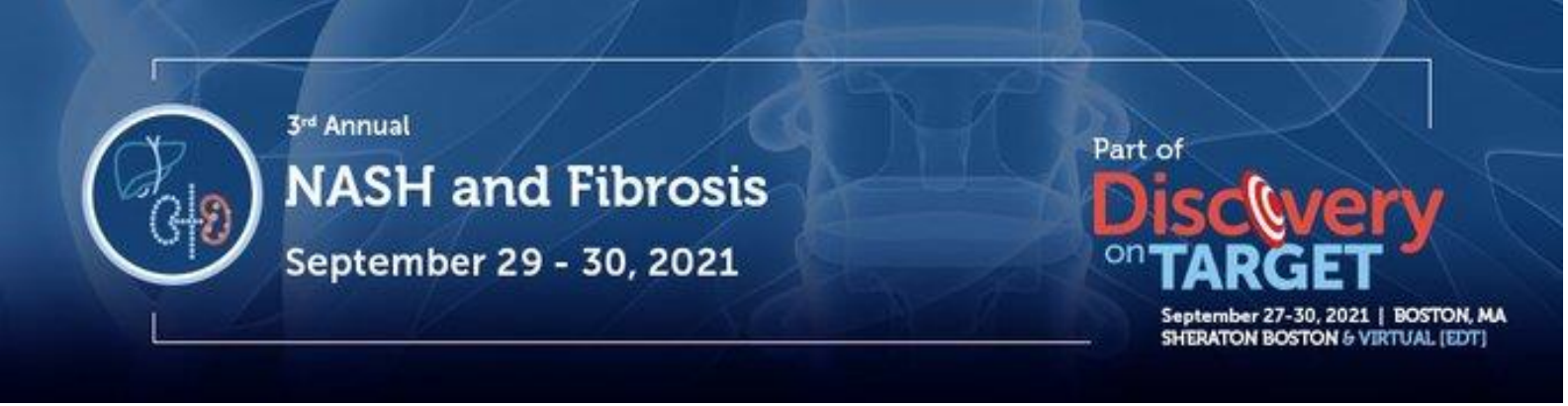

Translational Studies of Seladelpar

a PPAR-delta Agonist for the Treatment of NASH

NASH Clinical Study Team &
Yun-Jung Choi, Jeff D. Johnson, Jeffery Stebbins, Edward Cable, Jiangao Song, Xin Chen, Marc K. Hellerstein, Robert Martin, Charles A. McWherter

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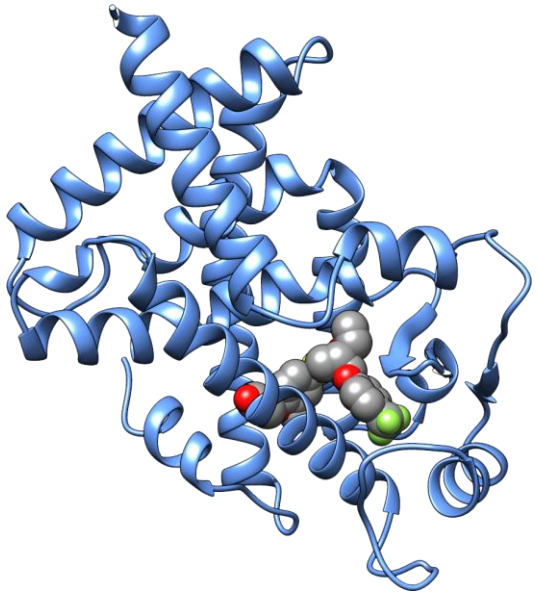
Seladelpar

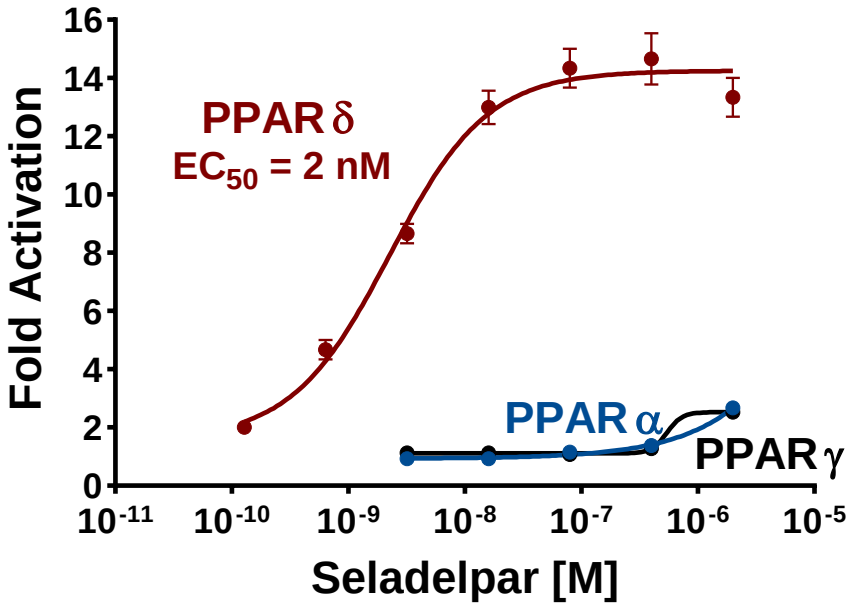
Peroxisome Proliferator-Activated Receptor (PPAR)-delta Agonist

- In clinical development for liver disease
- Clinical experience ≥ 2 years
- Oral, Once-daily
- Potent and selective PPARδ agonist

X-ray Crystal Structure of Seladelpar and PPARδ Ligand Binding Domain 1.8 Å RMSD



Human PPAR Potency



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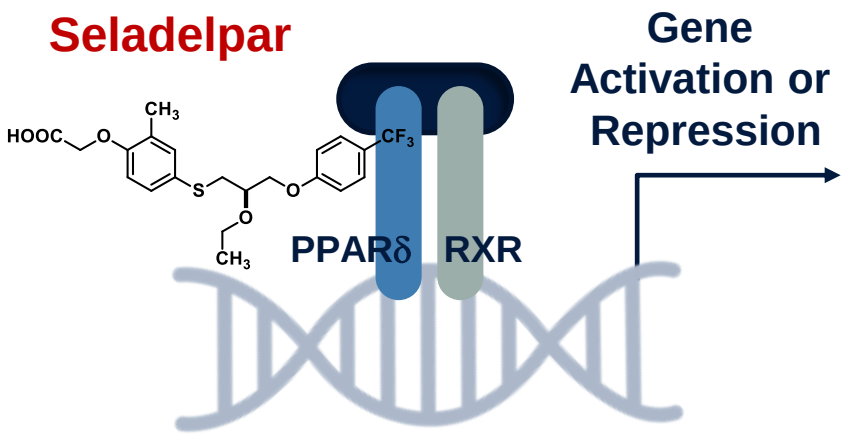
Seladelpar

Mechanism of Action by Transcriptional Regulation



Anti-Fibrotic

- ↓ Profibrotic genes
- ↓ Stellate cell activation
- ↓ Collagen synthesis/deposition

Decrease Bile Acids

- ↓ Cholesterol synthesis/absorption
- ↓ Bile acid synthesis (C4)
- ↑ Bile acid transport

Increase Lipid Metabolism

- ↓ Cholesterol/LDL-C
- ↑ Fatty acid oxidation

Anti-Inflammatory

- ↓ NFκB-dependent gene activation
- ↓ Inflammatory cytokines
- ↓ hs-C-Reactive Protein

