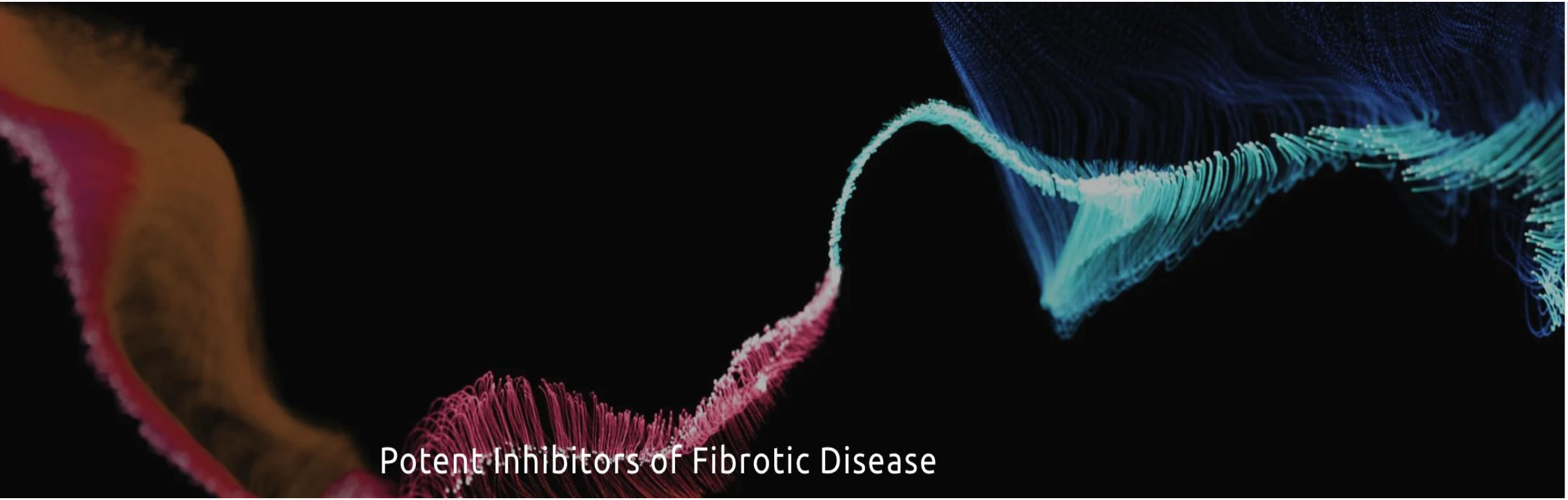
Shc Blockers for MASH and Alcoholic Liver Disease fibrosis



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Buto Investment Highlights

- MASH/NASH and Alcoholic Liver Disease have large TAMs and unmet need.
- Shc gene and protein expression rises in human MASH and ALD.
- Buto uniquely develops First-In-Class Shc Inhibitors (ShcIs) to ameliorate fibrosis.
- Buto has unique target understanding and 4 proprietary methods to move faster on ShcIs than the competition.
- ShcI B-105, 301 and 401 reduce tissue fibrosis in multiple mouse models of MASH and ALD.
- Buto owns composition of matter patents on New Chemical entity ShcI scaffolds.
- Safety: ShcI B-301 therapeutic efficacy occurs at 25mg/kg, no side effects until > 300mg/kg.

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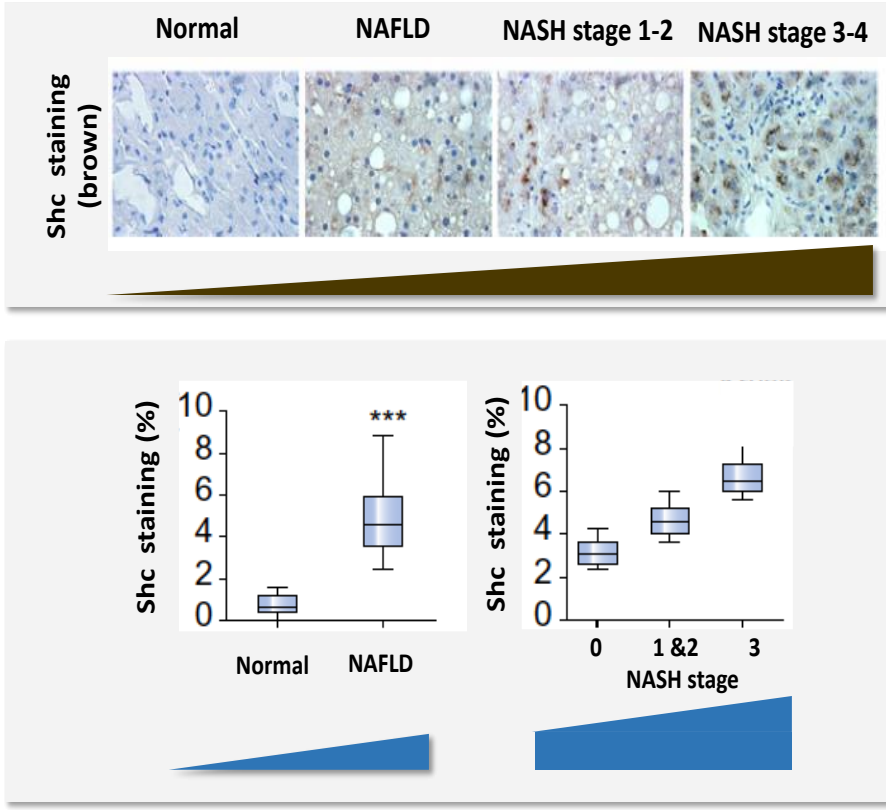
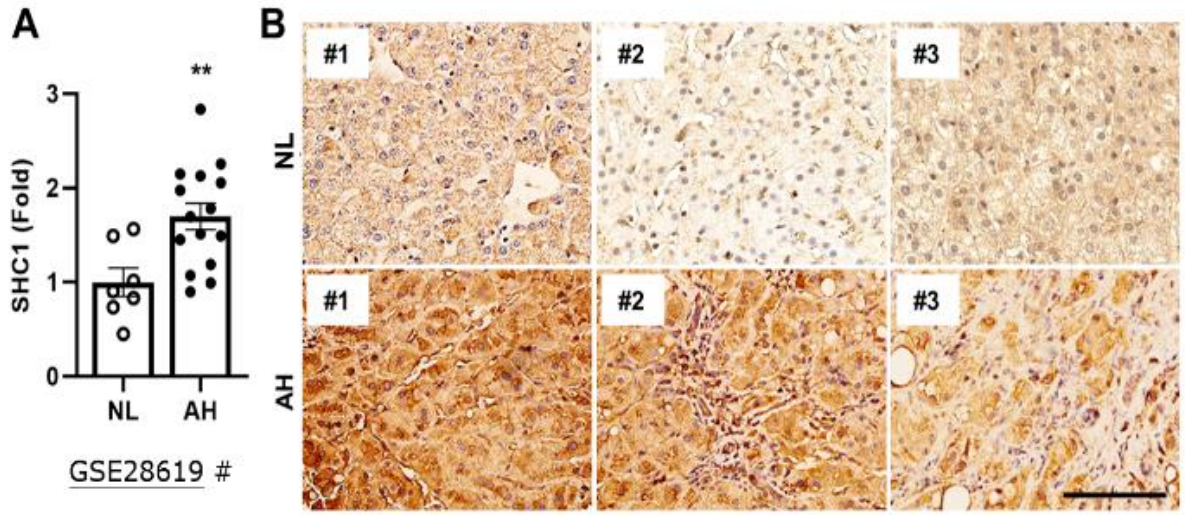
Shc rises in human MASH and ALD livers

