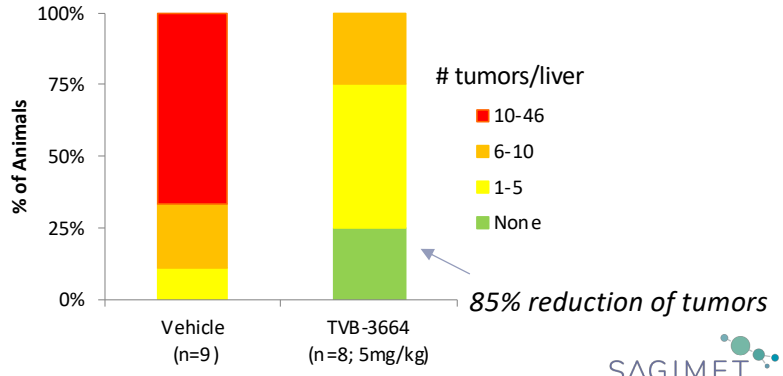
Collaboration with Dr. Scott Friedman

Reverses fibrosis



Vehicle (Placebo) | TVB-3664 3mg/kg | TVB-3664 10mg/kg

Blocked tumor formation



Dr. Scott Friedman Lab, Mt Sinai.

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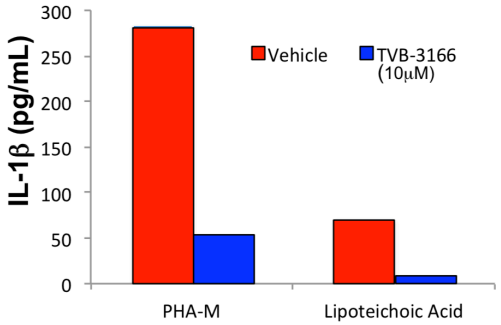
FASN inhibition inhibits pro-inflammatory signaling and acts directly on immune cells