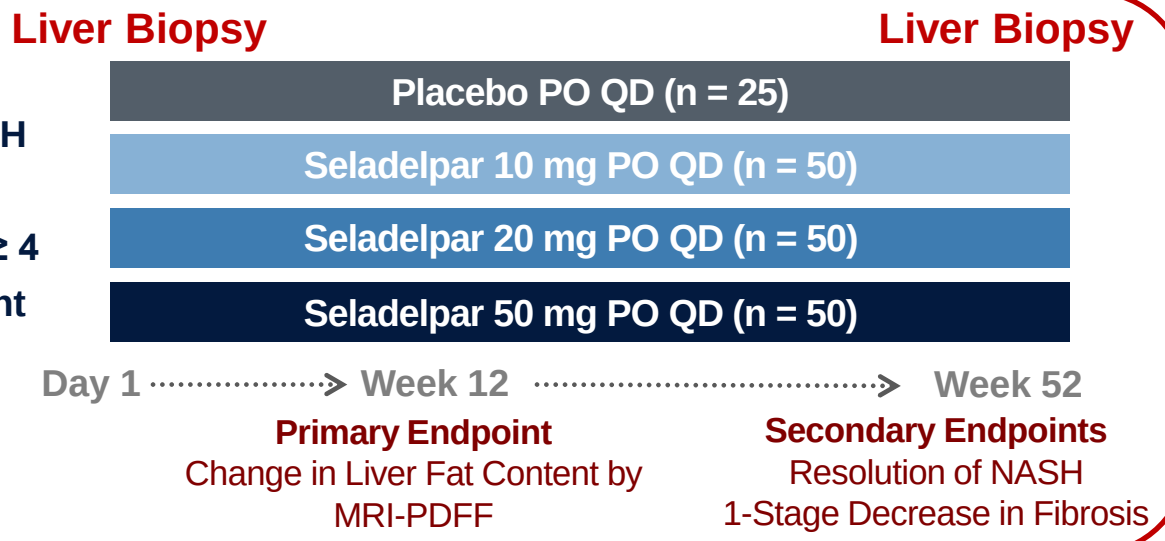
CYMABAY THERAPEUTICS

Translational Studies in NASH: Human vs. Mouse

Seladelpar Phase 2b Study in Patients with NASH

Eligibility Criteria

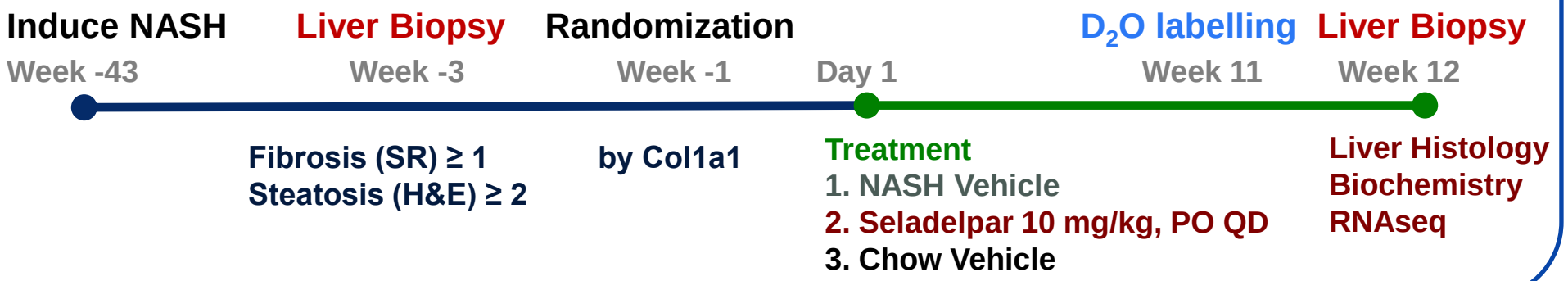
- Histologically confirmed NASH
- Liver fat ≥ 10% by MRI-PDFF
- NAFLD Activity Score (NAS) ≥ 4 with 1 point in each component
- F1 - F3 fibrosis stage
- Diabetes allowed



Mouse Model of NASH with Fibrosis

Male C57BL/6J Mice

Diet of 40% Fat, 20% Fructose, 2% Cholesterol for 55 weeks



CYMABAY THERAPEUTICS

Seladelpar Phase 2b Study in NASH

Demographics & Baseline Characteristics

Parameters (Mean ± SD)	Total (N = 152)
Age (Years)	55 (11.4)
Female, n (%)	104 (68.4)
Body Weight (kg)	100 (21.8)
MRI-PDFF (%)	21 (7.3)
NAFLD Activity Score (NAS)	5.1 (1.01)
Fibrosis Stage	2.2 (0.67)
F2 or F3, n (%)	131 (86.2)
ALT (U/L)	62.0 (33.47)
AST (U/L)	45.1 (23.42)
GGT (U/L)	81.6 (93.89)
LDL-C (mg/dL)	110.2 (41.28)
Triglycerides (mg/dL)	160.8 (76.94)

Mouse Model of NASH with Fibrosis

Characteristics at 55 Weeks on NASH Diet

Parameters (Mean ± SD)	NASH Mice	Chow Mice
Body Weight (g)	41 (2.6)	32 (1.0)
Liver Weight (g)	4.0 (0.73)	1.4 (0.08)
Liver fat (% fractional area)	26 (3.7)	1.2 (0.13)
NAFLD Activity Score (NAS)	5.8 (0.72)	0 (0)
Hepatocellular ballooning (%)	67	0
Lobular Inflammation (%)	100	0
Fibrosis Stage, F1-F3	2.2 (0.58)	0 (0)
F2 or F3, n (%)	11 (92)	0 (0)
ALT (U/L)	270 (94)	28 (6.6)
AST (U/L)	279 (98)	46 (9.5)
Total Cholesterol (mg/dL)	317 (45.6)	85 (9.1)
Triglyceride (mg/dL)	62 (14.1)	77 (10.5)