Shc RNA & protein levels rise by MASH & Fibrosis grade in humans



Shc RNA & protein levels rise in livers of ALD humans



Tomita et al., Journal of Hepatology 2012 vol. 57 | 837–843

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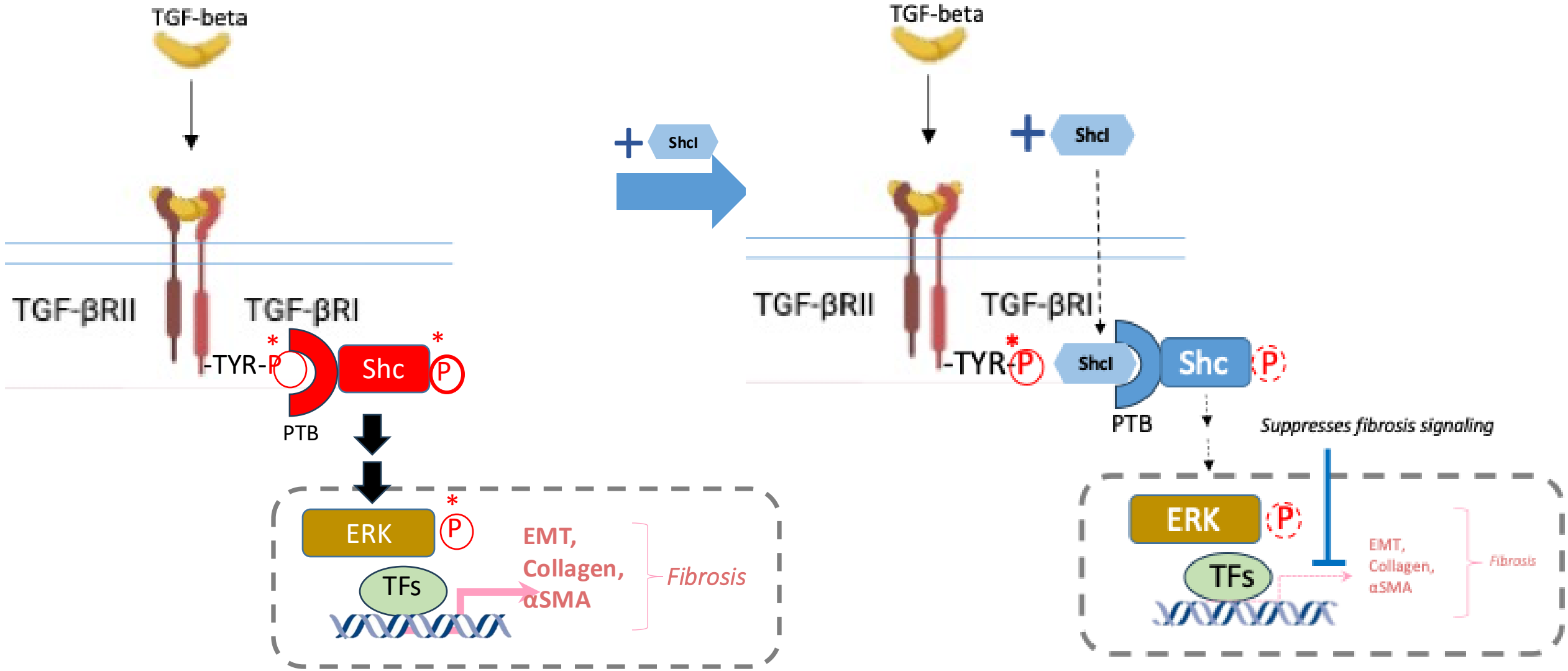
MoA: Shc activation is an important fibrotic mechanism; ShcI's block Shc activation and suppress fibrosis



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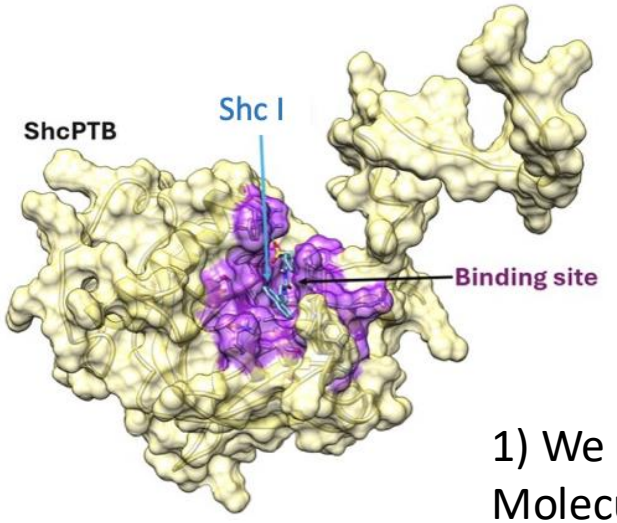
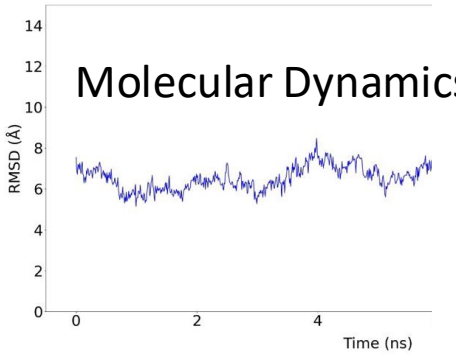
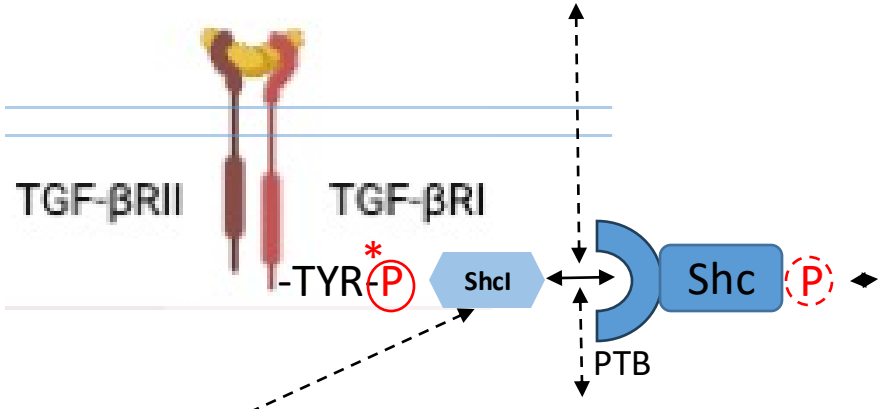
Buto's competitive edge: we predict small-molecule ShcI potency through 4 proprietary assays





1) We understand ShcI binding to PTB by Molecular Dynamics and Docking



4) We assay ShcI's potency by reduction of active phospho-Shc *in vitro* & *in vivo* and that activity correlates with #1, 2 & 3.