Human PBMC

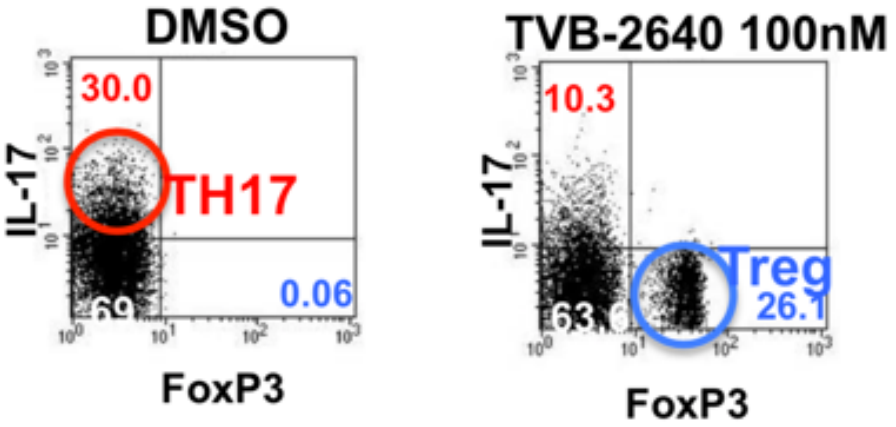
Blocks IL-1b production



- Other cytokines also decreased
- Likely via inflammasome inhibition

Human T cells

Blocks Th17 and increases Tregs



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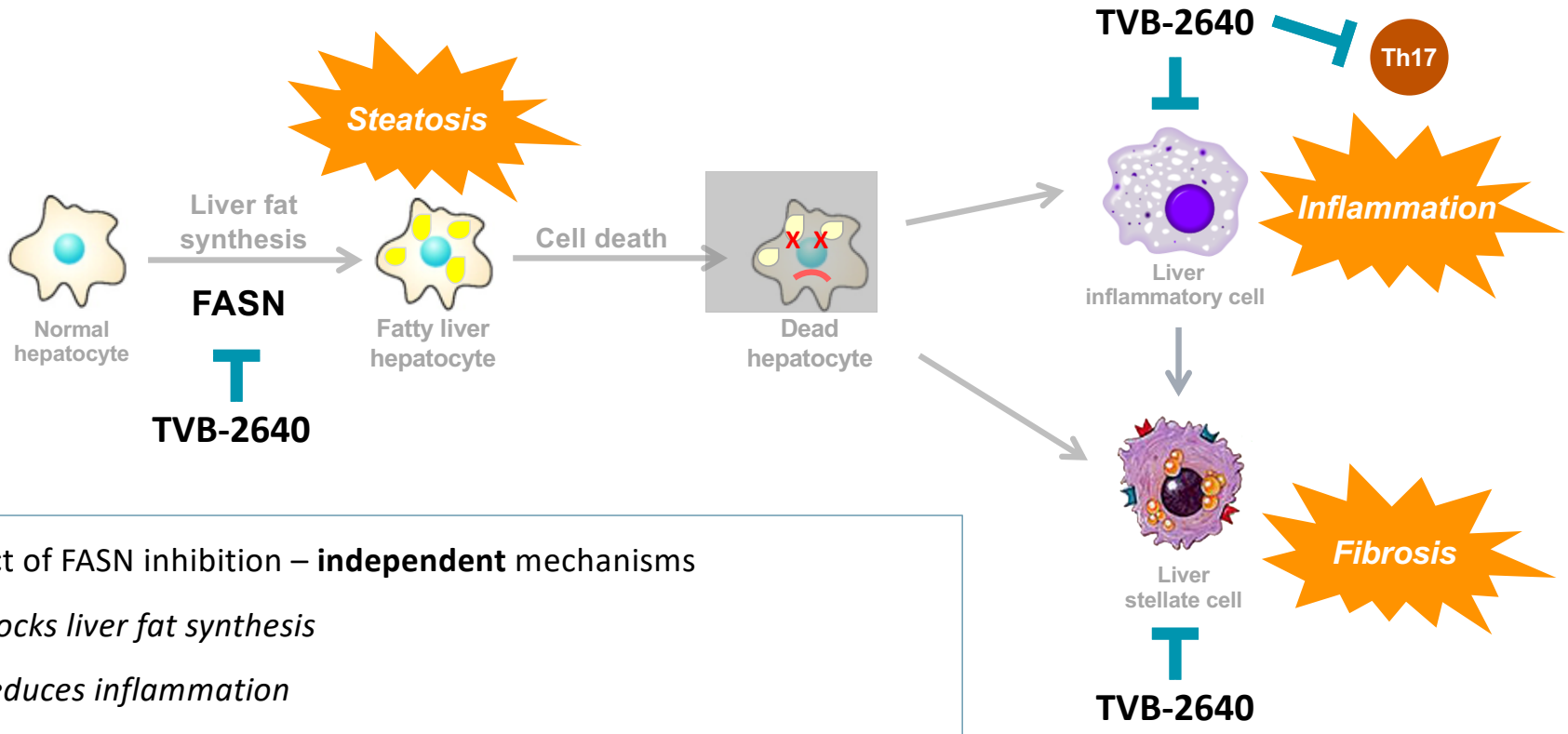
Inhibiting FASN blocks fat synthesis **and** other NASH drivers



Impact of FASN inhibition – **independent** mechanisms

1. *Blocks liver fat synthesis*
2. *Reduces inflammation*
3. *Blunts fibrosis*

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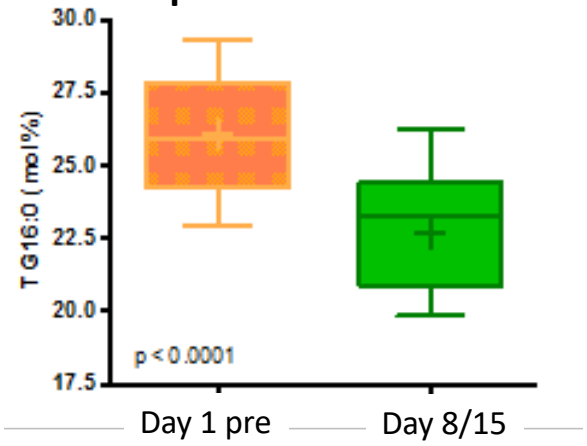
Clinical experience with FASN Inhibitor TVB-2640

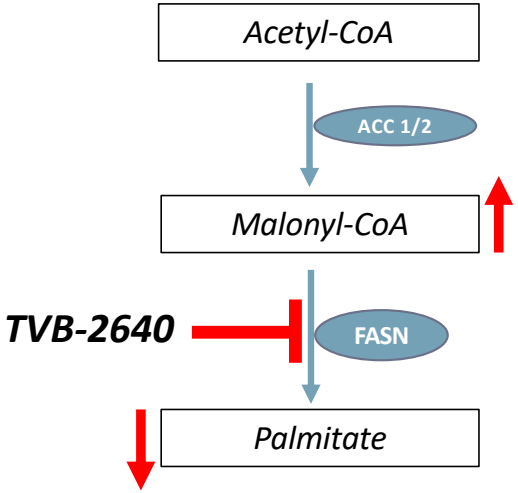
Phase 1 oncology
- **Completed[1]**
- **N = 136 cancer pts**
- **≤ 2 years on treatment**