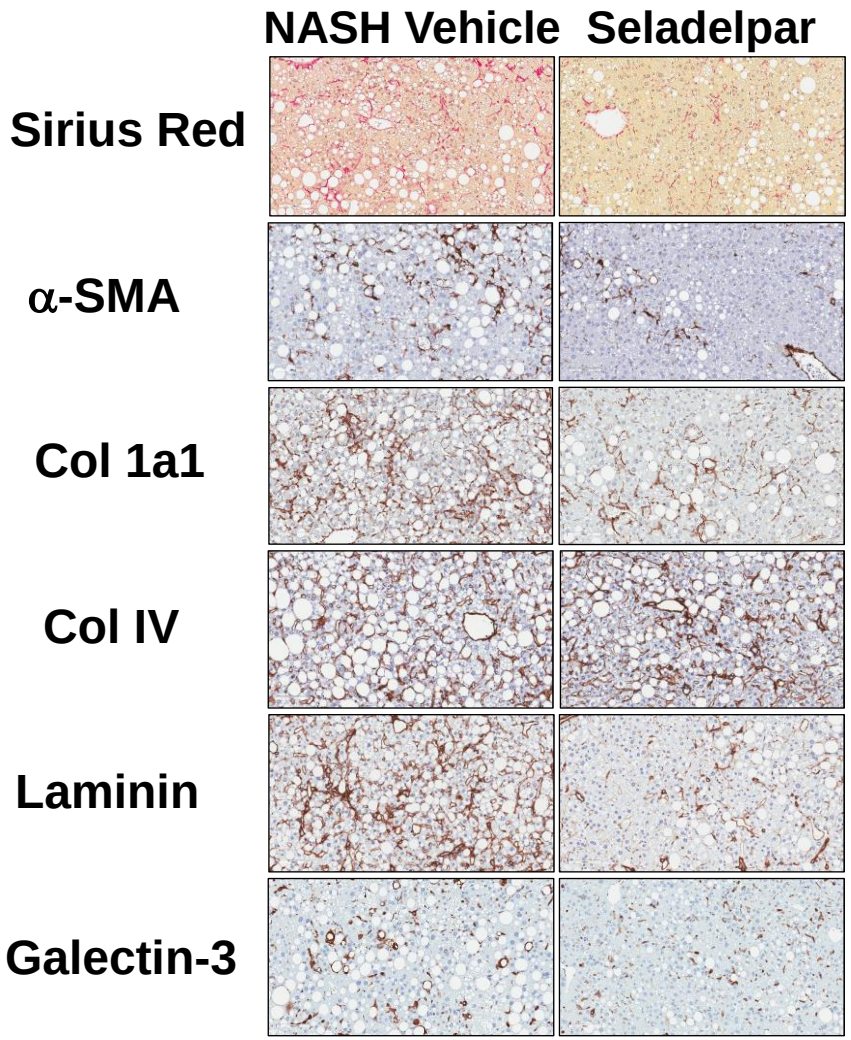
Seladelpar Phase 2b Study in NASH

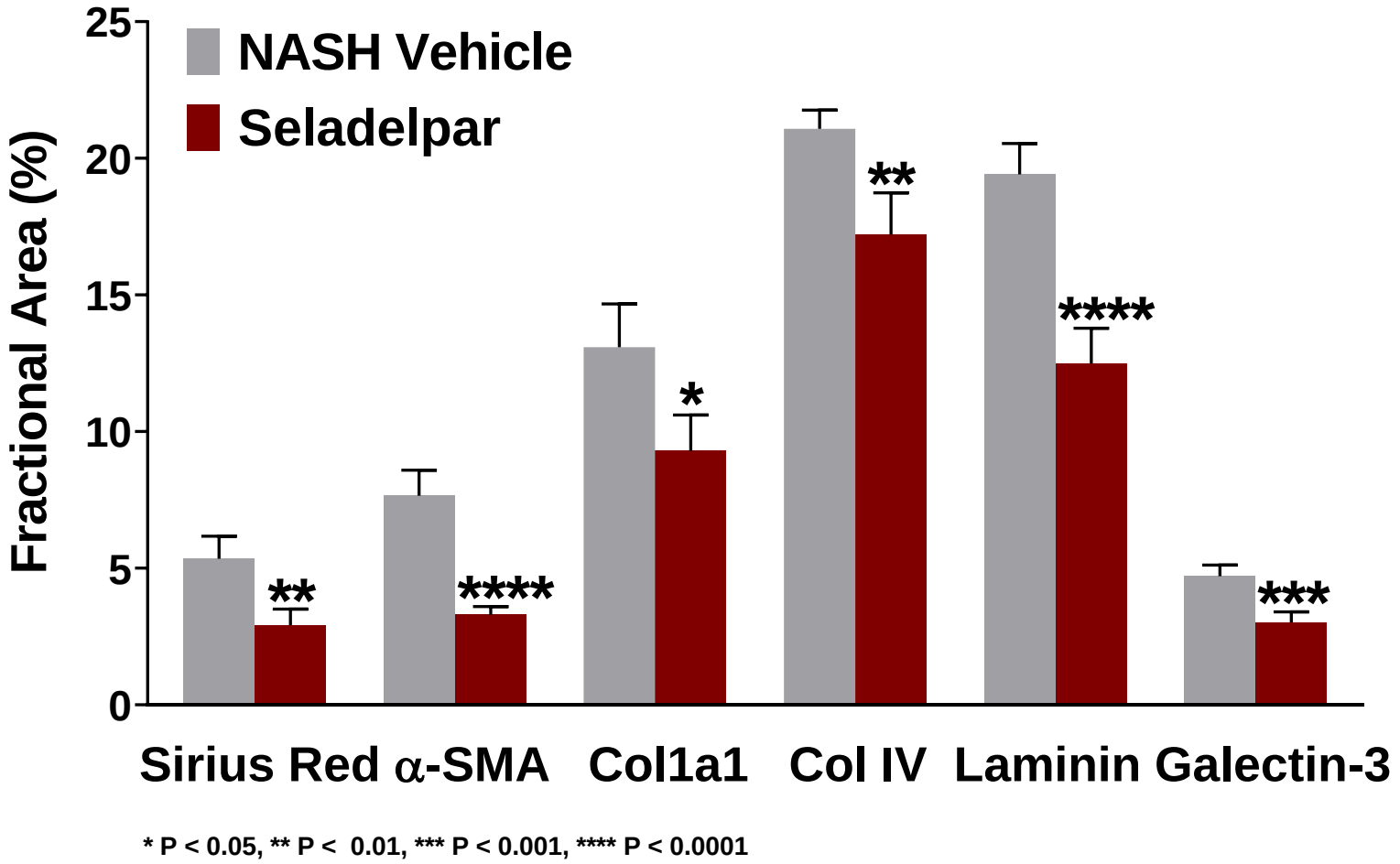
Baseline Demographics and Patient Characteristics (mITT Population with Biopsy)

Parameter (Mean ± SD)	Placebo (n = 25)	10 mg (n = 39)	20 mg (n = 42)	50 mg (n = 46)	Total (N = 152)
Age (Years)	54 (10.5)	55 (10.8)	57 (12.5)	54 (11.3)	55 (11.4)
Female, n (%)	17 (68.0)	29 (74.4)	28 (66.7)	30 (65.2)	104 (68.4)
Body Weight (kg)	103 (19.7)	94.5 (23.3)	103 (22.9)	100 (20.3)	100 (21.8)
MRI-PDFF (%)	22 (9.2)	22 (8.1)	21 (6.0)	20 (6.6)	21 (7.3)
NAFLD Activity Score (NAS)	5.4 (1.08)	5.1 (1.06)	5.0 (0.98)	5.0 (0.97)	5.1 (1.01)
Fibrosis Stage	2.1 (0.67)	2.2 (0.67)	2.4 (0.69)	2.2 (0.64)	2.2 (0.67)
F2 or F3, n (%)	21 (84.0)	33 (84.6)	37 (88.1)	40 (87.0)	131 (86.2)
ALT (U/L)	62.5 (34.54)	58.1 (29.89)	59.4 (26.98)	67.5 (40.68)	62.0 (33.47)
AST (U/L)	44.2 (24.69)	43.3 (21.94)	47.5 (21.52)	44.9 (26.05)	45.1 (23.42)
GGT (U/L)	102.3 (180.54)	64.7 (56.89)	101.0 (83.54)	67.0 (45.29)	81.6 (93.89)
LDL-C (mg/dL)	115.8 (45.76)	104.5 (32.50)	115.1 (47.56)	107.5 (39.65)	110.2 (41.28)
Triglycerides (mg/dL)	152.1 (51.96)	156.2 (67.26)	177.1 (74.72)	154.6 (95.74)	160.8 (76.94)

Liver Fibrosis

Mouse Model of NASH





* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001

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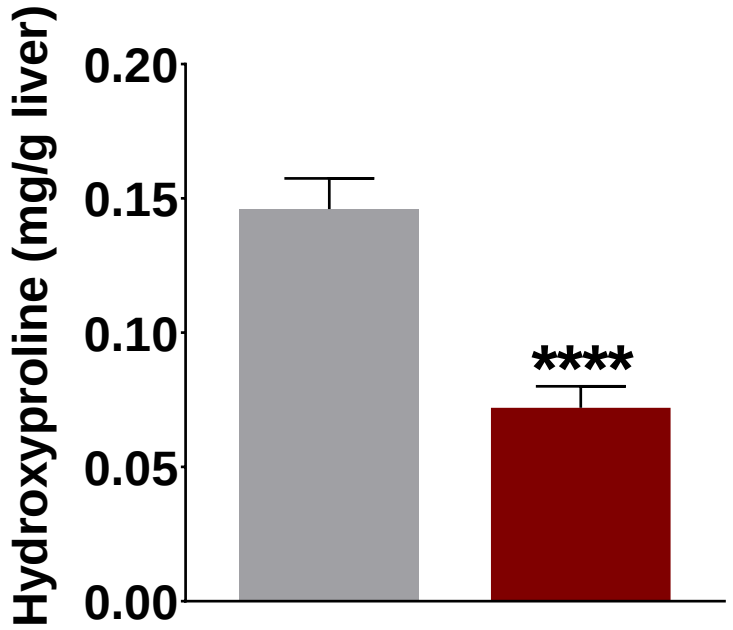
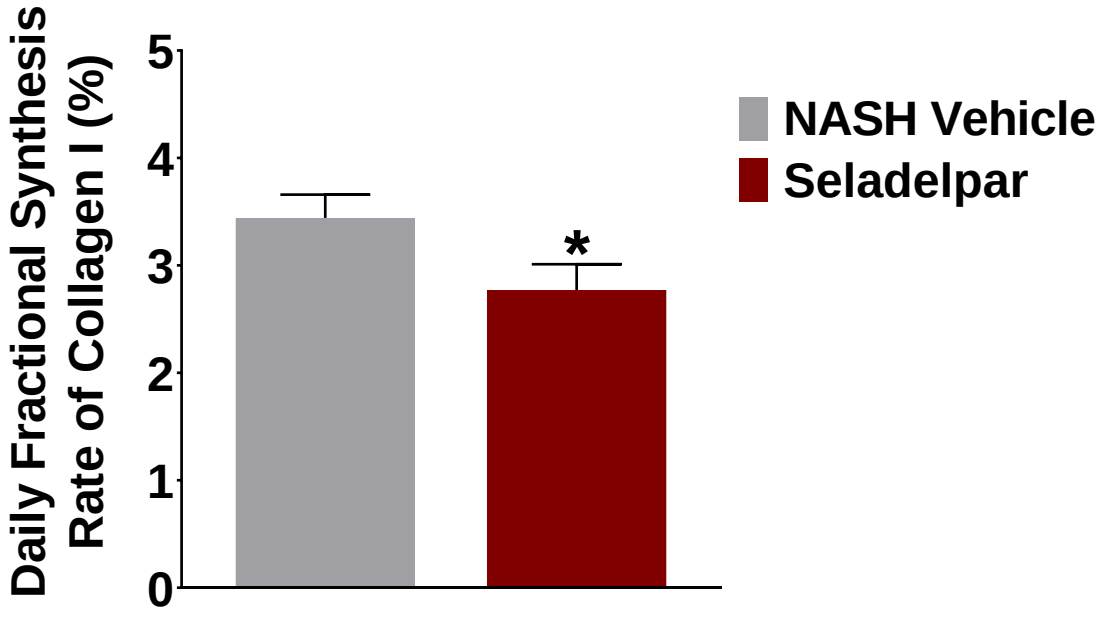
Liver Fibrosis