3) We assay ShcI's potency to block TYR-P ← → ShcPTB interaction and they correlate with #1 & 2.

2) We've measured binding affinities of 53 ShcIs to Shc by SPR and they correlate with computational methods

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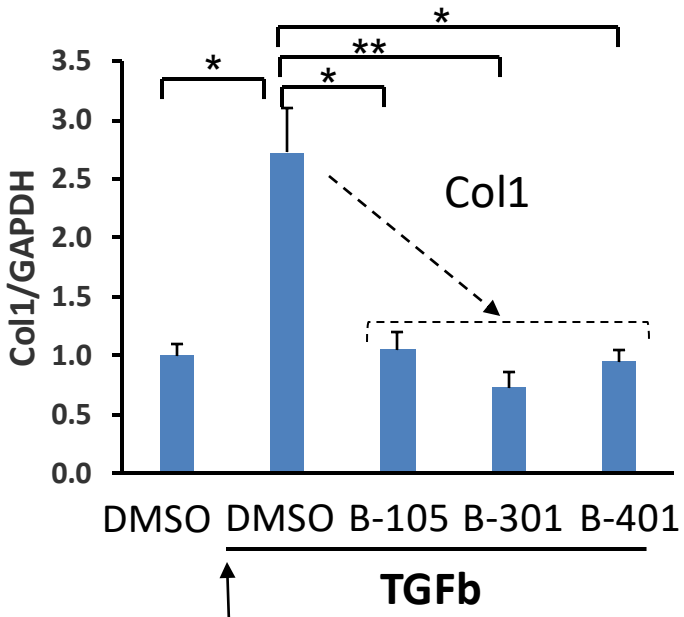
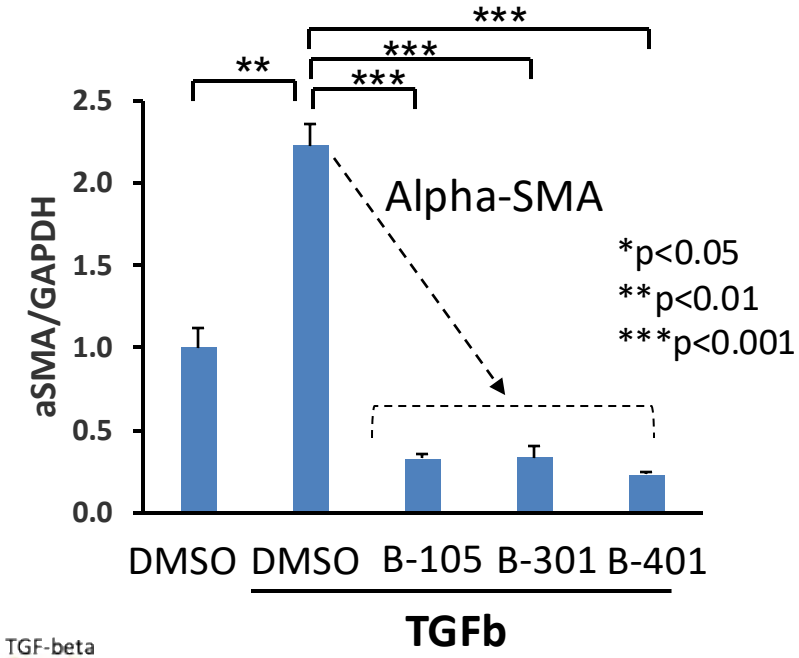
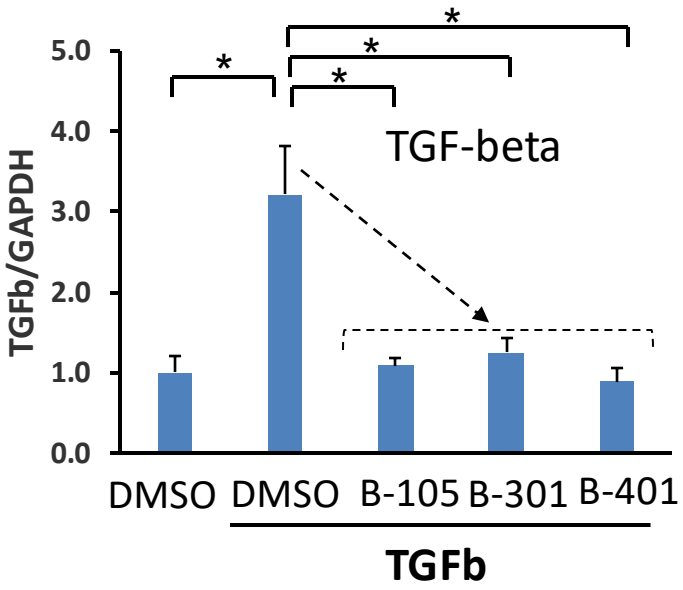
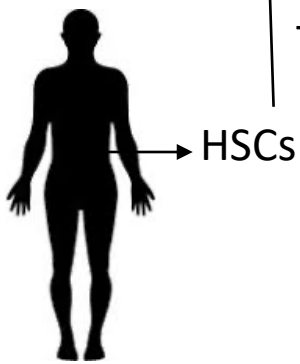
Shc Blockers 301, 401 and 105 reduce TGF-β-Mediated Fibrosis gene Activation in Human HSC line