- Robust PKPD shown
  - Decreased plasma tripalmitin
  - Increased plasma malonyl carnitine
- Inhibited DNL, measured in sebum

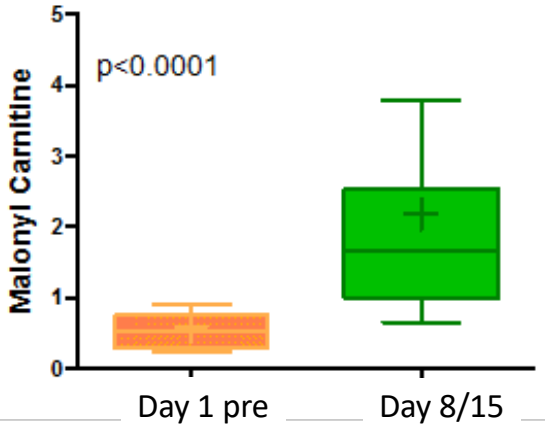
100 mg to 600 mg QD

Tripalmitin decreases





Malonyl carnitine increases



[1]Falchook et al., 2017, Cancer Research 77: CT153 NCT02223247), Tripalmitin and malonyl carnitine assays by Metabolon

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Clinical experience with FASN Inhibitor TVB-2640

Phase 1 oncology
• Completed[1]
• N = 136 cancer pts
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	  • Decreased plasma tripalmitin
	  • Increased plasma malonyl carnitine
	• Inhibited DNL, measured in sebum
		100 mg to 600 mg QD

Phase 1b DNL ^{13}C-acetate • **Completed[2]** • **N = 12 high BMI males** • **10 days**	• Inhibited hepatic DNL at all dose levels tested[2] • Decreased liver fat content within 10 days • Decreased cholesterol and triglycerides • Inhibited sebum DNL	50 mg, 100 mg, 150 mg QD
Phase 2a NASH • **Ongoing** • **N = 90 in US** • **12 weeks**	Ongoing NCT03938246	25 mg, 50 mg QD Lower doses than oncology

[1]Falchook et al., 2017, Cancer Research 77: CT153 NCT02223247),[2]Seyed-Abdul et al, 2019 Hepatology https://doi.org/10.1002/hep.31000

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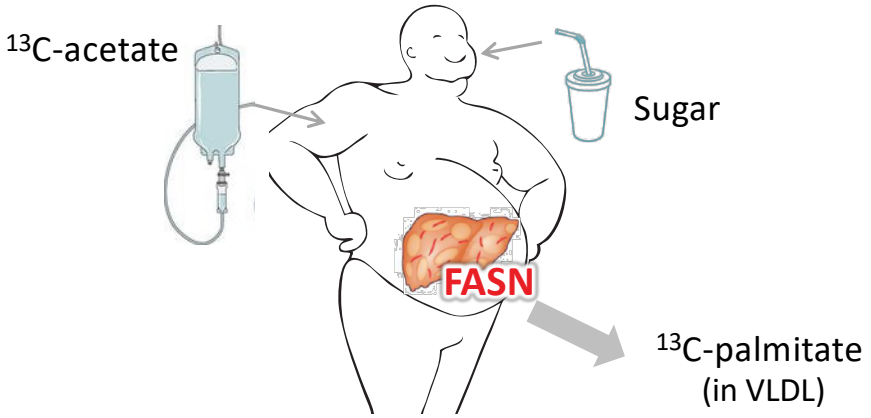
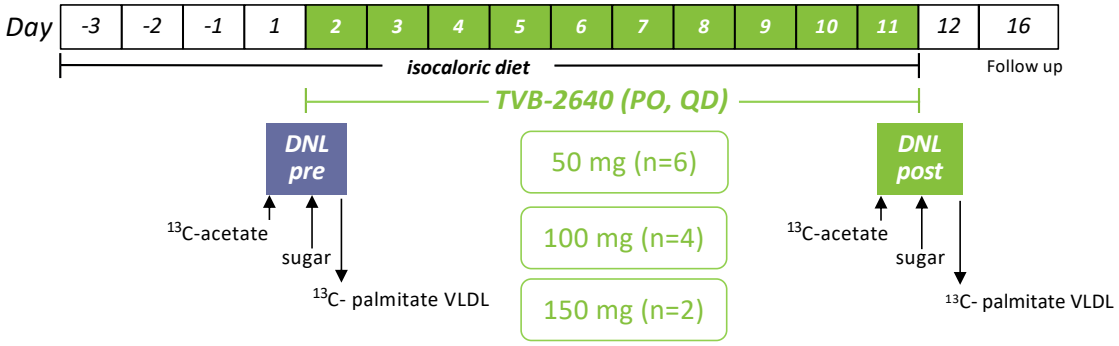
Human POC Study