Mouse Model of NASH

Liver Hydroxyproline

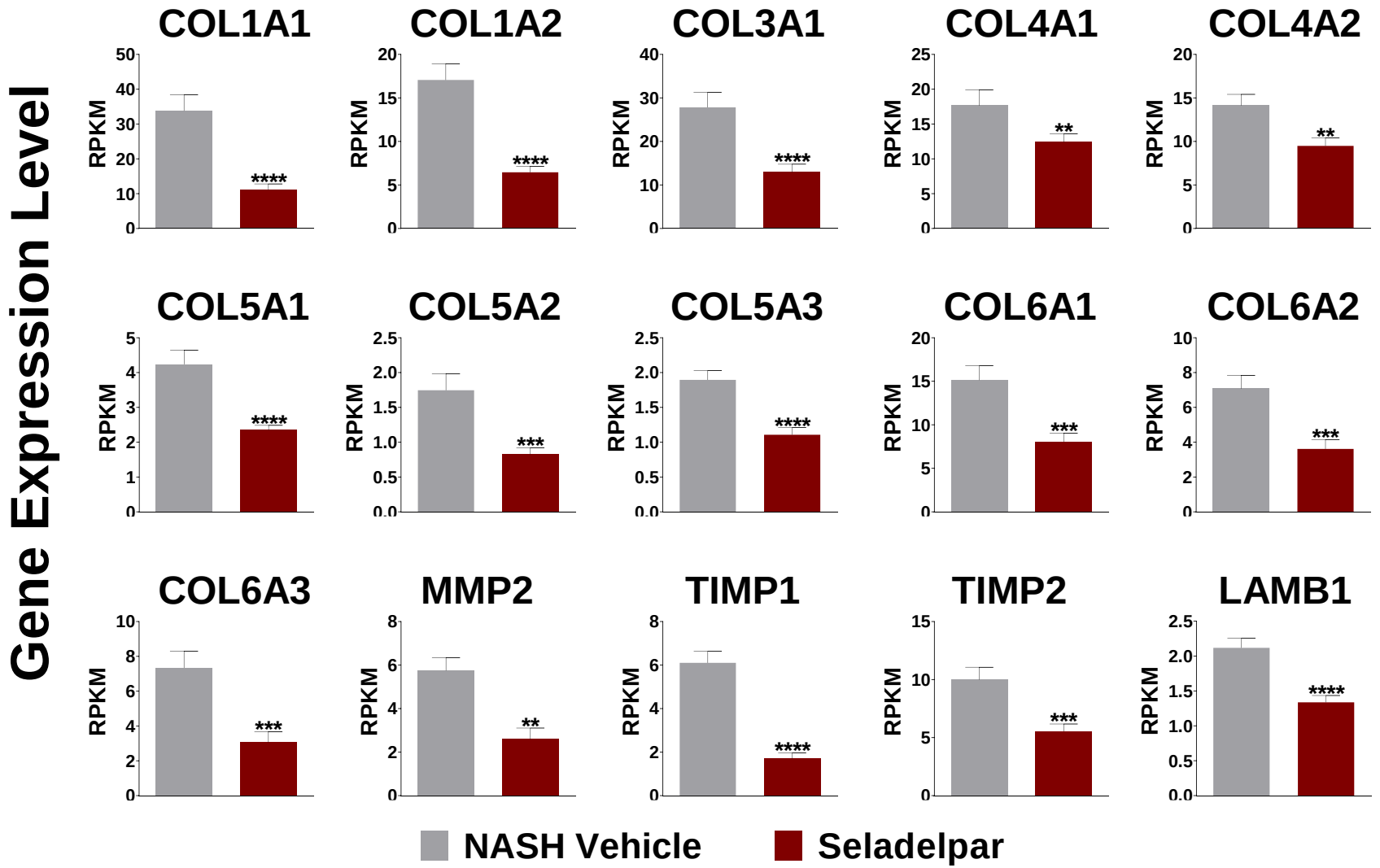


New Collagen I Synthesis



Gene Expression of Fibrosis Markers

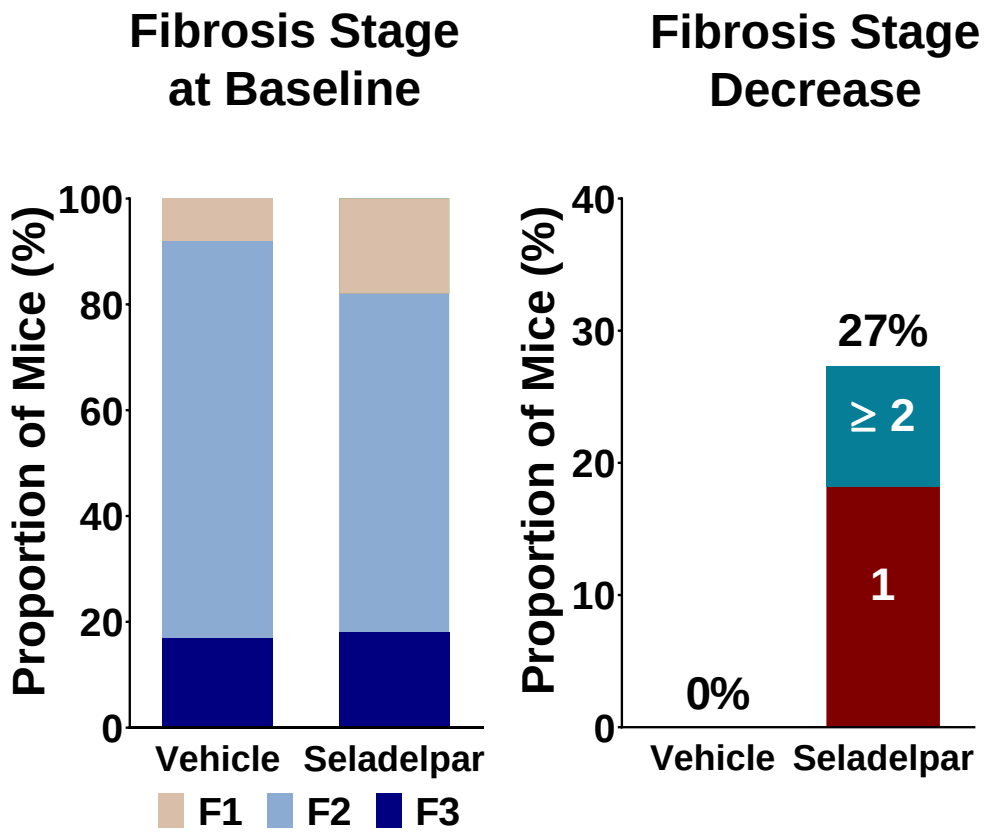
Mouse Model of NASH



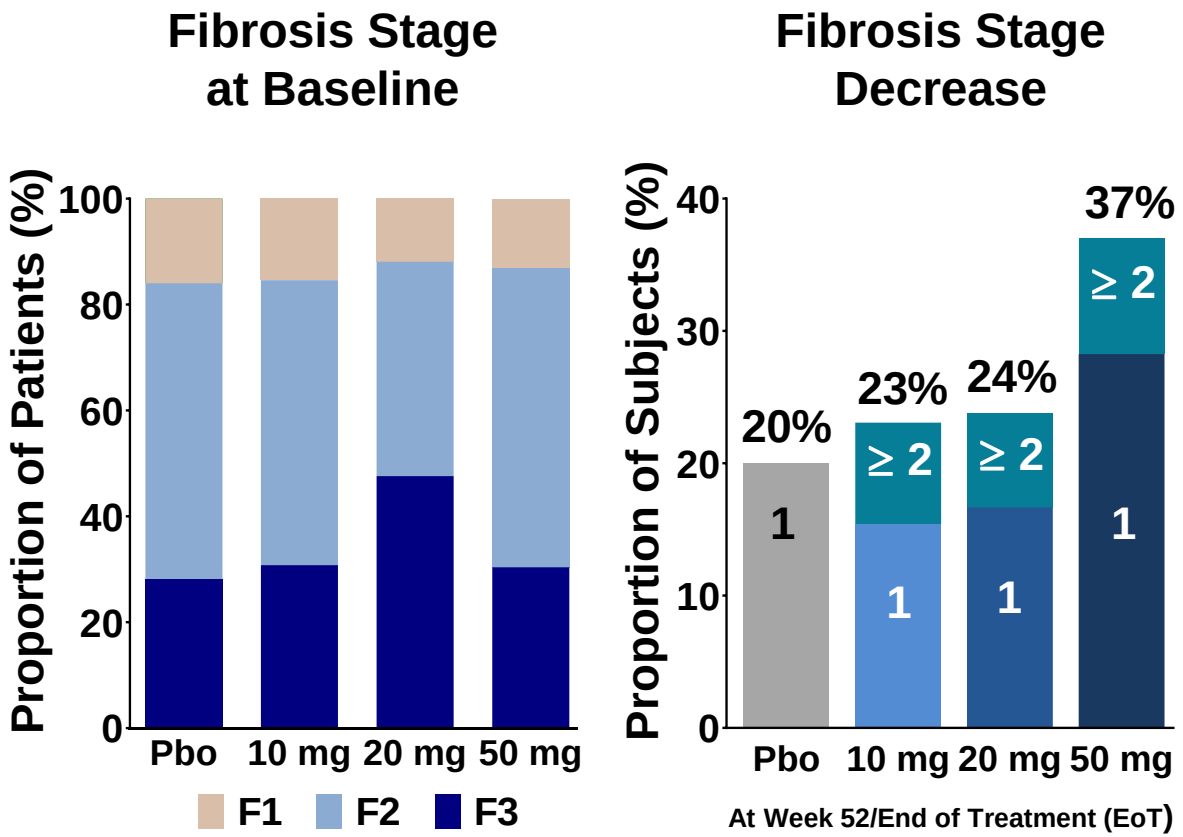
Fibrosis Stage

Mouse vs. Human

Mouse NASH Model



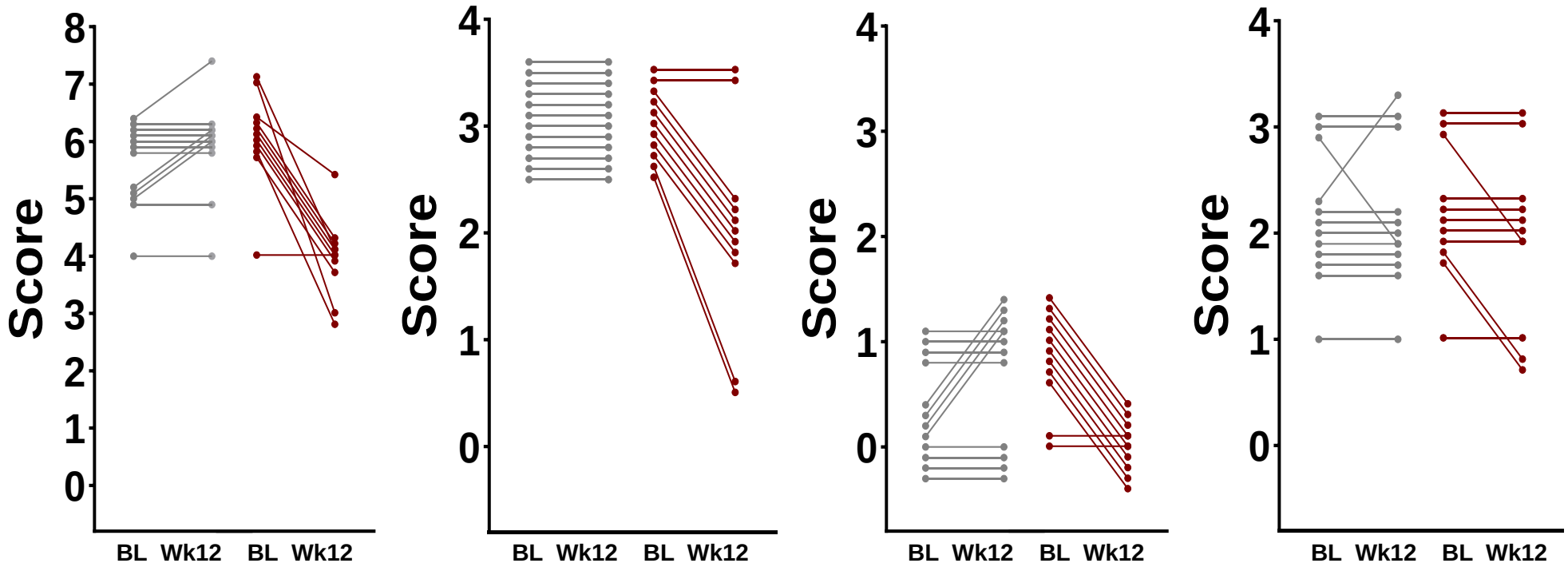
Human Phase 2 NASH Study



NAFLD Activity Score (NAS)