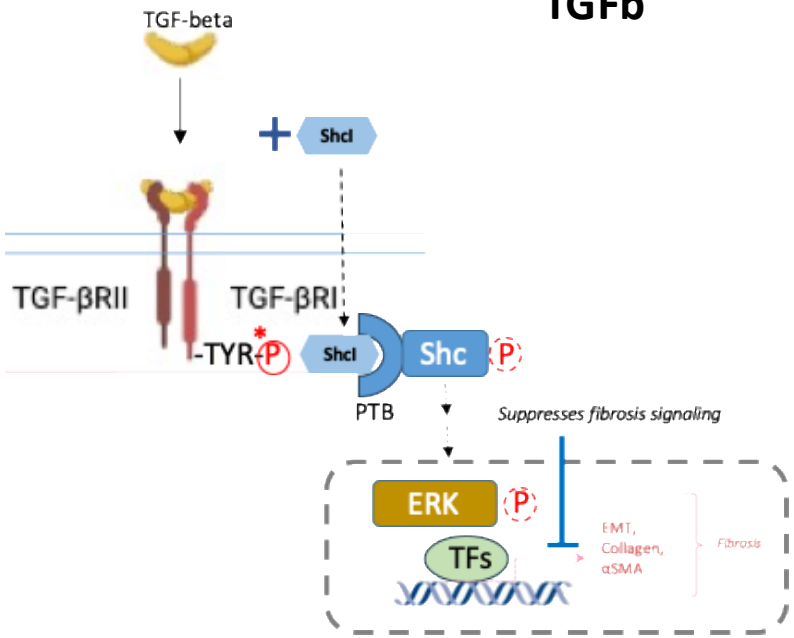






TGFb

HSCs



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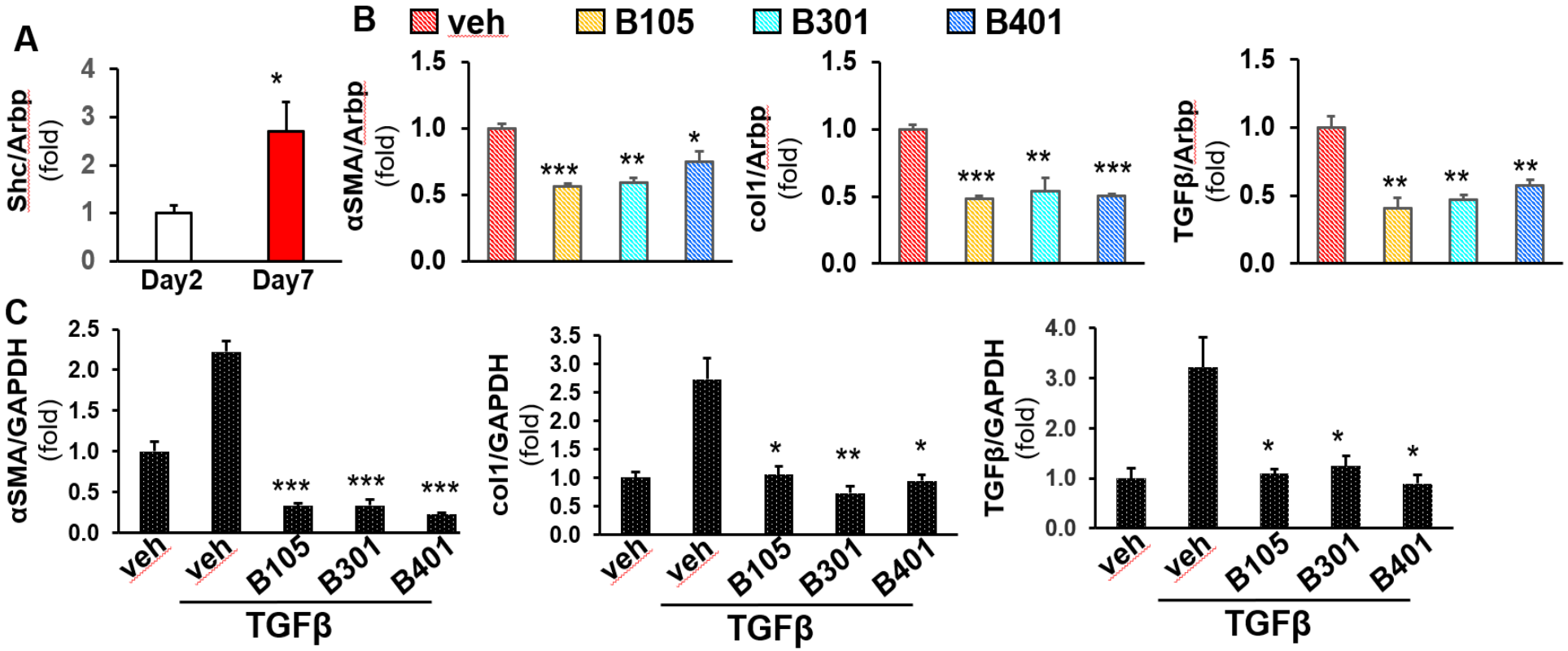
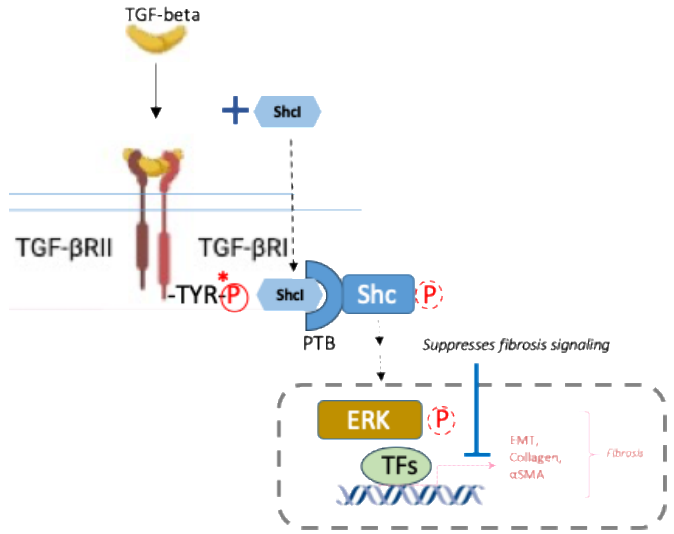
LX-2 cells

Shc Blockers Reduce Fibrotic Markers in Culture- or TGF-beta activated Mouse Hepatic Stellate Cells *Ex Vivo*