Hepatic De novo Lipogenesis

Human Phase 1b to test inhibition of hepatic DNL





- Investigator: Dr. Elizabeth Parks, University of Missouri
- 12 male subjects with high BMI (31-41)
- 10 days of TVB-2640 QD
- **Primary endpoint**
  - **Inhibition of hepatic de novo lipogenesis by TVB-2640 (predose vs day 10)**
- Other biological activity endpoints
  - Liver fat, clinical chemistry, OGTT, serum lipids, sebum lipids

Sugar challenge to stimulate DNL was a single bolus given 10 hr after last dose of TVB-2640

(different to other DNL study designs)

Seyed-Abdul et al, 2019 Hepatology https://doi.org/10.1002/hep.31000

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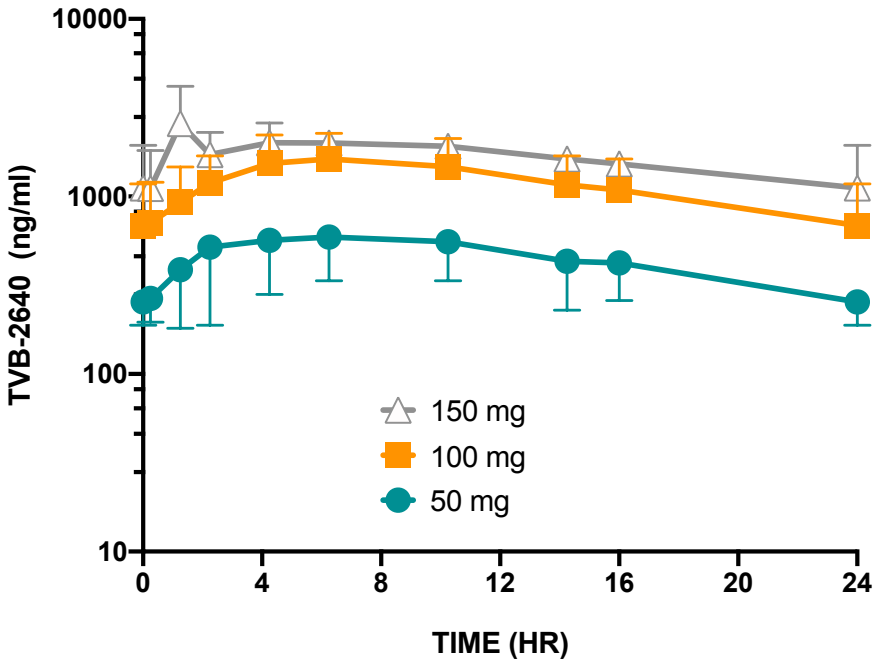
Demographics and Pharmacokinetics

Subject characteristics	50 mg	100 mg	150 mg
Mean +/- SE	n=6	n=4	n=2
Age (y)	41 ± 2	44 ± 4	43 ± 5
Body weight (kg)	124.0 ± 6.0	116.0 ± 10.3	117.3 ± 12.2
BMI (kg/m^2)	37.4 ± 1.4	37.6 ± 2.9	37.3 ± 3.6
Waist (cm)	125.0 ± 4.0	122.3 ± 5.6	119.5 ± 9.5
Plasma glucose (mg/dL)	100 ± 3	109 ± 3	100 ± 2
HDL (mg/dL)	37 ± 3	44 ± 6	34 ± 0
Triacylglycerols (mg/dL)	201 ± 32	171 ± 67	230 ± 75
HbA1c (%)	5.6 ± 0.1	5.8 ± 0.2	5.8 ± 0.2
ALT (U/L)	32 +/- 6	67 +/- 9	36 +/- 1
AST (U/L)	22 +/- 4	41 +/- 9	26 +/- 0
Alkaline phosphatase (U/L)	81 +/- 6	73 +/- 12	68 +/- 5

Steady state PK
TVB-2640 plasma levels increase with dose



Mean +/- SE

No statistically significant differences in baseline characteristics across groups.