Mouse Model of NASH

NAS = Steatosis + Ballooning + Inflammation



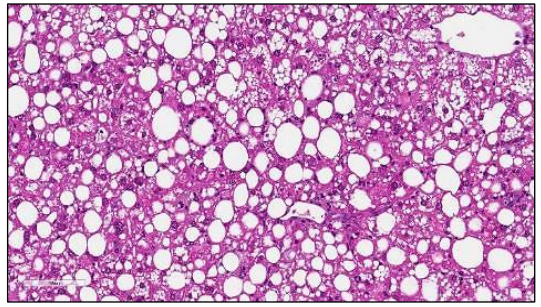
CYMABAY THERAPEUTICS

Liver Fat Content

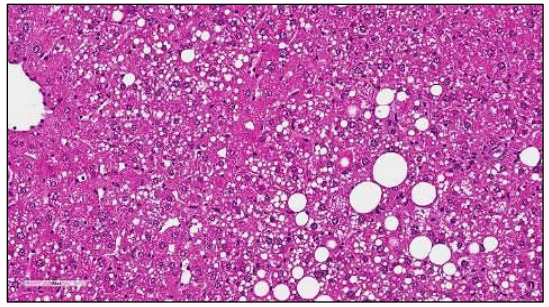
Mouse vs. Human

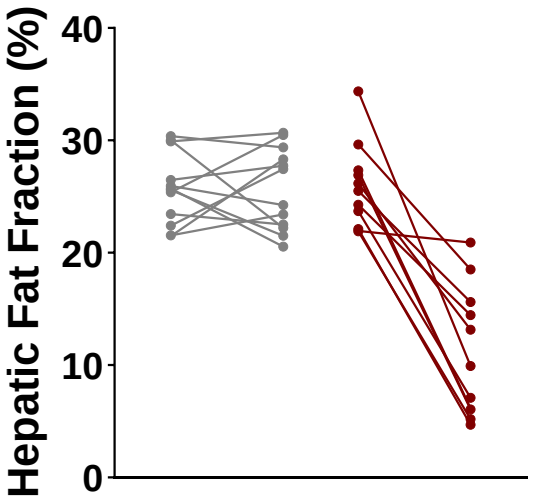
Mouse NASH Model

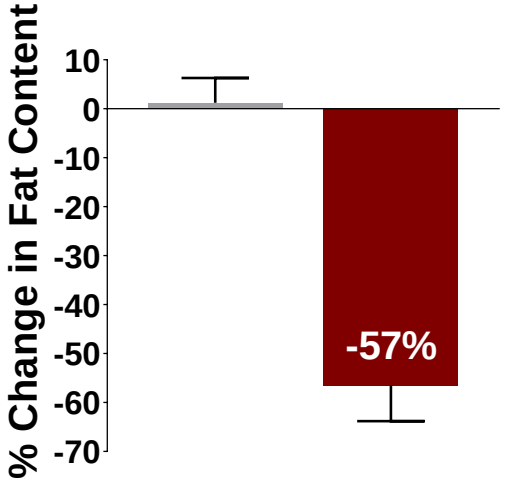
NASH Vehicle



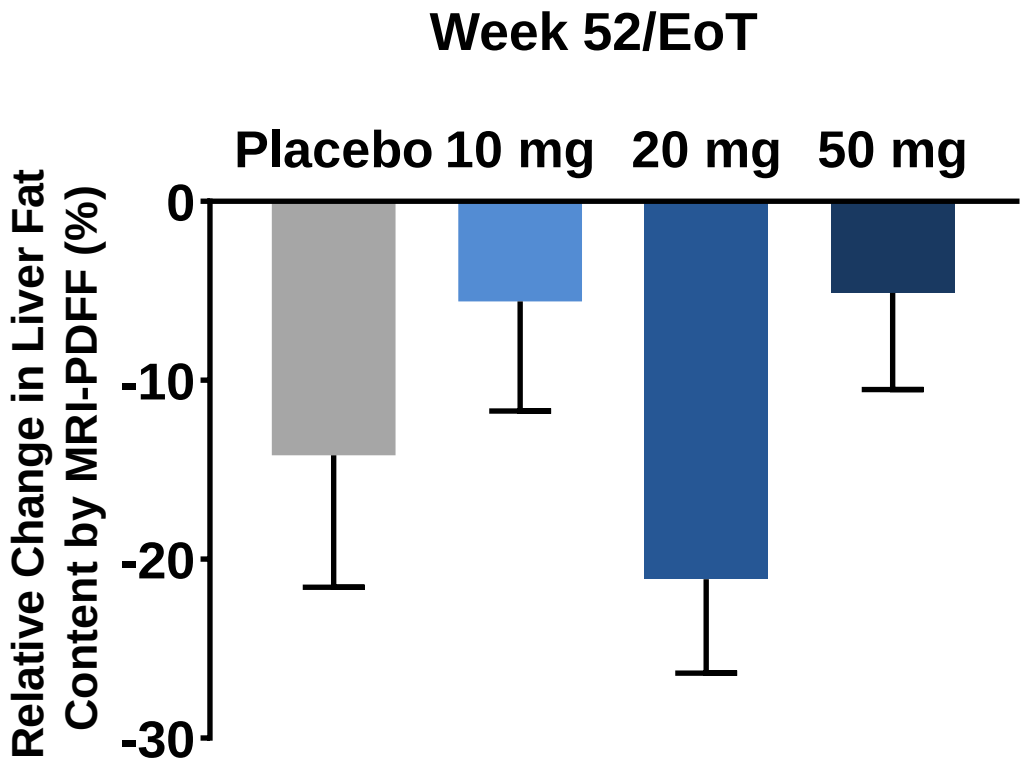
Seladelpar







Human Phase 2 NASH Study