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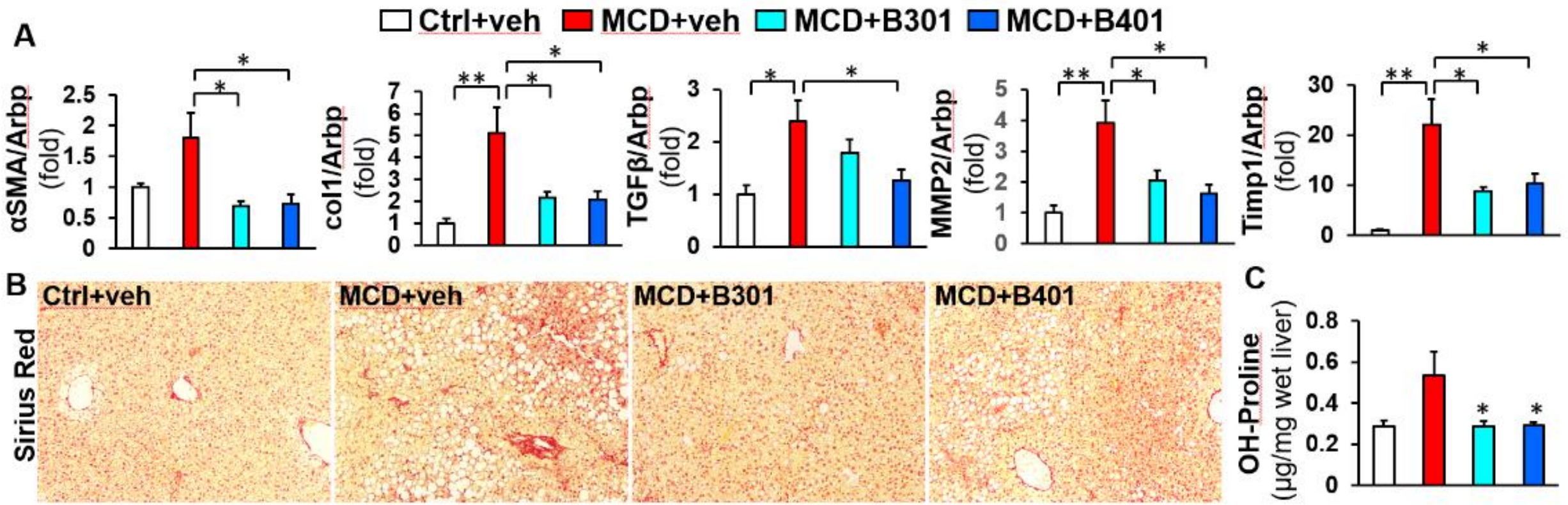
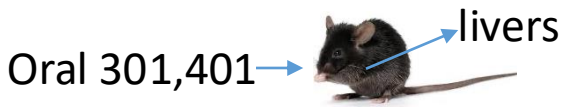
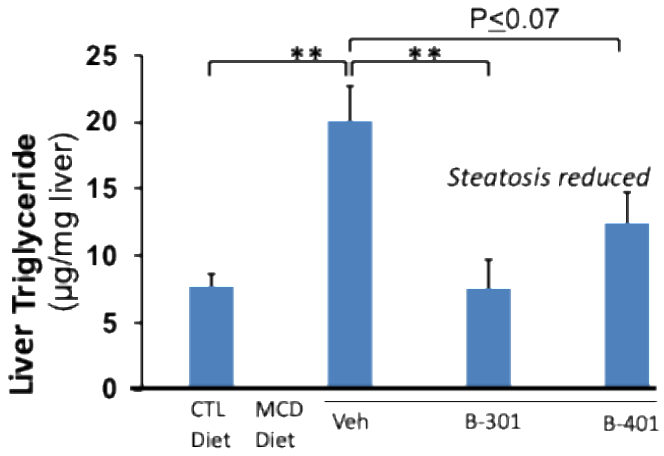
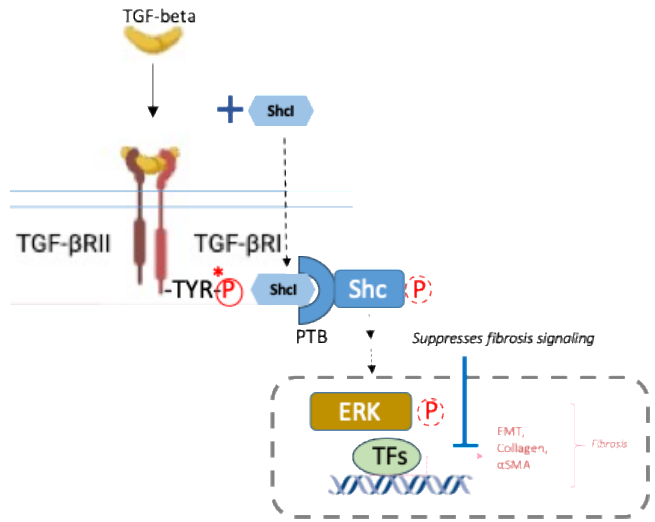
Mouse Hepatic Stellate cells

ShcB's 301 and 401 ameliorate fibrosis and inflammation in MCD MASH model *in vivo*









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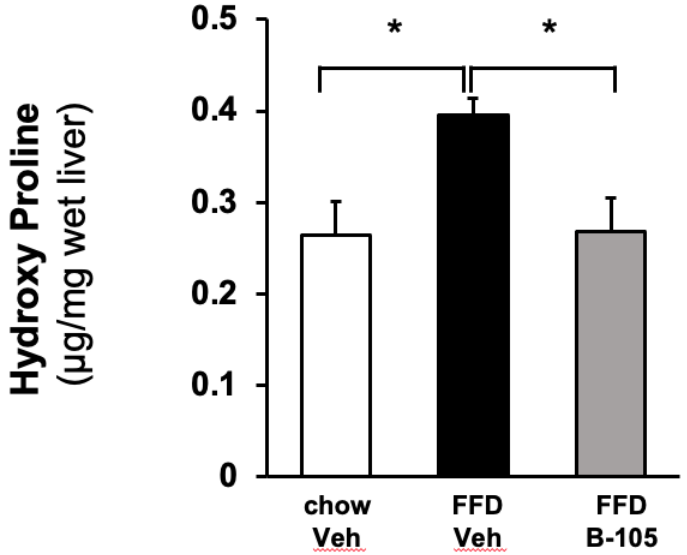
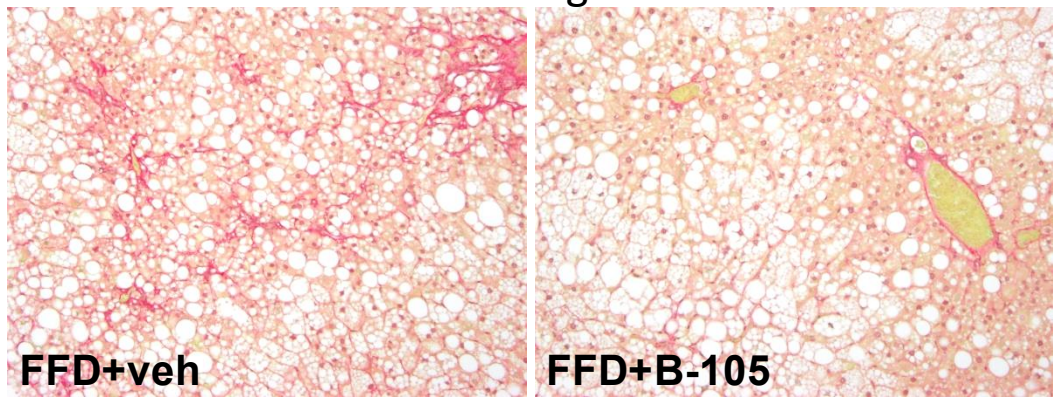
ShcB-105 is Antifibrotic, Insulin-Sensitizing and Glucose-Tolerizing in the Fast-Food Diet mouse model