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Adverse Events and Laboratory Values

- Overall, TVB-2640 was well tolerated
  - No SAEs
  - No discontinuations
  - No laboratory abnormalities
  - 1 pt at 50 mg with dry skin on hands, reversed
  - 1 pt each at 100 mg and 150 mg with mild hair thinning, reversed

- Laboratory liver enzymes and lipids
  - Trend of decreased ALT and AST levels
  - Decreased cholesterol levels
  - No significant effect on fasting blood glucose or insulin levels

Seyed-Abdul et al, 2019 Hepatology https://doi.org/10.1002/hep.31000

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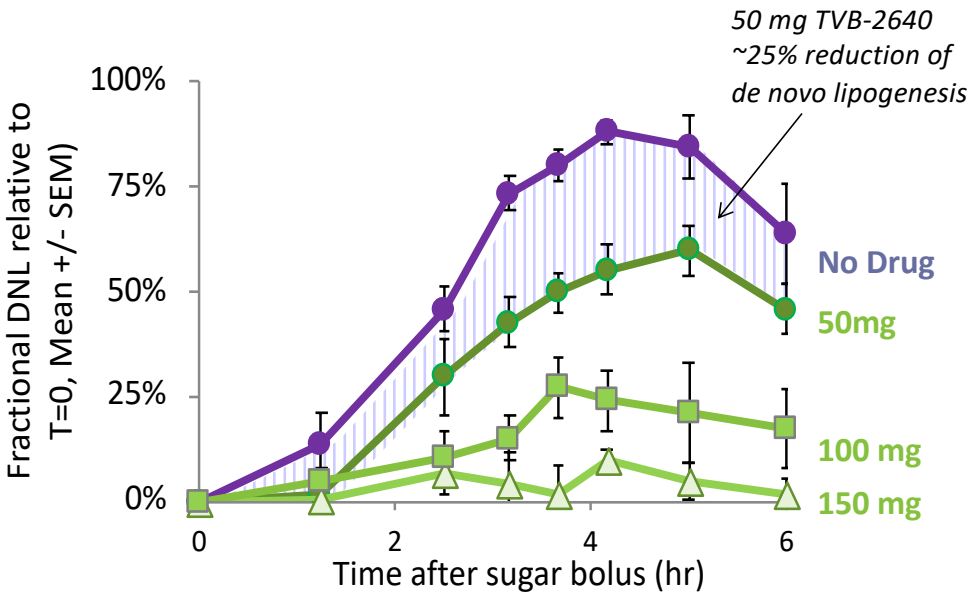
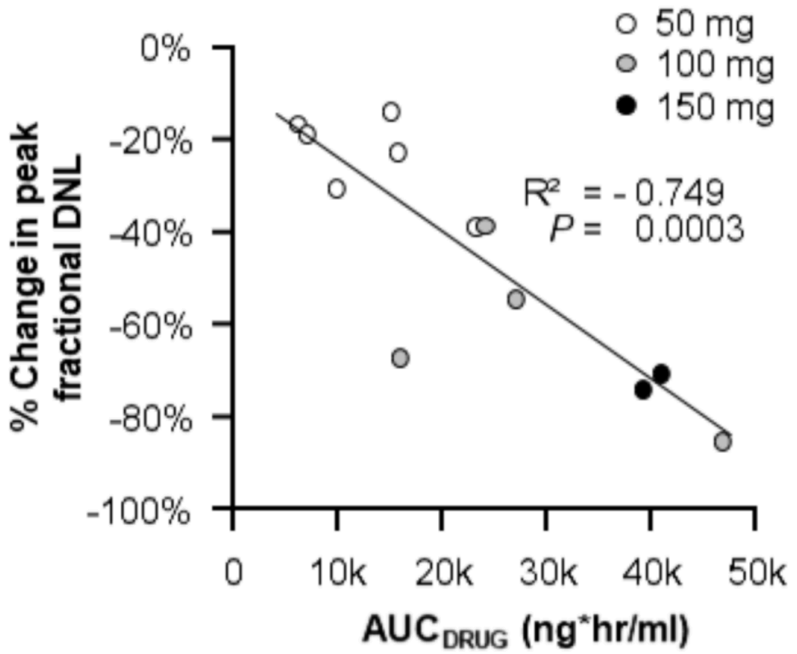
TVB-2640 reduced DNL by up to 90%