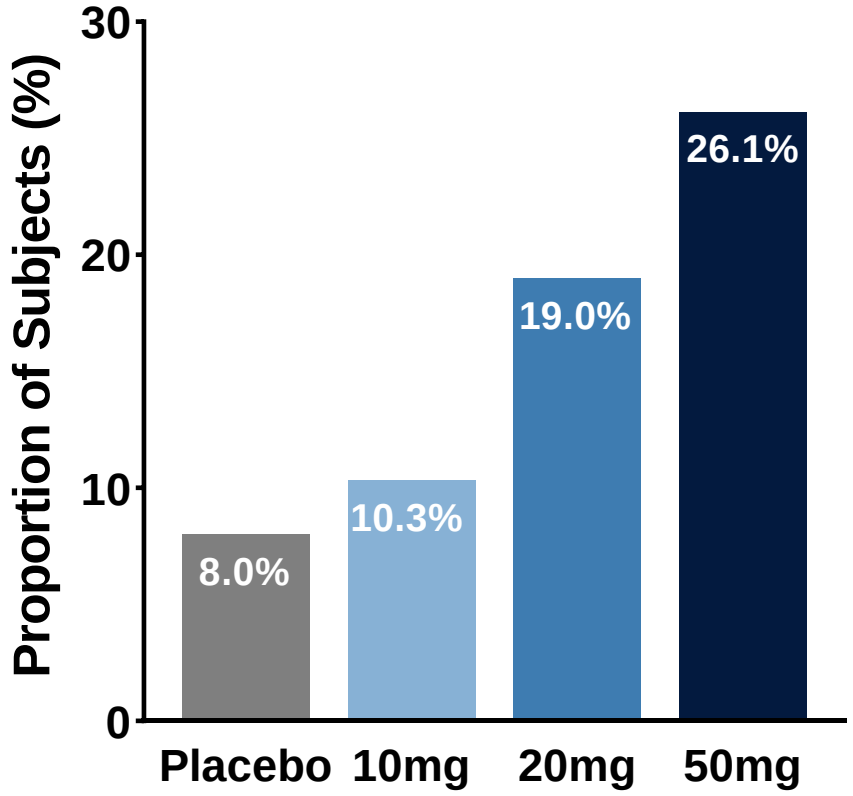


EoT: End of Treatment

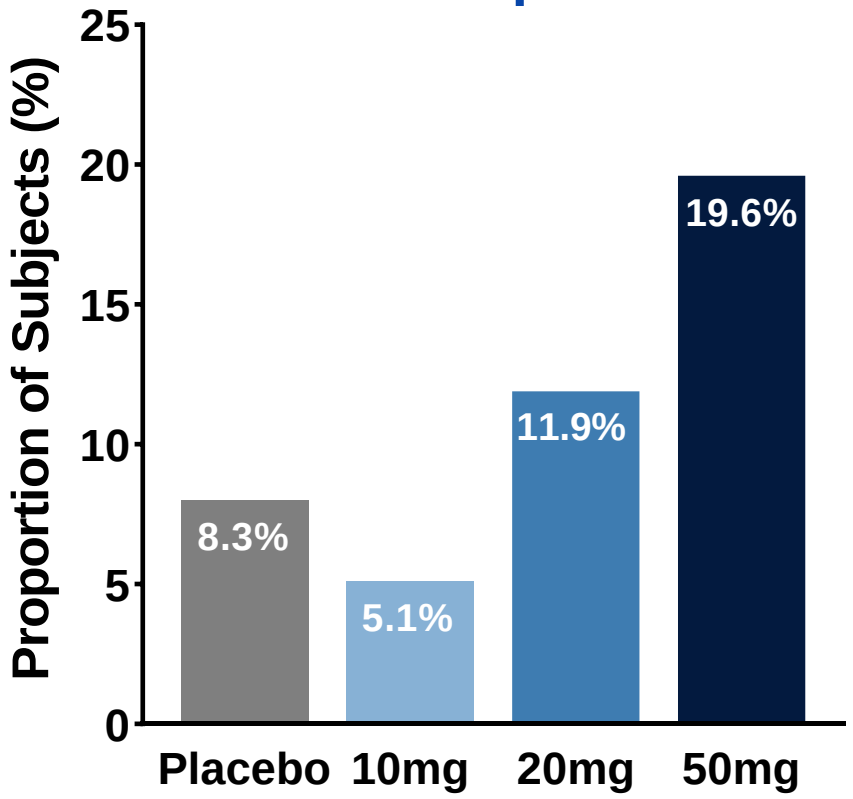
NASH Resolution and Fibrosis Improvement

Human Phase 2 NASH Study at Week 52/EoT

NASH Resolution



NASH Resolution and Fibrosis Improvement



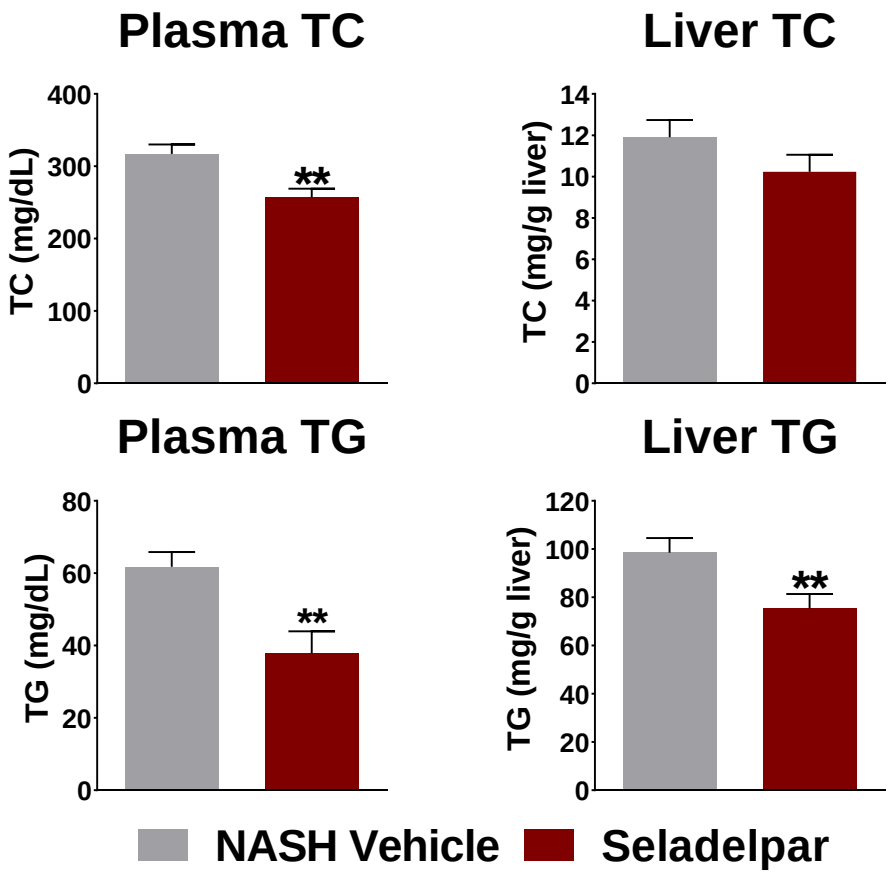
NASH resolution with no worsening of fibrosis: Absence of hepatocellular ballooning and lobular inflammation score of 0 or 1