Picrosirius Red Staining for Fibrosis

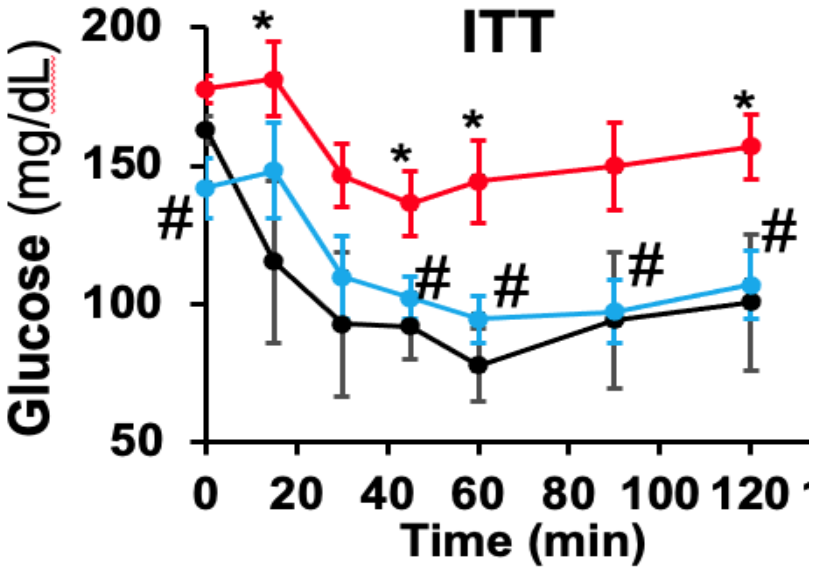


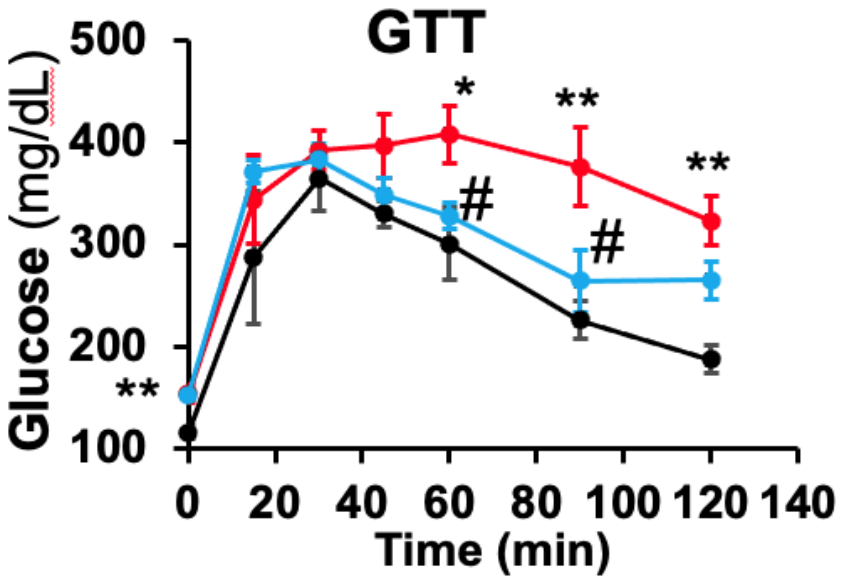
Chris Church, The Fast-Food Diet is a high-fat, high fructose diet described in this paper:

Jiang JX, Tomilov A, Montgomery C, Hui CK, Török NJ, Cortopassi G.
J Biochem Mol Toxicol. 2021 Oct;35(10):e22876. doi: 10.1002/jbt.22876. Epub 2021 Aug 8.
PMID: 34369032

Oral 105

Fast Food
Fibrosis diet





*p<0.05 vs ctrl+veh
**p<0.01 vs ctrl+veh
#p<0.05 vs FFD+veh

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B-105 and B-301 significantly protect livers from inflammation & fibrosis after EtOH injury

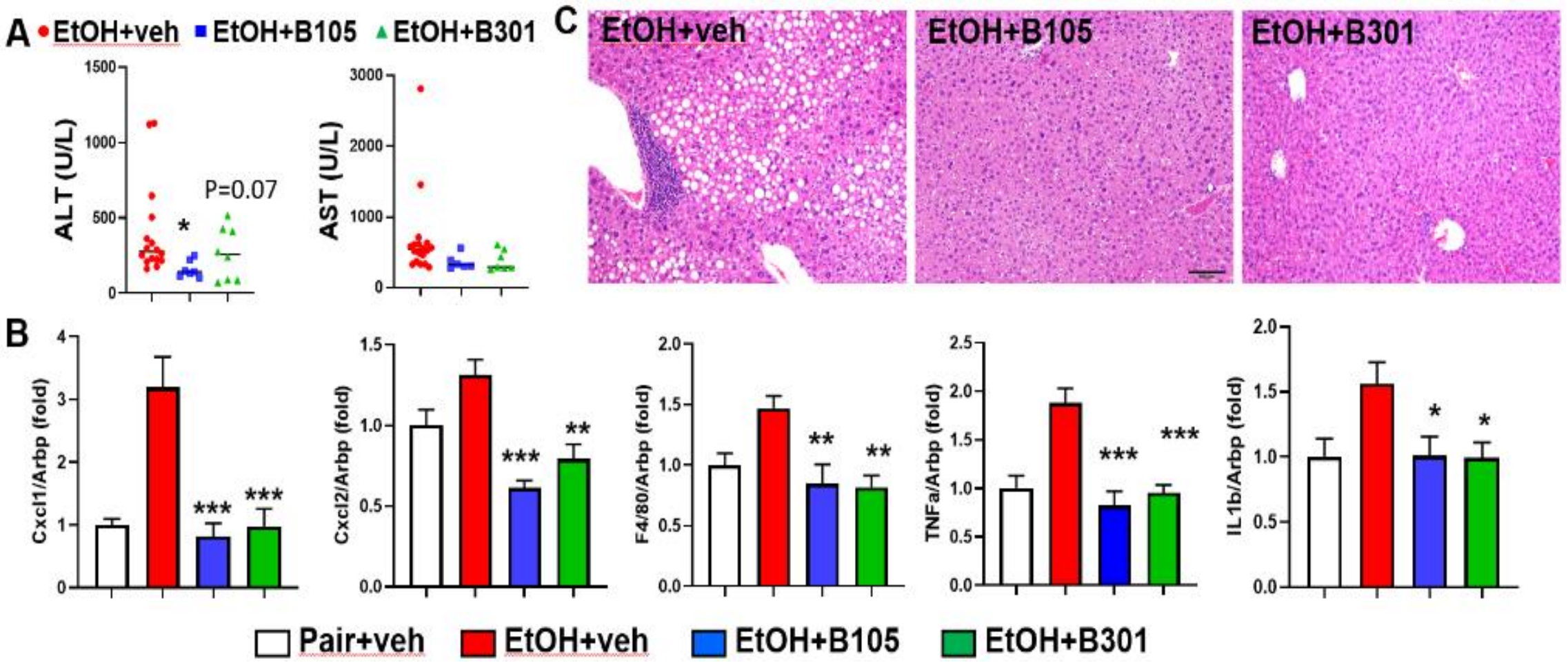

Fig. 3. ShcBs B105 & B301 protect mice from alcohol-induced liver injury

*Female C57B6/J mice were subjected to Lieber DeCarli alcoholic diet (5% v/v) for 10 days with the last day alcohol binge (5 g /kg). The mice were randomized for vehicle (peanut butter), B105 (20 mg/kg), or B301 (20 mg/kg) and dosed from day1 through the end. Pair fed mice were given same volume of vehicle. Serology studies (A) showed that B105 & B301 reduced the levels of ALT and AST. The liver tissues were processed for RT-qPCR to analyze inflammatory makers (B). Both B105 and B301 significantly reduced, Cxcl1 and Cxcl2, F4/80, TNFα and IL-1β (mean±SEM, N=8-16, *p<0.05, **p<0.01, ***p<0.001). C, H&E staining showed that both ShcBs improved the liver histology with less steatosis and inflammatory cell infiltrating (bar=100 µm).*