Liver fat synthesis (DNL)



Correlates with TVB-2640 exposure



Seyed-Abdul et al, 2019 Hepatology https://doi.org/10.1002/hep.31000

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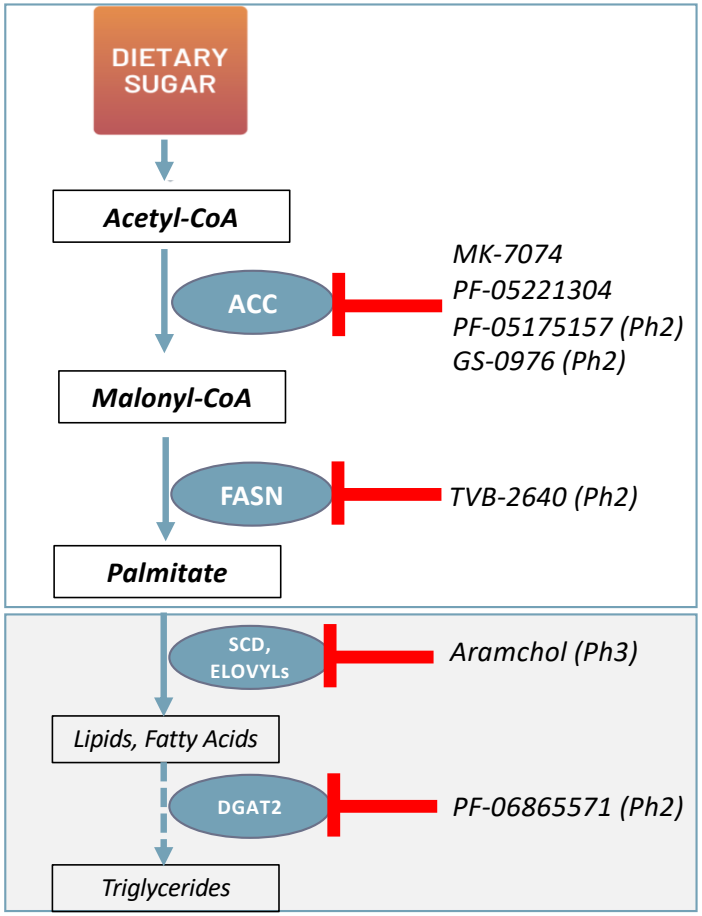
DNL pathway inhibitors show compelling clinical POC in NASH



DNL pathway has been mechanistically validated in Phase 1 and Phase 2 studies using ACC inhibitors[1-4]

Decrease DNL

↓

Decrease liver fat (steatosis)

↓

Improve markers of liver injury and inflammation

[1]Amin et al, AASLD 2019. [2]Loomba et al., Gastroenterology 2018;155:1463–1473.
[3]Kim et al., 2017, Cell Metabolism 26; 394, [4]Goedeke et al