CYMABAY THERAPEUTICS

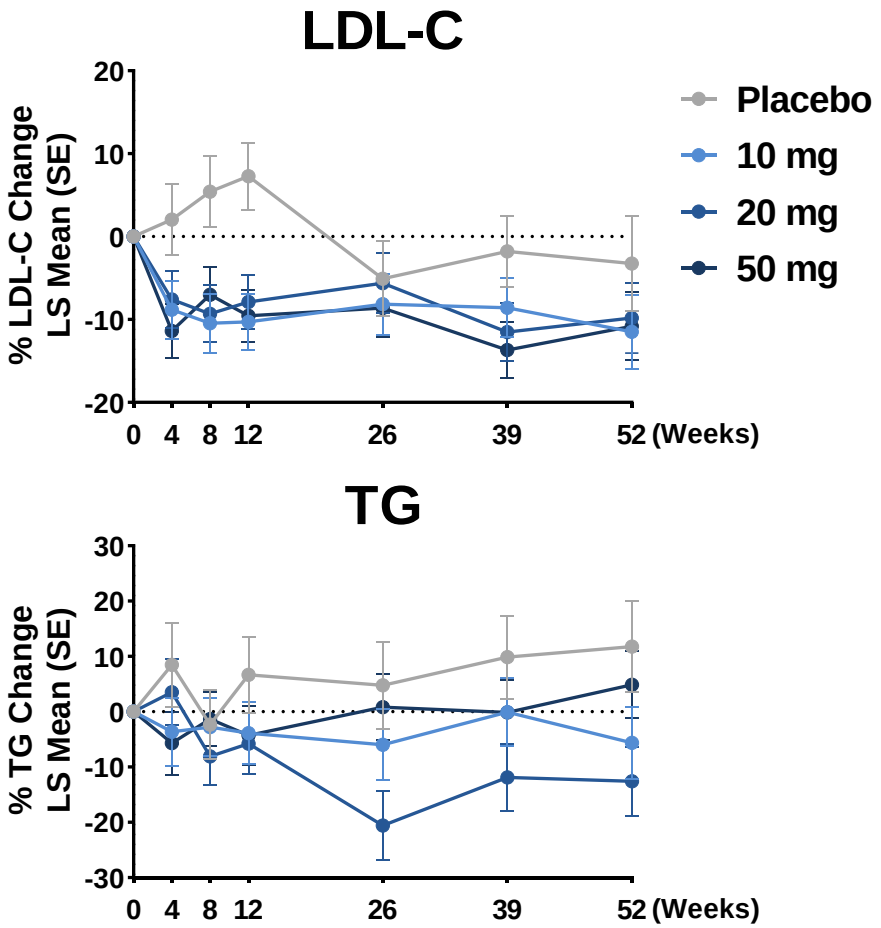
Lipids

Mouse vs. Human

Mouse NASH Model



Human Phase 2 NASH Study



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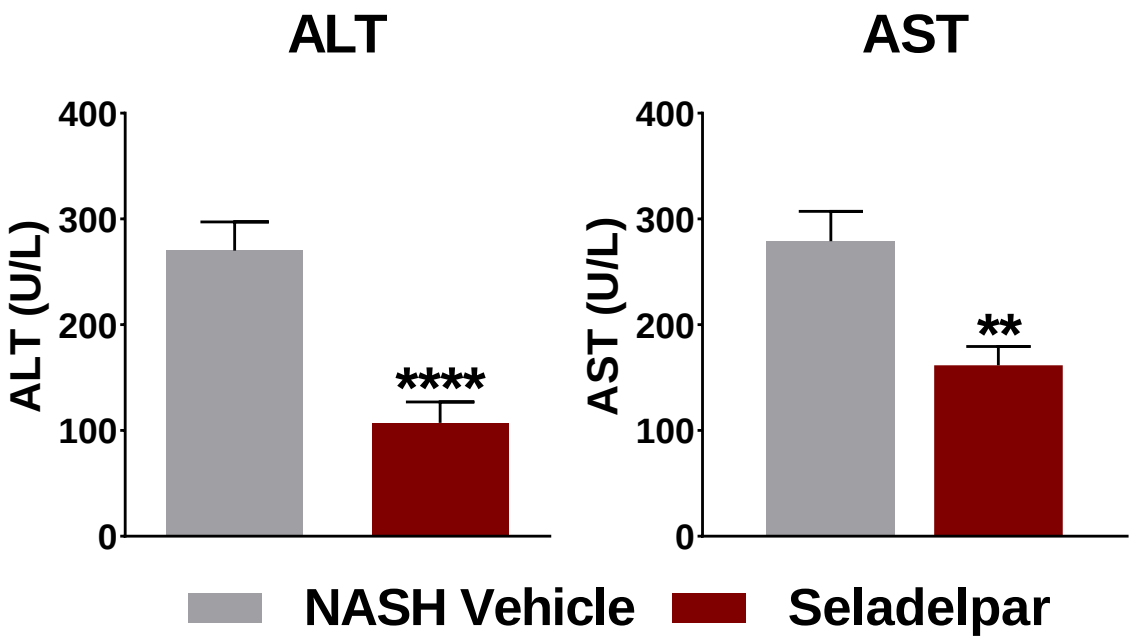
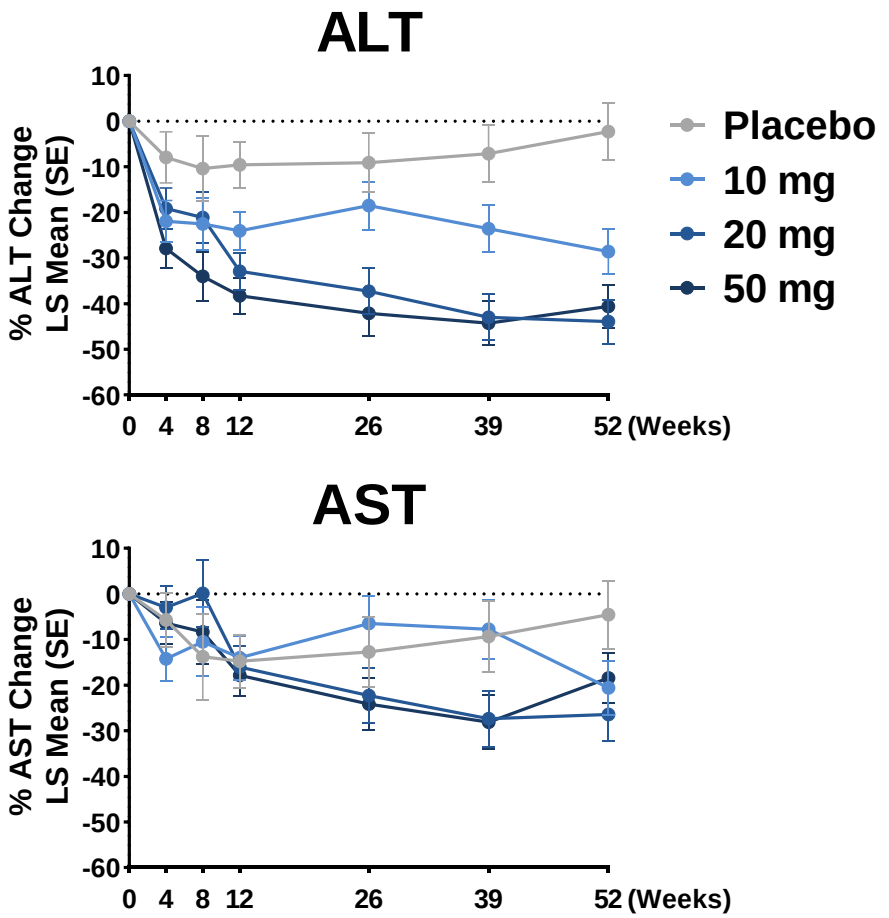
ALT and AST