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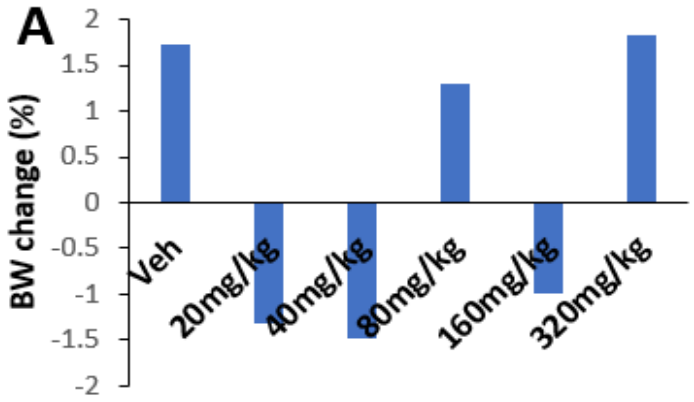
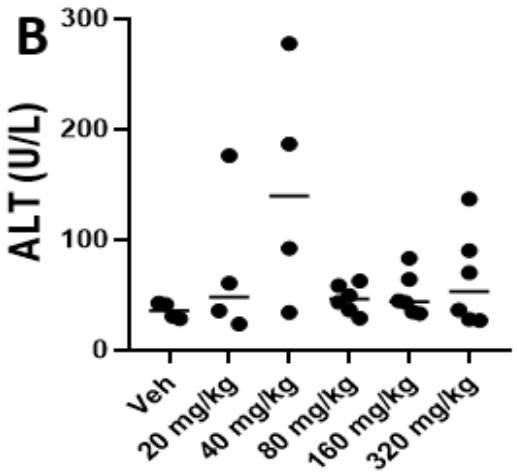
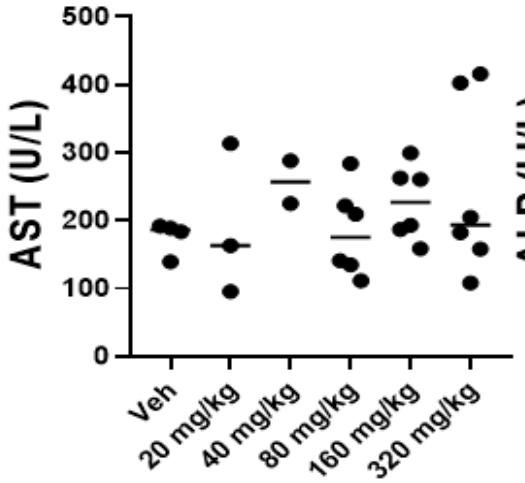
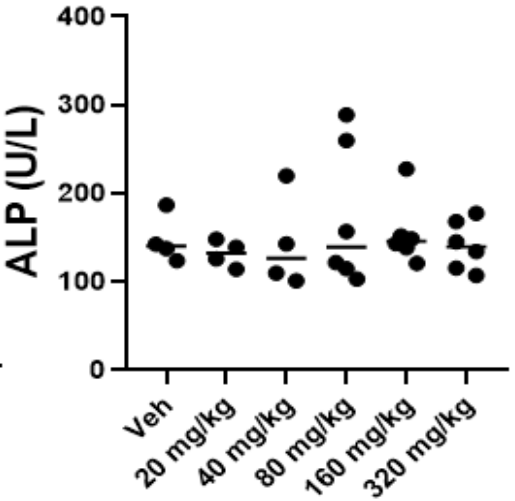
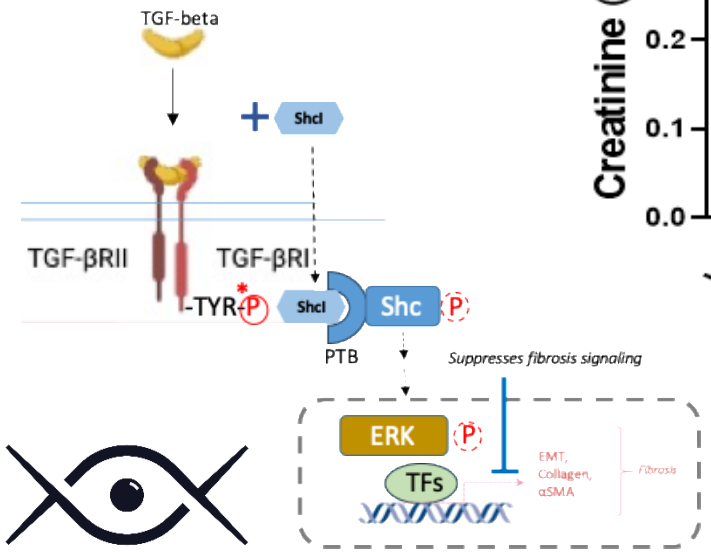
Safety: B-301 has therapeutic effect at 25 mpk, dosed 10X higher at 320mpk there is no weight loss, liver toxicity, or deaths

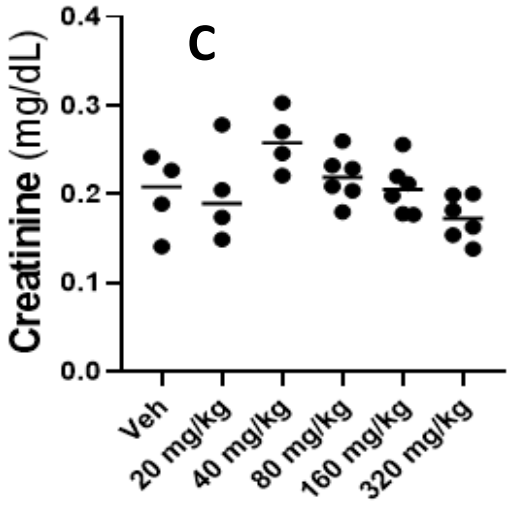


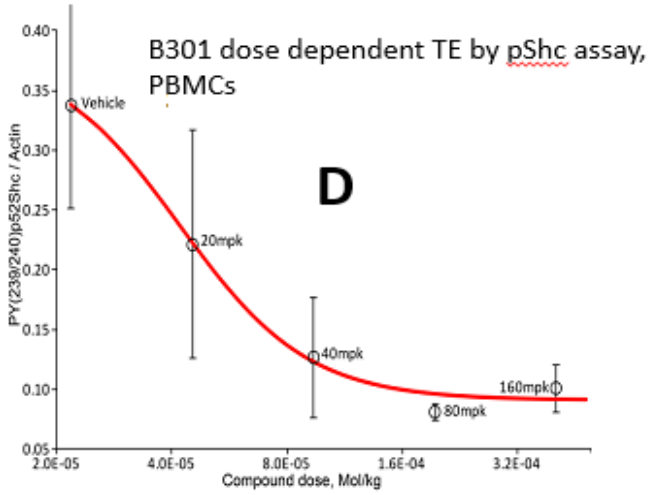


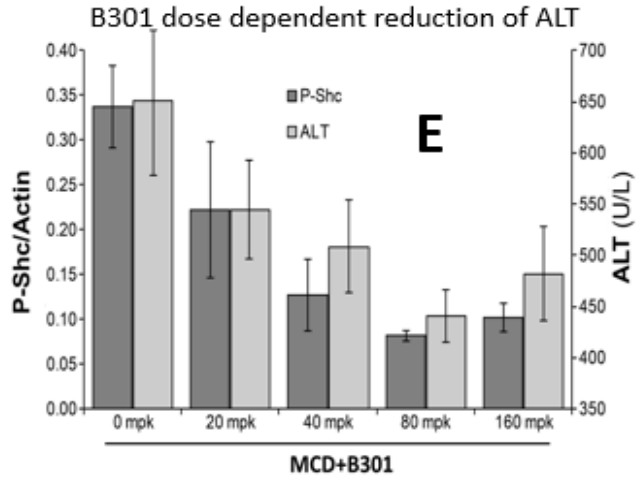












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- Safety: ShcI B-301 therapeutic efficacy occurs at 25mg/kg, no side effects until > 300mg/kg.