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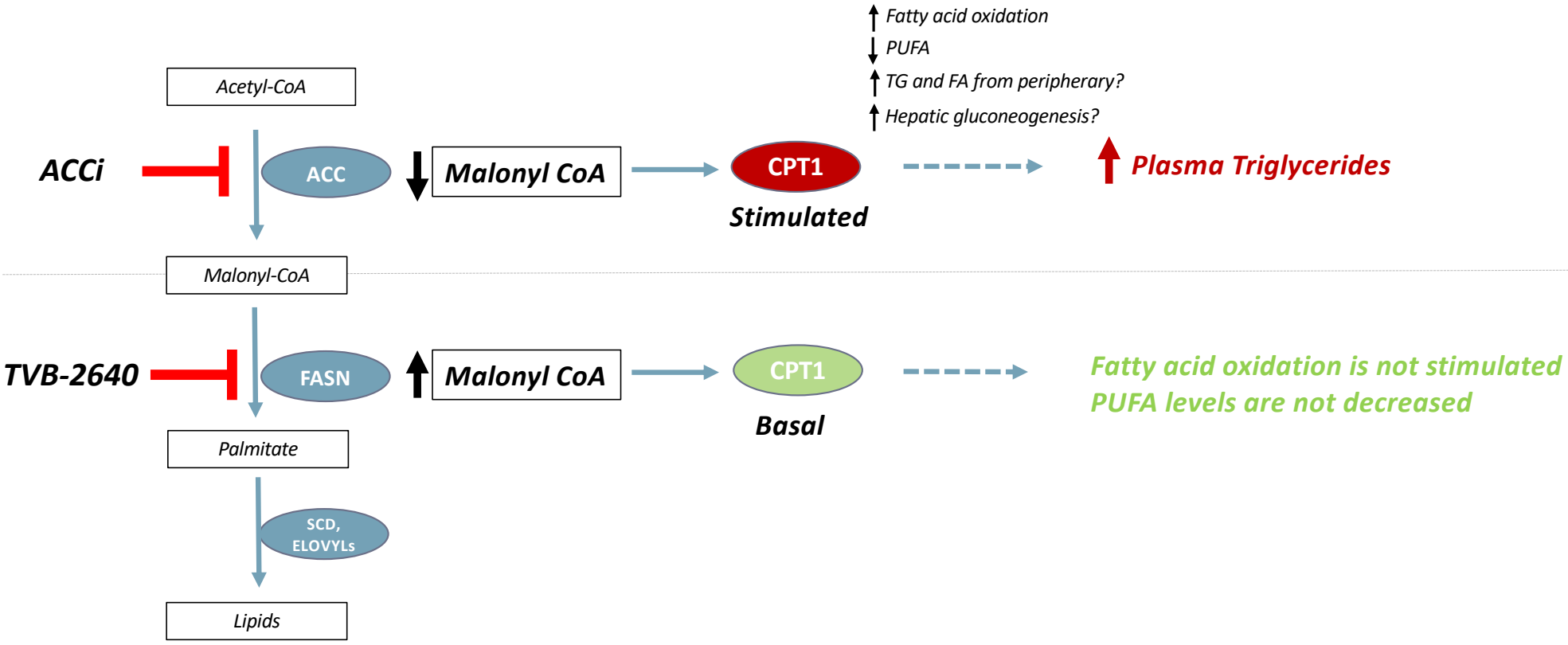
FASN and ACC inhibitors have different effects on Malonyl-CoA levels



ACC model based on data from Kim et al., 2017, Goedeke et al., 2018, Loomba et al., 2018, Stiede et al., 2018

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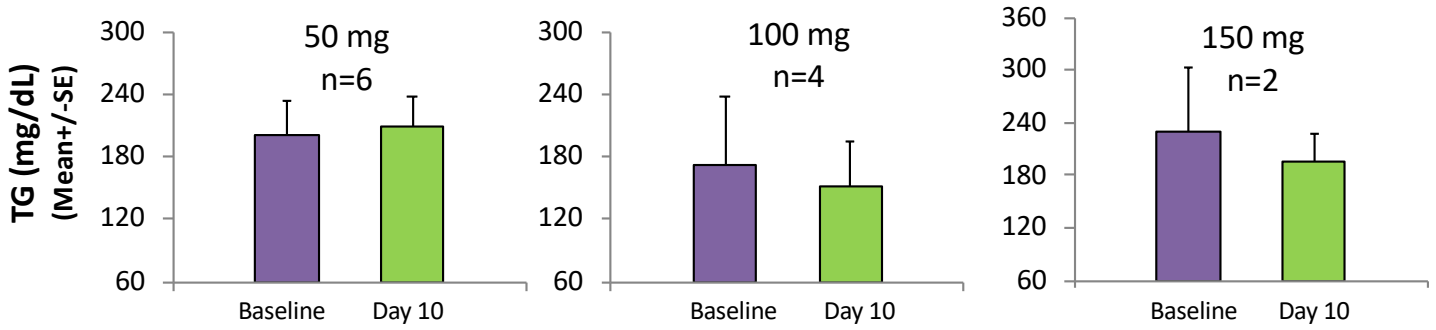
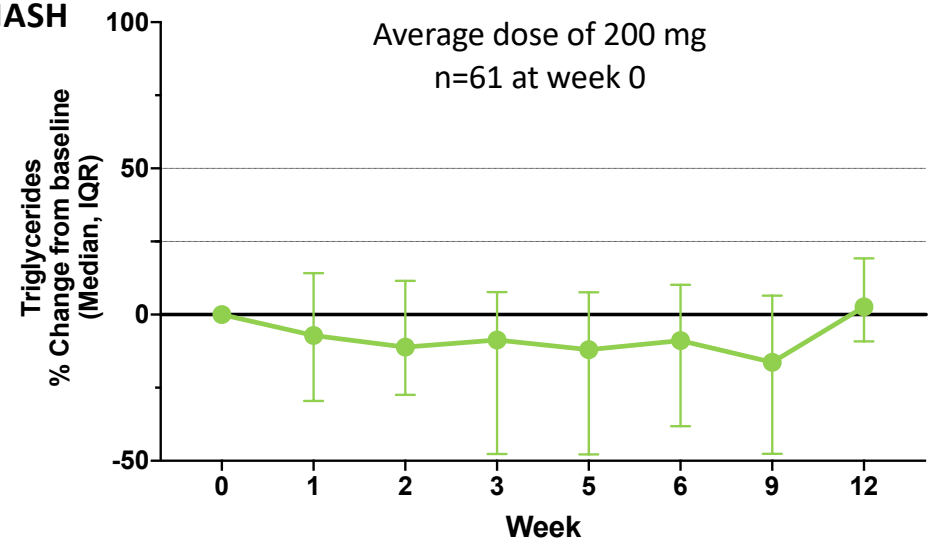
TVB-2640 does not increase plasma triglycerides in human