Mouse vs. Human

Mouse NASH Model



Human Phase 2 NASH Study

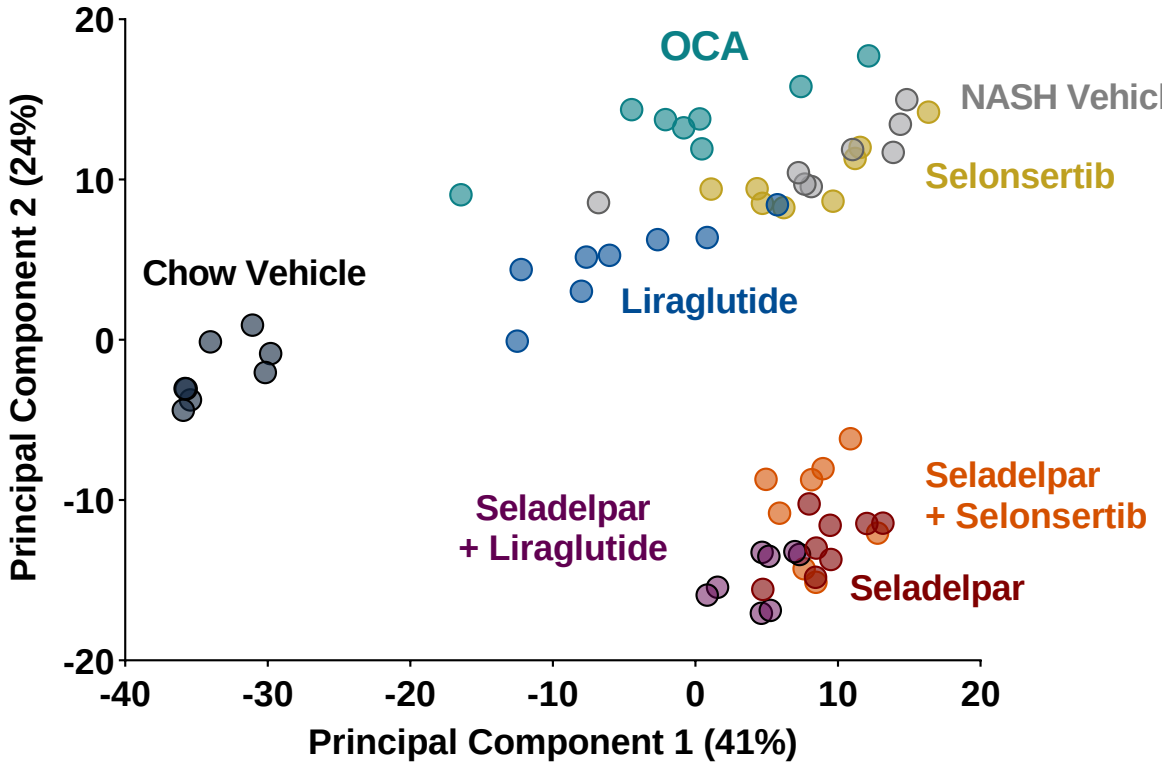


CYMABAY THERAPEUTICS

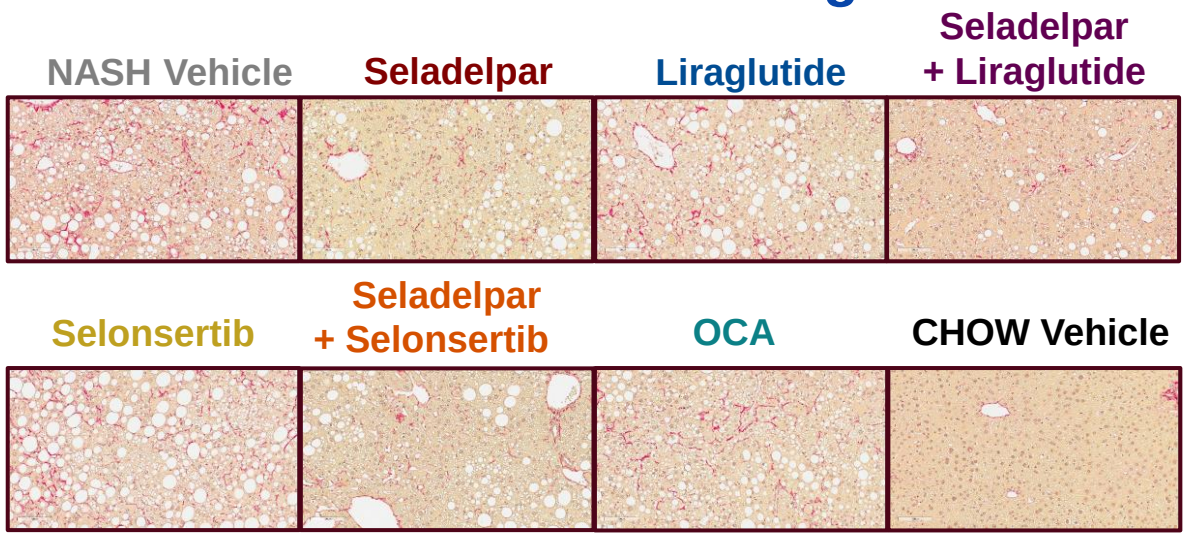
Seladelpar Combination

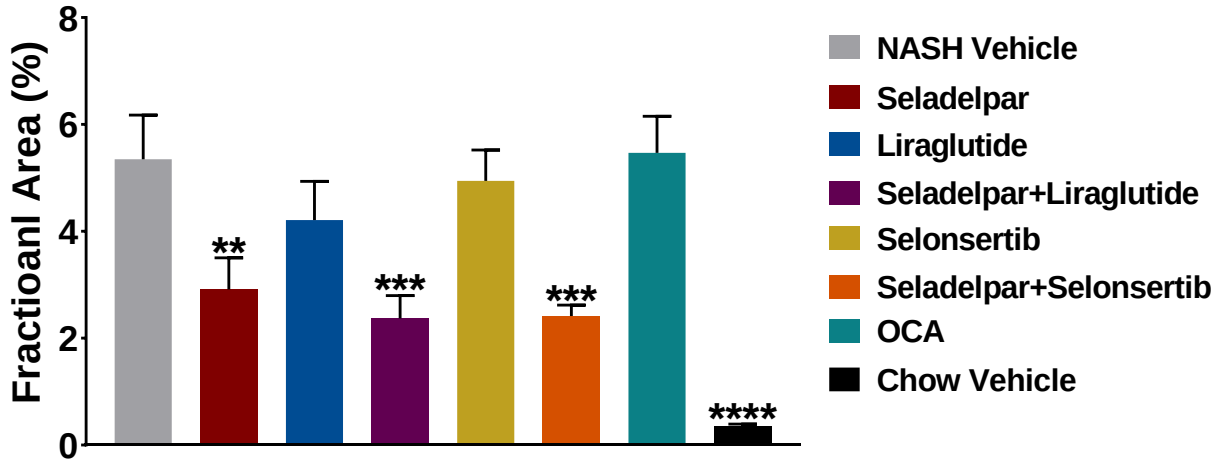
Mouse Model of NASH

Principal Component Analysis of RNAseq



Sirius Red Staining





Conclusion

Translational Studies of Seladelpar for the Treatment of NASH

- **While direct comparisons are not meant to be rigorous, it is interesting to see the many shared patterns of responses in mice and in clinical studies**
- **Liver fat decreases in NASH patients after seladelpar treatment were not consistent in spite of a substantial decreases seen in mice**
- **In contrast, many similar effects of seladelpar were seen in mice and humans**
  - **Improvement in fibrosis, lipids, ALT/AST and NASH resolution**
- **Mouse NASH models can help us understand mechanism of action of seladelpar and help to interpret results seen in clinical studies**
- **Mouse NASH models can provide a rationale to identify candidate drug combinations for future clinical development**