Buto

Buto seeks investment to bring its Shcl's to the clinic for liver fibrosis indications: MASH and ALD

ACTIVITY	BUDGET	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
LEAD OPTIMIZATION	**$ 705,000**								
Medicinal Chemistry	$ 240,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000		
Pharmacology (in-vitro/in-vivo_	$ 240,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000	$ 40,000		
PK/ADME	$ 100,000		$ 20,000	$ 20,000	$ 20,000	$ 20,000	$ 20,000		
Off-target profile	$ 125,000				$ 50,000		$ 75,000		
IND ENABLING	**$ 550,000**								
Process Chem/Scale up	$ 90,000						$ 30,000	$ 30,000	$ 30,000
Rat Oral BA and Dose Ranging PK	$ 50,000							$ 50,000	
Dog Oral BA and Dose Ranging PK	$ 250,000								$ 250,000
Complete ADME	$ 80,000							$ 40,000	$ 40,000
Complete Off-Target	$ 80,000							$ 40,000	$ 40,000
PRE-IND MEETING	**$ 125,000**								
Pre-IND Package	$ 75,000						$ 25,000	$ 25,000	$ 25,000
Reg Consultant	$ 25,000						$ 10,000	$ 15,000	
Tox Consultant	$ 25,000						$ 10,000	$ 15,000	
IP FILING	**$ 20,000**								
Provisional	$ 20,000						$ 20,000		
TOTAL	**$ 1,400,000**	$ 80,000	$ 100,000	$ 100,000	$ 150,000	$ 100,000	$ 270,000	$ 215,000	$ 385,000

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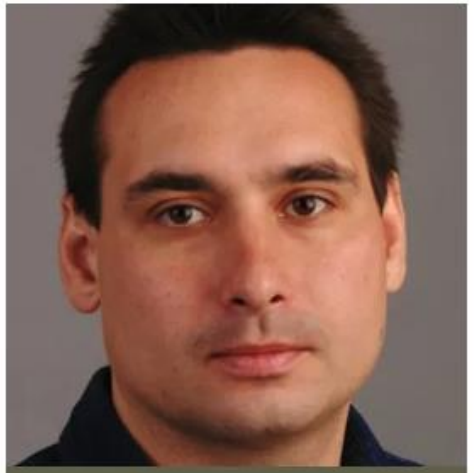
Buto Team

Gino Cortopassi, PhD

CEO

Sundeep Dugar, PhD

CSO



Alexey Tomilov, PhD

CTO

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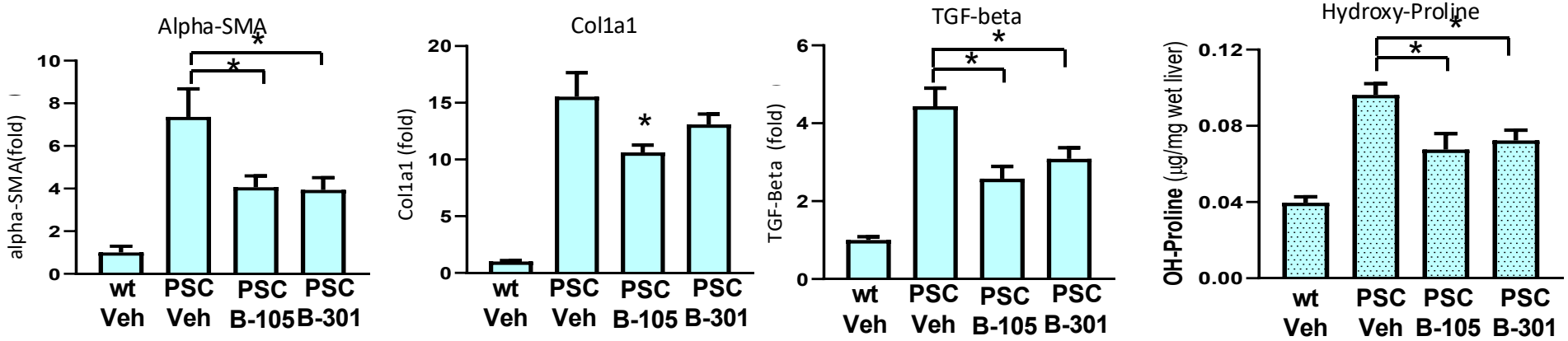
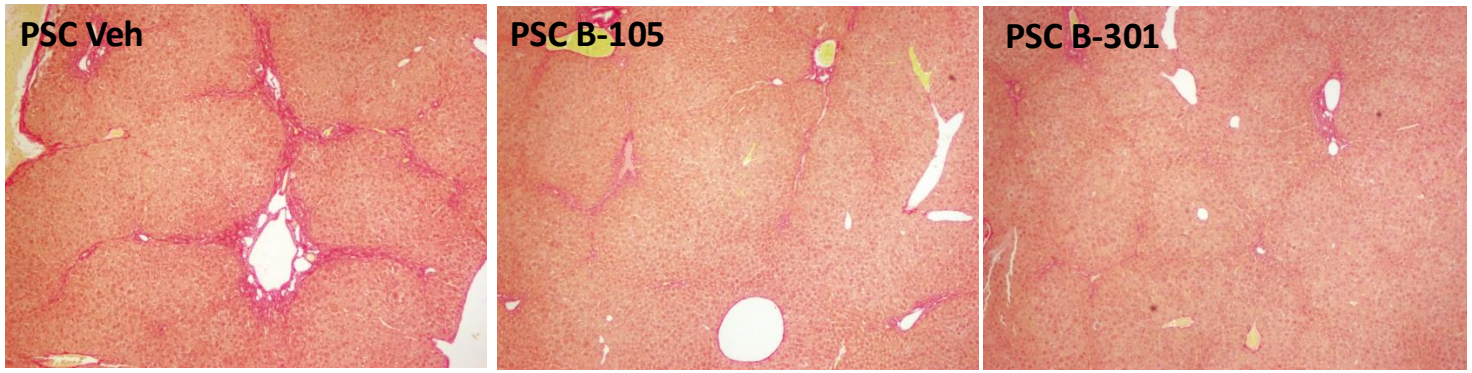
Extra Slides

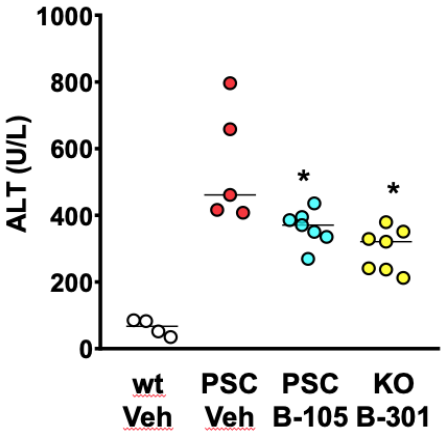
Shc Inhibitors reduce liver fibrosis in Orphan Cholestatic Liver Disease: PSC mice

PSC =Primary Sclerosing Cholangitis



Picrosirius Red Fibrosis Staining of Liver:





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