Phase 1b POC Study



Phase 1 Oncology Study
5-10x higher dose than NASH



PF'1304 50% increase at 10 and 25 mg
9.8% at 50 mg had asymptomatic TG >800 mg/dL[1]

GS-0976 25% increase at 5 and 20 mg
16% pts asymptomatic G3/4 TG >500 mg/dL[2]

[1]Amin et al, AASLD 2019, NCT03248882.
[2]Loomba et al., 2018, NCT02856555

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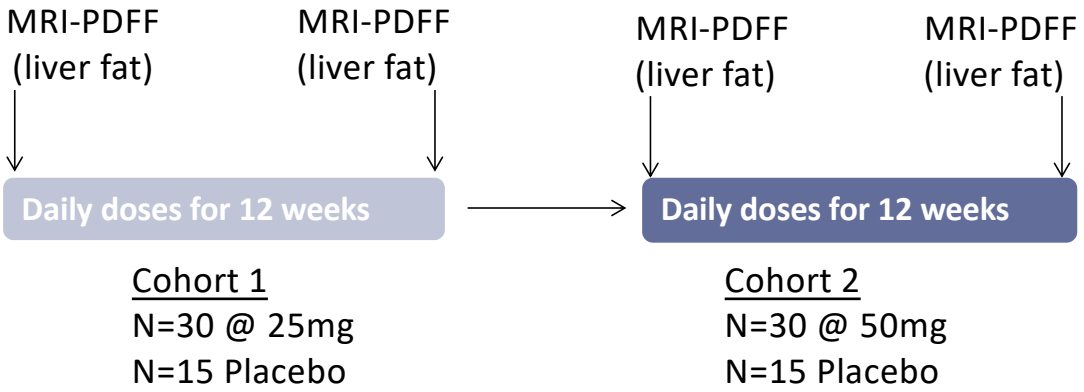
Phase 2 in NASH is ongoing: Primary endpoint of liver fat reduction

Enroll 90 NASH Patients

- ≥ 8% liver fat
- Evidence of fibrosis



Endpoints

- Liver fat reduction
- Percent of patients with ≥30% reduction of liver fat
- Liver enzymes (ALT, AST)
- Plasma triglycerides
- Other biomarkers of inflammation & fibrosis

 NCT03938246

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Summary

- FASN
  - The last committed step on the DNL pathway, and a multi-pronged MOA in NASH
  - In preclinical and translational models FASN inhibition decreases steatosis, directly inhibits pro-inflammatory/immune cells, decreases fibrosis and HCC tumor formation
- TVB-2640
  - A potent and selective once-daily orally administered first in class FASN inhibitor
  - Inhibits hepatic de novo lipogenesis
- FASN inhibition does not decrease malonyl CoA levels and is not expected to activate fatty acid oxidation or increase plasma triglycerides, different to ACC inhibition - clinical data are consistent with this hypothesis
- A 12-week Phase 2a study in NASH patients is ongoing with TVB-2640

Acknowledgements

Sagimet Team

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Clinical Sites and Patients

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Sagimet NASH Clinical Advisory Board

Ph1b DNL Study

University of Missouri School of Medicine

Elizabeth Parks
Majid Syed-Abdul
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Ayman Gaballah
Kimberlee Bingham
Ghassan Hammoud

Metabolon

Gubra

InSphero